COGNITIVE AND NEURAL RESERVE IN CHILDREN WITH BRAIN INJURY

Maureen Dennis
Program in Neurosciences and Mental Health, The Hospital for Sick Children
Departments of Surgery & Psychology, University of Toronto

9th Nordic Meeting in Neuropsychology
Göteburg 19 August 2007
Maureen.dennis@sickkids.ca

Learning Objectives

- To understand concepts of brain reserve capacity (BRC), cognitive reserve capacity (CRC) and age-based functional plasticity.
- To demonstrate how these three concepts apply to neurocognitive group outcomes of childhood congenital and acquired brain injury
- To identify key factors that produce variations in BRC, CRC, and age-based functional plasticity in individual children and adults who have sustained congenital or acquired brain injury.

Why Reserve?

- The job of any brain, mature or immature, intact or injured, is to learn and to change.
- In a perfect brain, any lesion would be followed by structural and functional changes sufficient to restore or maintain function; this is not so, and the response to brain lesions is incomplete/ maladaptive.
- More important, the functional outcome of brain insult in both children and adults is usually predictable for groups but variable for individuals.
- In adults, individual differences in functional outcome have been explained by two constructs: passive brain reserve capacity (BRC) and active cognitive reserve capacity (CRC) that maintain function after brain insult.

Brain Reserve Capacity (BRC)

- BRC is not directly observed, but is rather a hypothetical construct referring to a critical or threshold level of brain size, synapse count, or the like.
- Functional deficits occur when the pathology burden reduces brain substance below a critical level.
- Deficits emerge when a BRC threshold is reached; individuals with more BRC will be deficit-free for longer after similar-sized lesions or require larger lesions to generate symptoms.
- Variables like head circumference, brain volume, and less direct indices such as education and occupation have been used as proxies for BRC.

Cognitive Reserve Capacity (CRC)

- CRC is the ability to optimize or maximize performance through differential recruitments of brain networks that reflect the use of alternate cognitive strategies.
- Cognitive reserve is present in healthy individuals: an individual who uses a brain network more efficiently or generates cognitive strategies in response to increased demand is deemed to have more CRC.
- In the standard formulation, cognitive reserve refers to individual differences in recruiting either the same or alternative networks.

Functional Plasticity, BRC, & CRC

- The concept of functional plasticity links outcomes to brain-related changes in behavior and cognition, and encourages the search for a biological account of the effects of age and risk and resilience factors on children's response to brain insult.
- Plasticity is an intrinsic property of the human brain to adapt to environmental pressures, physiologic changes, and experiences.
- Plasticity involves:
  - dynamic shifts in the strength of preexisting neural connections
  - modifications of neural circuits in response to changes in afferent input or efferent demand.

Why Study Reserve In Children?

- In children as in adults, outcome is generically predictable for condition, somewhat predictable for groups, and poorly predictable for individuals.
- Perhaps concepts of reserve can help us
  - Account for variability in outcome in a principled way
  - Better predict outcomes for individuals?
- This workshop examines evidence for childhood reserve and considers factors that contribute to variations in BRC and CRC as moderators of functional plasticity in this age group.
- The general proposition is that childhood brain insult constitutes a pathological load, but that functional outcome is mediated by reserve, as evidenced by
  - Accelerated aging in adulthood
  - Greater vulnerability to subsequent brain insult
  - Diminished capacity to make age-appropriate developmental progress.

Outcome Domains

- Outcome after childhood brain insult involves multiple domains of function.
- *Physical* outcome refers to whether the child's height, weight, fatigue tolerance, endurance, and motor performance are normal for age.
- *Cognitive-academic* outcome is usually measured by standard intelligence tests and by assessment of academic skill attainments.
- *Neuropsychological* outcome refers to capacities such as motor speed, attention, perception, memory, language, and executive function.
- *Psychosocial* outcome refers to the ability to function in the social world of family, school, and community.

Moderators

•Moderators are qualitative or quantitative variables that affect the direction and/or strength of a relation between an independent or predictor variable and a dependent or criterion variable.

•Moderators specify the condition under which a given effect occurs, as well as the conditions under which the direction or strength of the effect will vary, and so interacts with a predictor variable in such as way as to have an impact on the level of the dependent variable or outcome.

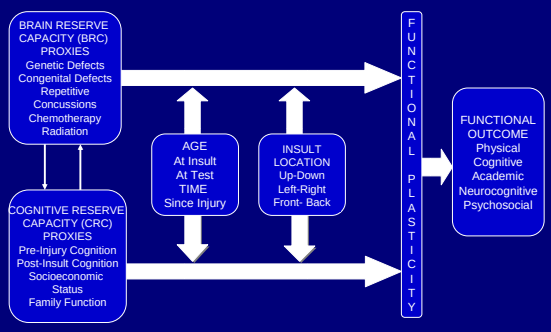
•Moderators up-regulate or down-regulate the expression of the predictor variables.

Mediators

•A mediator specifies how (or the mechanism by which) a given effect occurs.

•A mediated relationship is one in which the independent variable influences the mediator which, in turn, influences the outcome.

•In the present context, a mediator is a construct that is influenced by an independent variable and that then influences the cognitive outcome.



Assumptions Of Model: 1

- There exists a quantum of brain reserve capacity or BRC
- BRC is a form of passive reserve that varies in degree among children due to single or multiple challenges to brain status.

Assumptions Of Model: 2

- The amount of BRC can be measured directly by variables such as residual brain volume on voxel-based morphometry or structural connectivity on diffuse tensor imaging (DTI).
- Alternatively, BRC can be measured by the extent or likelihood of brain abnormality in persons subsequently exposed to unrelated brain insults or the effects of aging. In the latter instance, proxies for reduced BRC include genetic anomalies (polymorphisms, microdeletions, repeats, or mutations) that affect brain development or prior brain lesions stemming, for example, from past concussions or from treatment-related insults such as radiotherapy and chemotherapy.

Assumptions Of Model: 3

- BRC may additionally be indexed by multiple brain insults. Some individuals suffer an initial brain insult that is followed either by a second injury of the same type, such as a repetitive concussion, or by treatment required by the initial insult, such as radiation and chemotherapy.
- Childhood brain tumors represent a well-studied childhood model of multiple brain insults in that a primary insult, the tumor, is treated either by a relatively benign procedure, surgery that does not add to tumor morbidity, or by treatments such as radiotherapy and chemotherapy that by themselves constitute an additional brain insult that diminishes BRC.

Assumptions Of Model: 4, 5, & 6

- 4. There is a quantum of CRC after developmental brain insult. This is a form of active reserve that varies in degree among individuals, again reflecting both single and multiple challenges.
- 5. The amount of CRC is not measured directly, but rather by proxies such as pre-injury cognitive function, socioeconomic status, and family function.
- 6. BRC and CRC mutually influence each other.

Assumptions Of Model: 7

- Moderators are variables that specify the condition under which a given effect occurs, as well as the conditions under which the direction or strength of the effect will vary, and so interacts with a predictor variable to affect outcome.
- Outcomes of brain disorders in childhood are moderated by two sets of variables that contribute to variations in BRC and CRC as mediators of functional plasticity and thus of functional outcome.

Assumptions Of Model: 8

- The first moderators are age and time variables:
  - the age of the child at the time of injury
  - the amount of time that has passed since the injury
  - the child's age at the time of outcome evaluation.
- Age-and time-related issues are relevant to the outcomes of brain insult at any point in the lifespan, but especially in childhood brain insult.
- Almost all neurocognitive skills show age-related improvements, and a number of outcomes vary with age at onset of brain insult.
- Time is important, and outcome may be different when evaluated at different time points after brain insult, from acute, subacute, and long-term to very long-term.

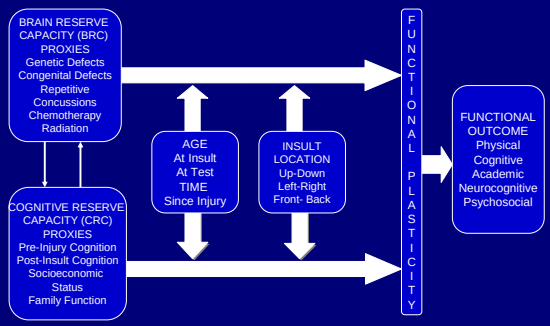
Assumptions Of Model: 9

- The second moderators are gradients of brain lesion location
  - up-down
  - left-right
  - front-back.
- Recent studies of childhood brain lesions have allowed BRC in children to be conceptualized in terms of spatial gradients with varying degrees of age-based functional plasticity and outcomes.
- Spatial gradients are considered moderators because they interact with BRC to influence outcome.

Assumptions Of Model: 10 & 11

- 10.Functional plasticity is the reorganization within an individual that emerges from the action of the two mediators BRC and CR, measured in physical, cognitive, academic, neuropsychological, and psychosocial domains.
- 11.The moderating influences of age variables and lesion characteristics predict individual differences in functional plasticity and thus help to explain group and individual variability in functional outcome.

QUESTIONS?



Proxies For BRC: Direct

- BRC may be measured directly.
- Residual brain connectivity constitutes a direct measure of BRC.

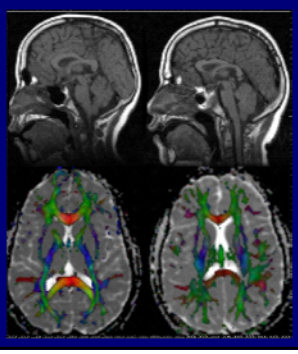
Diffusion Tensor Imaging

- Diffusion tensor imaging (DTI) measures displacement of water molecules across tissues.
- Water diffusing equally in all directions (e.g., in CSF) is isotropic.
- Myelin restricts molecular movement of water, and restricted diffusion of water (e.g., within axons) is anisotropic.
- Fractional anisotropy (FA) is the degree to which diffusion is directionally dependent.
- Areas of dense white matter (compact, homogenous fibre bundles like corpus callosum) have more FA.
- DTI provides information about microstructure of white matter and can be used to examine models of connectivity between cortical areas.

Diffusion Tensor Imaging (cont.)

- DTI images outline white matter bundles and direction of propagation.
- DTI numbers are rotationally invariant.
- Colours are orientation map for different fibre paths.
  - PROJECTION FIBRES BLUE (S-I)
  - COMMISSURAL BUNDLES RED (L-R)
  - ASSOCIATION FIBRES GREEN (A-P)
- Saturation shows strength of fibre paths: less colour, less connectivity.
- Following images of DTI and outcome in twins from Ewing-Cobbs et al., AJNR, 2006

Comparison Of Conventional MRI And DTI in FRATERNAL Twin (R) And Co-twin (L).



- Childhood brain trauma reduces functional brain connectivity, as evidenced by changes in the directionality and integrity of white matter tracts like corpus callosum, esp. genu, rostrum and posterior body.

Proxies For BRC: Indirect

- More commonly, BRC can be measured indirectly by brain integrity prior to a neurological insult.
- Proxies like head size are used in adults but have generally not been studied in children.
- For one reason, head and brain size in children change over development.
- For another, some size changes are not linear increases (e.g., frontal cortical development involves thinning of the frontal polar cortex, asynchronous in different frontal areas).

Genetic Heterogeneity

- Investigation of children with genetic disorders reveals the effects of reduced BRC.
- Genetic defects in children (repeats, microdeletions, mutations, or polymorphisms) are associated with deficits in the functions specific to brain regions that depend on neurotransmitters controlled by the deficient genes.
- These children have reduced brain substrate compared with those without genetic disorders.
- Studying effects of genetic defects on recovery from childhood brain insults and on later age-related loss of skills can illuminate the

Genetic Heterogeneity: *Phenylkenonuria*

- Phenylketonuria is a genetic disorder associated with high phenylalanine and low dopamine.
- Catechol gene affects duration of dopamine activity in prefrontal cortex, and the Methionine polymorphism results in a slower breakdown of prefrontal dopamine.
- Children with phenylketonuria and high phenylalanine levels have impairments in the dorsolateral prefrontal cortex functions of inhibitory control and working memory and in visual contrast sensitivity, which varies with retinal dopamine levels.
- Children homozygous for the Methionine polymorphism perform poorly on tasks sensitive to the level of dopamine.

Genetic Heterogeneity: *Fragile X*

- Genetic disorders may progressively slow the trajectory of development.
- Males with the fragile X mutation show loss of cognitive abilities as they mature, with increasing inability to master more complex cognitive skills as they progress into adolescence.
- In this instance, reduced BRC is evidence by slowing in the rate of development.

Genetic Heterogeneity: *Williams-Beuren*

- Genetic heterogeneity in the apolipoprotein E (ApoE) genotype is a factor in diminished reserve in adults with Alzheimer's, and heterogeneity in childhood genetic disorders produces accelerated aging.
- Williams-Beuren Syndrome (WBS) is a rare genetic disorder related to a sporadic heterozygous contiguous gene deletion on chromosome 7). WBS produces physical signs of premature aging (reduced longevity, early graying of hair, premature skin aging.
- Adults with WBS show a chronologically early and precipitous age-associated decrease in long-term episodic memory (not observed in age peers with

Genetic Heterogeneity: *Down Syndrome*

- Another form of genetically based mental retardation, Down syndrome, produces premature aging and Alzheimer disease.
- Because of the triplication of chromosome 21, individuals with this condition have an increased gene dosage for amyloid precursor protein (cleavage of which is involved in generating the main constituents of neuritic plaques), and they develop amyloid plaques and neurofibrillary tangles during the fourth and fifth decades of life.
- Risk factors for development of Alzheimer Disease in individuals with Down syndrome include age, apolipoprotein E (ApoE) genotype, brain size, ability level, and head trauma.

Genetic Heterogeneity: Spina Bifida

- Individuals with spina bifida meningomyelocele (SBM) have genetic anomalies.
- Those with a genetic mutation in the folate metabolic pathway have more compromised brain tissue in the cerebellum and midbrain, and corpus callosum dysgenesis, especially in the splenium, which results in more severe neurocognitive deficits.
- As adults, individuals with SBM have clinical memory problems, and the hypothesis that their aging is accelerated is supported by:
  - faulty folate metabolism and B-group vitamin deficiency as risk factors for Alzheimer Disease in Down Syndrome
  - declines in the corpus callosum splenium as part of the neuropathology of Alzheimer Disease.

Genetic Heterogeneity: The Net

- We think of genetic disorders as somehow being fixed in the gene. In fact:
  - Variations in the genetic profile produce variations in outcome
  - The genetic disorder is typically accompanied by specific brain dysmorphologies
  - Rate of development may be changed
  - Aging is accelerated.
- Genetic disorders diminish BRC.

Multiple Insults: Repetitive Concussions

- Repetitive brain injuries in adults, such as those from sports injuries, diminish BRC and accelerate dementia, likely because of cumulative damage to hippocampal cells.
- For many children, brain insult involves a single event, although repetitive insults (e.g., series of concussions) may exacerbate cognitive deficits.
- Compared to those with no prior concussion, amateur athletes with a history of three or more concussions show more pre-season cognitive problems and are nearly 8 times more likely to show a major drop in memory function after an additional concussion.

Treatment-Related Insults: Radiation

- In children, compromised intelligence is associated with conventional cranial radiation treatment, the mechanism involving a progressive vascular and demyelinating neuropathology, beginning after the end of treatment, peaking over the next few years, and then maintaining a less steep decline.
- The concomitant cognitive impairment is inversely related to age of treatment and directly related to the dose and field of cerebral radiation.
- Attempts to adjust radiation dose on the basis of age or tumor site have not fully eliminated the cognitive deficits, and hyperfractionation of the radiation dose reduces but does not eliminate cognitive deficits.

Treatment-Related Insults: Radiation 2

- Radiation damage includes generalized brain atrophy, calcifications distant from the site of the primary tumor, and white matter abnormalities.
- Serial neuroimaging shows increasing number of lacunae within the white matter in some children whose brain tumors were treated with radiation.
- Progressive white matter damage has also been documented after cranial radiation for medulloblastoma, and the volume of normal-appearing white matter declines over time in children radiated for medulloblastoma, a decline that is faster in children with higher radiation dose.

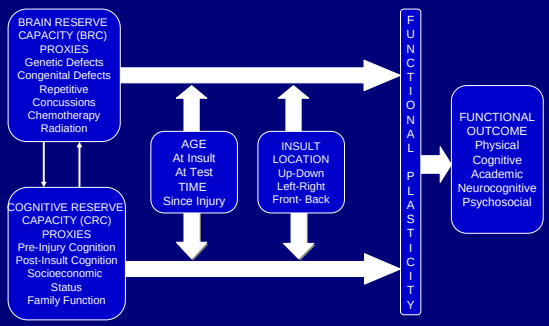
Treatment-Related Insults: Chemo

- Intraventricular methotrexate combined with radiotherapy produces poor outcome.
- In children treated for medulloblastoma, radiotherapy in association with intrathecal methotrexate impairs cognitive development.
- Intravenous chemotherapy alone may produce a better outcome in young children.

Treatment-Related Insults: The Net

- Children with higher radiation doses may have less BRC to maintain age-appropriate rates of skill acquisition.
- Chemotherapy may add to morbidity of radiation.
- Effects of these treatments are seen in rate of cognitive development and so should be monitored over time.
- Radiation and/or chemotherapy diminish BRC.

QUESTIONS?



Proxies For CRC

- CRC involves risk and resilience factors that hamper or promote various outcomes.
- Some CRC factors are intrinsic to the child (e.g., pre-injury cognitive ability).
- Other factors others reflect environmental influences (e.g., socioeconomic status, parenting skills).

Proxies For CRC: Pre-Injury Status

- Proxies for CRC, including pre-morbid cognitive and behavioral status, predict outcome after childhood TBI.
- Cass et al. (2005) hypothesized that CRC moderates neuropsychological outcome attributable to TBI, with outcome being poorer for children with lower rather than higher CRC (pre-injury cognitive status).
- Growth curve analyses revealed that CRC predicted individual differences in neuropsychological functioning.
- An effect of CRC on subsequent cognitive development is consistent with the hypothesis that additional CRC was conferred by higher cognitive abilities prior to injury.

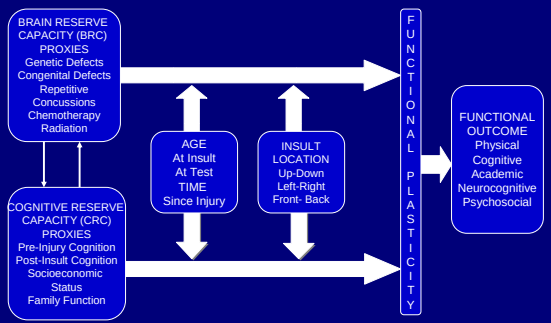
Proxies For CRC: Pre-Morbid ADHD

- A vexed question for clinicians has always been whether post-trauma ADHD existed prior to the trauma.
- One of the challenges of studying attention problems in children with TBI is that they have more attention problems and higher rates of attention-deficit hyperactivity disorder (ADHD) prior to injury compared with non-injured controls or normative expectations.
- Yeates et al. (2005) found that group differences in behavioral symptoms pf ADHD (not cognition) were significantly larger for children with more pre-morbid symptoms than for children with fewer pre-morbid problems.

Proxies For CRC: Social And Family

- Childhood TBI increases deficits in social information processing and social adjustment.
- Broader aspects of the family environment, including poverty and parental unemployment, parental conflict, and parent mental health, also may influence children's social outcomes. Childhood TBI associated with adverse social outcomes, effects that are exacerbated by fewer family resources/ poorer family function.
- Better outcomes observed in children with TBI from more advantaged circumstances suggest:
  - more environmental supports for behavioral change
  - privileged environments imparting greater CRC.

QUESTIONS?



Moderators Of Relation Between BRC, CRC, And Outcome

- Study of age-related factors on outcomes of childhood brain insult suggests that BRC and CRC are not constant across development, but vary with:
  - –age at insult
  - –age at testing
  - –time since insult.

Moderators: Age At Insult

- Lower IQ and poor language is related to earlier age at diagnosis/ treatment in children with brain tumors.
- Younger children with TBI demonstrate a slower rate of change over time and more significant residual deficits after their recovery plateaus than do older children with injuries of equivalent severity.
- Younger children more adversely affected because their brains are in more rapid phases of development and have had less opportunity to develop cognitively.
- Compared to later insult, early brain insult diminishes BRC and CRC over a larger portion of the development period, so child's neural substrate is less able to support subsequent developmental change.

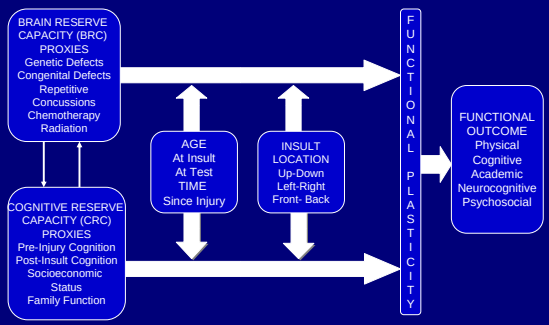
Moderators: Time Since Insult

- Children generally display a gradual recovery over the first few years after an acquired brain injury.
- Initial rate of recovery is often more rapid with severe injuries, although severe injuries are associated with persistent deficits after rate of recovery slows down.
- With brain insult at birth, age and time factors are indistinguishable. Nevertheless, studies examining both factors have found that time since injury predicts outcomes independent of age at injury.
- Childhood brain insult depletes CRC, yielding less capacity to support post-injury skill acquisition.

Moderators: Age At Test

- Age at test effects would be reflected in demonstrations of latent sequelae (failure to meet new developmental demands).
- Levin et al. (1988) found greater memory impairment in adolescents than in children following severe TBI.
- Taylor and colleagues, examining the consequences of several forms of early brain insult across the school-age years found that some skills decline relative to age expectations with advancing age, while other deficits remain stable over time.
- The inability of children to maintain age-appropriate rates of skill acquisition implies loss of reserve, although it is unclear if age-related declines in functioning reflect loss of BRC, CRC, or both.

QUESTIONS?



Moderators: Spatial Gradients Of Brain Injury: Up-Down

- An earlier era of research into brain injury in children concluded that cortical lesions in children had fewer consequences for outcome than did cortical lesions in adults, although comparisons were often made between different pathologies or without appropriate benchmarks of typical development.
- A revision in the view of privileged cortical plasticity in children was prompted by outcome studies involving children with subtentorial and brainstem lesions, which has suggested an up-down BRC gradient in the immature brain, with limited plasticity and thus reduced reserve, following lesions to subcortical, subtentorial, and midbrain lesions.

Moderators: Periventricular Lesions

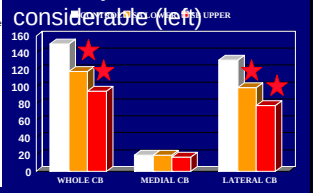
- Deficits following early periventricular brain insults are highly persistent.
- Evidence for limited plasticity of subcortical functions provided by a recent study that examined long-term outcomes at age 16 of <750 g birth weight.
- Compared to term controls, low birth weight group had memory, executive function deficits, suggesting a limited capacity for recovery after subcortical, fronto-striatal, and medial temporal insults.
- Slower age-related increases in executive function tests in low birth weight group compared with term-born controls, offering further evidence for limitations in plasticity following perinatal subcortical lesions.

Subtentorial: Cerebellum Volume Loss And Perceptual And Motor Timing

Cerebellum In Spina Bifida

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to se

Cerebellum reduced in volume (cubic cm, below) in lateral but not medial regions, but variability is considerable (left)



The Cerebellum And Timing

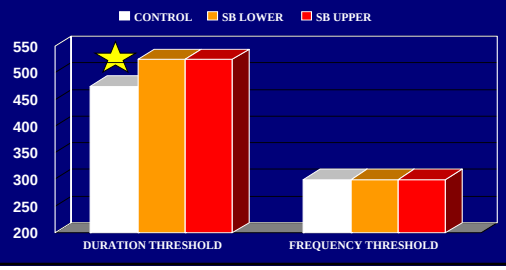
- Traditional view of cerebellum:
  - Fine motor control and coordination
  - Not movement as such, but “harmony” of movement.
- Contemporary view includes timing and rhythm.
- Adults + children with cerebellar lesions impaired in:
  - Perceptual timing (e.g., judgment of short durations around 400 ms)
  - Motor timing (e.g., precisely timed isochronous tapping movements)
  - Rhythm discrimination and production.

Perceptual Timing Task

- Timing. Duration threshold
  - Children heard two empty intervals defined by 50 ms, 1000-Hz boundary tones
  - Target interval 400 ms, foil interval always longer
  - Depending on response accuracy, foil duration adjusted up or down in 8 ms increments
  - Procedure stopped after 6 reversals of direction, averaging last 5 reversal values for estimate of discrimination threshold.
- Pitch. Frequency threshold
  - Similar format. Target frequency of 3000Hz
- Threshold is measure of interest
  - the difference from the target duration (or frequency) that can be discriminated with 80% accuracy.

Perceptual Timing Results

- Children with SB have higher thresholds for perception of duration (but not frequency)
- Similar magnitude of timing perception deficit in upper and lower spinal lesion groups



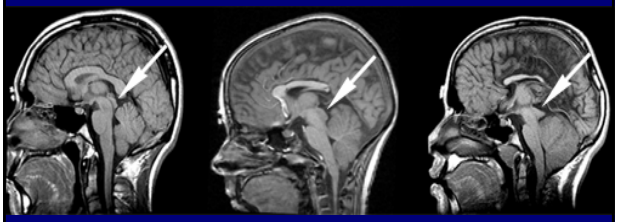
Summary of Timing Results

- Children with SB show
  - Reductions in cerebellar volume
  - Perceptual timing deficits
  - Motor timing deficits.
- Motor timing (but not perceptual timing) is related to genetic-embryological heterogeneity (level of spinal cord lesion).
- Perceptual and motor timing measures are correlated with each other, although not with non-timing measures.
- Perceptual and motor timing deficits are correlated with cerebellar volumes.

Midbrain: Tectal Beaking and Attention Orienting Deficits

Midbrain In Spina Bifida

(L control; M normal tectum in SB; R beaked tectum in SB)



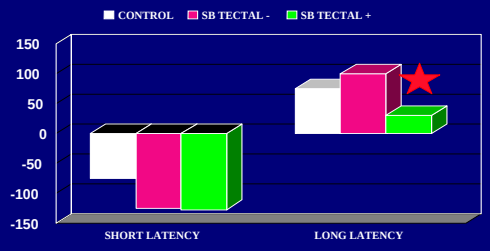
Inhibition Of Return

- Midbrain controls shifting and moving of attention, including inhibition of return, by which we do not orient repeatedly to the same location (biologically, increases chance of good foraging and full environmental exploration).
- We can study this in covert orienting paradigm by manipulating latency differences between validly and invalidly cued targets.

Studying Covert Orienting

- Fixate centre cross and press button when target (star) appears.
- The cue (a bright flash of light before the target) is HELPFUL if it appears right where the target will appear but MISLEADING if it appears opposite to where the target will appear.
- Better detection of targets after HELPFUL cues represents the benefit associated with having attention oriented to the cue.
- Slower detection of targets after MISLEADING cues represents the cost of having had attention misdirected.

Inhibition Of Return

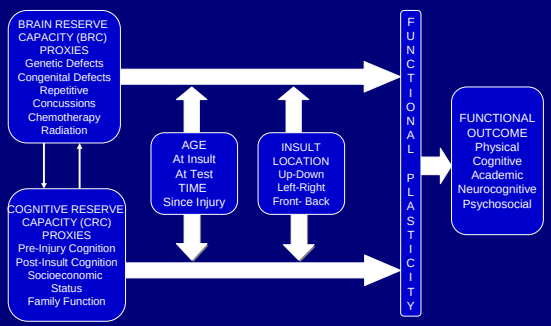


- At the short (200 ms) latency, the minus values show the DISENGAGEMENT COST associated with misdirecting attention on invalidly cued trials. At the longer (1000 ms) time interval, the faster response time to misleadingly cued targets results in positive numbers, which shows INHIBITION OF RETURN.
- Compared to controls or to children with SB and no tectal beaking, children with SB and tectal beaking have less inhibition of return.

Are "Up-Down Functional Deficits" Important?

- Timing deficits represent a temporal disconnect of sensation and movement and produce a lack of synchrony between action and the unfolding perceptual world.
- Deficits may be involved in clinical motor slowing, clumsiness, lack of movement rhythmicity, "dysmetria of thought."
- Attention orienting deficits involve sluggish disengaging from the old and shifting attention to the new, which creates problems in orienting flexibly to salient information.

QUESTIONS?



Left-Right Gradient: Morphology

- Components of the language production system are important for producing free-standing function words and inflectional morphemes in sentences, including the inflectional (I) system subcategories, tense, subject agreement, and object agreement.
- Compared to those with right hemispherectomy, children with left hemispherectomy have difficulty producing inflectional morphology, use restricted I-system morphemes and auxiliaries, despite intactness of other syntactic and morphological structures.
- Left-hemisphere insult may allow for only a limited form of plasticity, implying a relatively constrained capacity of reserve in this hemisphere to support certain language skills.

Left-Right Gradient: Syntax

- Syntactic structures are representations that assign important aspects of sentence meaning, especially of functional roles (who acts, who is acted on).
- Adult left hemisphere has a strong association with syntax.
- Functionally, it constructs syntactically licensed dependencies in real time and assigns syntactic structure during language comprehension.

Left-Right Gradient: Congenital Lesions & Syntax

- The immature left hemisphere also has a strong association with syntax.
- Compared to those with early right hemispherectomy, individuals with left hemispherectomy are slower and less accurate in understanding sentences with non-canonical word orders (e.g., reversible passive sentences such as *the dog is chased by the cat*) in which meaning is provided by syntactic structure but not semantic plausibility.
- Syntactic comprehension deficit is evident whether comparisons are made between hemidecorticate groups with early lateralized hemispheric damage from varying pathologies or from a single pathology or to chronological age, mental age, or brain-intact co-twins.

Left-Right Gradient: *Parsing & Resources*

•Syntactic comprehension disorders in adults arise from two separable impairments: a specific disturbance with parsing processes and linguistic representations, including problems with functional argument structure and difficulties with non-canonical word orders, and a reduction in computational resources available for syntactic comprehension.

•Individuals with early left hemispherectomy have a combined impairment. They are insensitive to the role of function words that cue syntactic structure, which suggests that they have trouble constructing functional argument structures. They make fewer errors on non-canonical sentences when they respond slowly, allocating more resources to comprehension.

Left-Right Gradient: Acquired Lesions

•Later in childhood, more restricted left-sided lesions to the perisylvian region as a result of left middle cerebral artery ischemic stroke produce language deficits, the syntactic component of which shows some recovery but limited development.

•In a co-twin control study, Hetherington & Dennis (2004) studied language in 13-year-old same-sex twins raised together but discordant for left hemisphere stroke that one twin sustained at age 7, causing him to change handedness.

Left-Right Gradient: Acquired Lesions 2

•5 years post-stroke, affected twin had specific difficulty with parsing and syntactic representations:

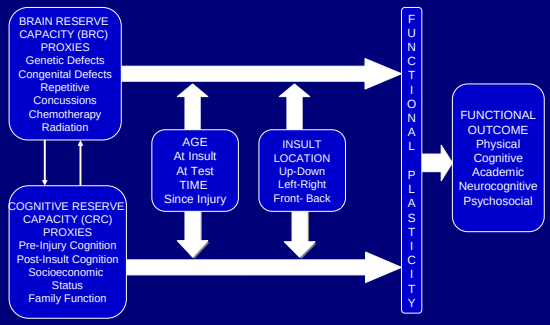
- broke rules for negation and polarity
- poor understanding of sentences with non-canonical word orders.

•Also required more time for syntactic operations in sentences with either canonical or non-canonical word order, suggesting limitation in computational resources.

•Recovery but not development of syntax: syntax skills improved only to their level at the time of the injury.

•Follow-up of affected twin shows effect of depleted BRC, and the arrest of syntactic development is presumptive evidence of limited BRC.

QUESTIONS?



What Does Prefrontal Cortex Do?

- Binds together what cannot be seen, heard, touched, smelled, or tasted.
- Time binding
- Mind binding
- Emotion binding.
- These features make us uniquely human and able to reflect on our past, our present, our future, our own mind, and others' minds.

Front-Back: Frontal Lobe Functions After Anterior Lesions In Children

•Traumatic brain injury (TBI) is often associated with damage to anterior brain regions.

•Prefrontal damage after childhood TBI is of 3 types.

- •Contusional injury to the frontal cortex
- •Diffuse axonal injury in the form of gliosis, hemosiderin deposits, and volume loss, throughout corpus callosum and frontal lobe white matter
- •Reduction in brain connectivity, as shown by changes in the directionality and integrity of white matter tracts .

•Some cognitive-behavioral outcomes are highly vulnerable to frontal lesions, implying that frontal reserve may be limited in support of these functions.

Time Binding

•The ability to link the past and the future, termed *time travel* or *chronesthesia*, is an important prefrontal function, possibly a distinctly humanly one.

•Time travel enables

- autobiographical memory
- prospective memory
- planning.

Time Binding In Childhood TBI

• School-age children who have sustained a TBI at least two years prior to testing are impaired on event-based and activity-based prospective memory tasks.

• For adolescents with TBI, event-based prospective memory worsens with increased cognitive demands.

• Compared with those with mild TBI, children with severe TBI do not benefit from prospective reminders.

• Adolescents with early damage to the prefrontal cortex are inaccurate planners, like younger, typically developing children.

• Planning deficits occur in children with TBI and performance is correlated with lesion volume of orbitofrontal, dorsolateral, and frontal white matter.

Metacognition In Childhood TBI

• Flexible access to one's own mind occurs through metacognition.

• Children with TBI exhibit problems with

–metacognitive monitoring, being unable to judge the adequacy of ambiguous directions or to detect anomalies in sentences, especially sentences with high memory load

–metacognitive knowledge, being unable to predict the ease with which they will learn specific items or to estimate their memory span accurately.

•Problems in metacognition are especially apparent when TBI occurs early in development and/or includes evidence of contusional damage to the frontal lobes

Social Information Processing In Childhood TBI

• Children with TBI have deficits in social information processing that predict their social and academic function.

• They prefer solutions to social dilemmas and evaluate the outcome of dilemmas in a less developmentally advanced fashion than their peers, although they can define the problem and generate alternative solutions.

• Adolescents with TBI have poorer social information processing than age peers.

Theory of Mind In Childhood TBI

• Theory of mind is the ability to think about mental states (thoughts, beliefs, intentions, desires) and predict what other people need to know and how they will act.

• Childhood TBI is associated with deficits in making pragmatic inferences about the presuppositions, entailments, and implications of mental state verbs, a class of words including *know, remember, forget, think, believe*, and *pretend*, and in producing speech acts, prototypical forms of pragmatic communication that express mutual intentions of a speaker and a listener.

• Children with severe TBI (not those with mild TBI) fail to understand literal statements concerned with first

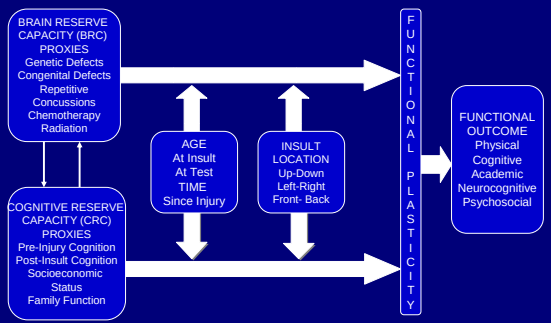
Anterior-Posterior: The Net

• Children with preserved anterior brain regions provide a useful contrast to those with lesions in this area, and allow assessment of variations in BRC along an anterior-to-posterior gradient.

•Children with preserved anterior brain appear to have more preserved anterior brain functions. For example, children with SBM have normal frontal volumes (on voxel-based morphometry), despite volume loss and loss of connectivity in the posterior cortex, and retain normal top-down attention control.

•The implication of these data for BRC is that there are distinct ways in which anterior and posterior brain insults constrain subsequent development.

QUESTIONS?



Discussion: Burden & Reserve

- That children sustain brain insults does not speak to the issue of reserve.
- Both children and adults have a pathological burden as a direct effect of brain insult.
- What does speak to reserve is that functional outcome of childhood brain insult is mediated by BRC and CRC, as evidenced by
  - –accelerated aging in adulthood
  - –greater vulnerability to subsequent brain insult
  - – diminished capacity for age-appropriate development.

Discussion: Brain-Injured Adult vs. Child

- Cognitive development may require more neural resources (BRC and CRC) than the maintenance of cognitive structures that are already developed.
- After brain insult, mature brain must support restitution, reorganization of lost/disrupted functions.
- The child with a CNS insult faces:
  - –normal task of cognitive development (acquisition of new functions, skills, and knowledge)
  - –abnormal task (strategic, adaptive response to insult to recover functions existing at the time of the injury.
- Children with CNS insult exhibit two changes:
  - –an adaptive or maladaptive response to the injury
  - –normal or abnormal development of skills not yet

Discussion: Genetic Syndromes & Reserve

- The cognitive deficits of children with genetic deficits reflect deficient genetic control of the neurotransmitter systems and other neural processes underlying cognition.
- Genetic syndromes and genetically based congenital malformations of the brain are more common in children than in adults.
- Genetic heterogeneity is a proxy for diminished brain reserve in a number of childhood conditions. As these individuals age, the consequences of diminished BRC become increasing evident in the form of accelerated normal or abnormal aging.

Discussion: Genetic Syndromes & Aging

- For many years, genetic anomalies such as those in Down syndrome have been known to reduce BRC brain reserve and accelerate aging.
- What is emerging as a new research area is normal and abnormal aging in childhood brain disorders such as spina bifida meningomyelocele.
- Recent advances in genetics of complex neurobehavioral conditions (dyslexia, ADHD, autism, also raise the possibility of investigations of BRC and CRC in these populations.
- Perhaps forms of genetic anomalies in adults other than the apolipoprotein allele diminish brain reserve and accelerate aging?

Discussion: Adult Survivors Of Childhood Brain Insults

- In recent years, medical advances have created cohorts of survivors of formerly lethal or cognitively devastating childhood brain disorders who are moving from childhood to adulthood and gradually into old age.
- Older individuals who face aging with diminished reserve because of early brain insults have diminished BRC and CRC and so are at high risk for poor outcome (e.g., children with lower IQ scores are more likely than those with higher IQ to develop cognitive decline in mid-life and beyond).

Discussion: Direct Measures Of BRC

- Advances in pediatric neuroimaging now allow direct measures of BRC.
- Measures of fractional anisotropy from DTI measure residual connectivity in the brain, and studies of DTI in relation to various forms of functional plasticity after childhood TBI should provide important new perspectives on BRC in pediatric populations and add to the information base for studying reserve as these individuals reach adulthood.

Discussion: White Matter In Childhood And Aging

- Most studies of reserve have emerged from cortical function in adults.
- New studies of adult aging have suggested that white matter hyperintensities on MRI correlate with cognitive burden in old age.
- White matter lesions are more common in children than in adults, and important evidence about age-based functional plasticity will come from comparisons of similar outcomes following white matter lesions in children and adults.

Discussion: Cortical Chauvinism

- Studies of spatial gradients as a moderator of outcome provide a new perspective on functional plasticity and, by implication, BRC.
- An up-down gradient is supported by evidence of some cortically mediated functional plasticity.
- BUT the timing functions of the cerebellum, the attention orienting functions of the midbrain, and executive and memory functions mediated by the periventricular region exhibit little age-based functional plasticity, and deficits appear similar over the child-to-adult age span.
- The midbrain has little reserve tissue, so orienting deficits follow midbrain lesions over the lifespan.

Discussion: Left-Right Gradient

- Congenital left hemisphere produces deficits in
  - –use of the inflectional morphology system
  - –parsing processes and/or linguistic representations
  - –computational resources for syntactic comprehension.
- A left-right BRC gradient appears to allow for some functional plasticity following early brain disease, but is insufficient to support normal syntactic development after left hemisphere cortical lesions
- Depletion of BRC is implicated to the extent that children with early left hemisphere lesions fail to acquire skills at a normal rate and children with later left hemisphere lesions have syntactic skills arrested at the time of the insult.

Discussion: Anterior-Posterior Gradient

- With respect to an anterior-to-posterior gradient, anterior cortical lesions in children produce deficits in a number of functions associated with the prefrontal lobes.
- These impairments are correlated with the presence of frontal lobe injury.
- Similar lesion-function relations are not observed with posterior lesions, evidencing a front-to-back gradient for a number of functional outcomes.

Discussion: Compensation

- Studies of childhood brain insult can also address issues of compensation, whether reserve involves undamaged brain tissue in a typical substrate or new functionality in an atypical substrate.
- For children with hemispherectomy, the limitation is related to an atypical substrate because cortical mass of one hemisphere has been removed.
- Syntactic comprehension deficits occur for non-canonical word orders only part of the left hemisphere is removed but speech control has shifted to right hemisphere, showing that residual left hemisphere tissue does not support normal syntax with language shift to right hemisphere.

Discussion: Strategies

- Supporting the idea of atypical cognitive strategies, individuals with either congenital or acquired lesions require additional time to make accurate syntactic discriminations
- Those with left hemispherectomy use a simpler, canonical functional argument structure.
- Data suggest recruitment of distinct, atypical top-down networks.

Discussion: Gradients Of Reserve

- The notion of a gradient of reserve, rather than all-or-none thresholds, deserves further study as well.
- Although there may be thresholds of damage which when exceeded preclude plasticity of function, the concept that reserve varies in degree has considerable support.
- Interpretative and methodological issues are also important (e.g.,impaired developmental progress after brain insult may reflect lack of environmental supports or motivational changes, as well as brain-based mechanisms implied by brain reserve; measures of reserve must be distinguished from outcomes they purport to explain

Discussion: Future Directions

- Further studies are needed to advance knowledge of the vulnerabilities of children with congenital or acquired brain disorders to further brain insult or to difficulties in making developmental transitions.
- Little research has been conducted in this area, and children with pre-existing conditions are often excluded from studies of long-term outcomes of brain insult.
- Additional research is also required to examine brain regions that have greater reserve capacities and the neural basis of reserve, perhaps using cortical activation and functional imaging methods.

The Wrap Up

- Issues of reserve – both BRC and CRC – concern the brain's capacity for adaptive changes, optimal or suboptimal, any time in development.
- While reserve questions about BRC, CRC and compensation have not generally been addressed with children, the new research discussed here suggests that comparative studies of reserve in adults and in children might be mutually informative.

Grant Support

SPINA BIFIDA

US National Institutes of Health
Program Project Grants
(1998-2010)
P01 HD35946
P01 HD35946-06

CHILDHOOD TBI

- Ontario Mental Health Foundation
- The Physicians' Services Research Institute Foundation
- National Institute of Neurological Diseases and Stroke Grant 2R011NS 21889-16

Colleagues

- **HOUSTON**
  - *Amy Boudousquie*
  - *Michael Brandt*
  - *Kim Copeland*
  - *Linda Ewing-Cobbs*
  - *Jack Fletcher*
  - *David Francis*
  - *Jon Frederick*
  - *Julia Hannay*
  - *Harvey Levin*
  - *Jefrey Max*
  - *Malcolm Mazur*
  - *Hope Northrup*
  - *Andrew Papanicolaou*
  - *Akis Simos*
  - *Irene Townsend*
- **TORONTO**
  - *Alba Agostino*
  - *Marcia Barnes*
  - *Susan Blaser*
  - *Raymond Buncic*
  - *James Drake*
  - *Kim Edelstein*
  - *Ross Hetherington*
  - *Robin Humphreys*
  - *Susan Inwood*
  - *Jennifer Janes*
  - *Derryn Jewell*
  - *Daune MacGregor*
  - *Andrea Martin*
  - *Karen Purvis*
  - *Joanne Robitaille*
  - *Caroline Roncadin*
  - *Michael Salman*
  - *Steve Scherer*
  - *Margaret Wilkinson*
  - *Ellen Winner*