

Movement



Motor Function: Cerebellar Signs

Dysmetria

- Dysdiadochokinesis (Jewell et al., 2010)
- Reaching (Norrlin et al., 2004)
- Motor reaction time (Dennis et al., 2009)
- Motor speed (Zeiner et al., 1985; Ziviani et al., 1990)
- Manual rotation time (Wiedenbauer & Jansen-Osmann, 2007)
- Speech fluency (Fletcher et al., 1995; Huber-Okrainec et al., 2002; Dennis et al., 1987)

•Ataxia

- Truncal ataxia
- Limb ataxia (Hetherington & Dennis, 1999; Jewell et al., 2010; Lomax-Bream et al., 2007)
- Motor rebound abnormality (Jewell et al., 2010)

Dysarthria

- Ataxic dysarthria (Huber-Okrainec et al., 2002)



Motor Function: Performance vs. Learning

Eye-hand control

↓ Eye-hand control, dexterity, bimanual coordination (Fletcher et al., 1995; Hetherington & Dennis, 1999; Lomax-Bream et al., 2007; Wills, 1993)

↓ Drawing & handwriting (Edelstein et al., 2004; Pearson et al., 1988; Sandler et al., 1993; Soare & Raimondi, 1977; Ziviani et al., 1990)

Motor learning and adaptation

↑ Adapting saccades to backward target displacement (Salman et al., 2006)

↑ Adapting to prism-distorted visual input (Colvin et al., 2003)

↑ Adapting drawing to mirror image (Edelstein et al., 2004)

↑ Adapting ballistic arm movement to changes in relation between movement and vision (Dennis et al., 2006)

↑ Learning manual rotation task (Wiedenbauer & Jansen-Osmann, 2007)



Timing in Spina Bifida

Sensory motor (subsecond) timing

↓ Brief auditory durations (~400ms) (Dennis et al., 2004)

Rhythm

Discrimination

↓ Auditory rhythms (Dennis et al., 2009a; Hopyan-Misakyan et al., 2009; Snow et al., 1994)

Production

↑ Synchronizing tapping to external beat (Dennis et al., 2004)

↓ Entrained tapping to internally entrained beat (Dennis et al., 2004)



Cognition



GENERAL DOMAIN

Entrainment **TIMING** Synchronicity

Exogenous **ATTENTION** Endogenous

Predictive **MOVEMENT** Adaptive

SPECIFIC DOMAIN

Coordinate **PERCEPTION** Categorical

Constructed **LANGUAGE** Retrieved

Text **LITERACY** Word

Computation **NUMERACY** Numeration



Dennis, Barnes: *Developmental Disabilities Research Reviews*, 2010)

Healthier Children. A Better World.™

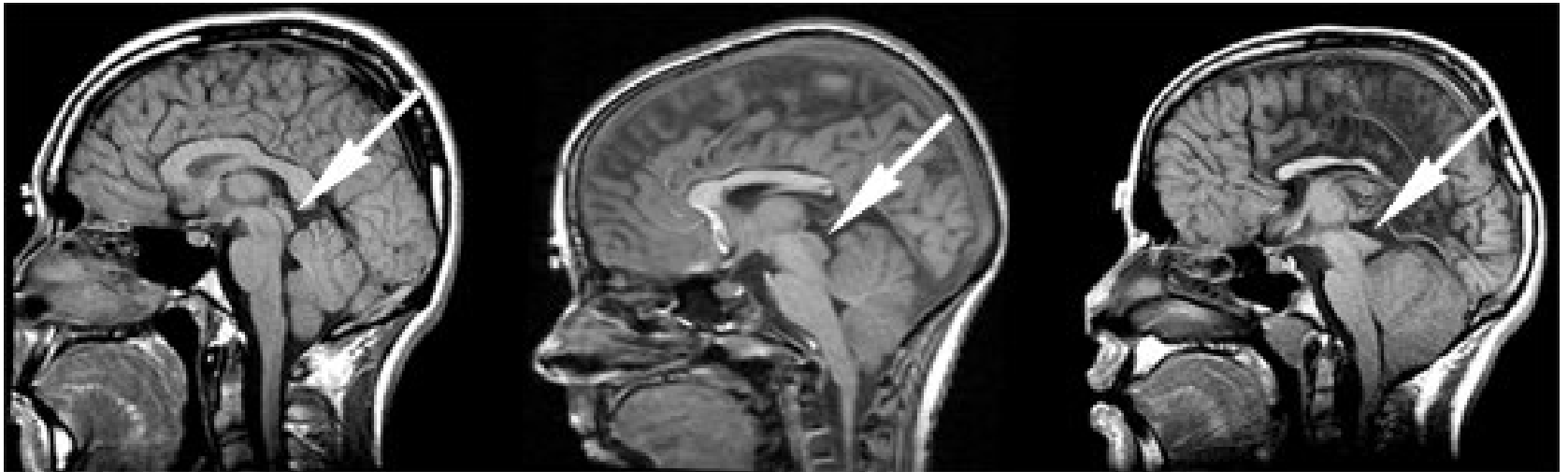


Tectal Beaking And Midbrain

- The caudal expansion of the cerebellar vermis blocks the outlets of IV ventricle and may even cause death.
- The rostral expansion of the cerebellar vermis comes at a cost to the midbrain, producing a signature midbrain tectal beaking.

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

Dennis et al., Neuropsychologia, 2005)

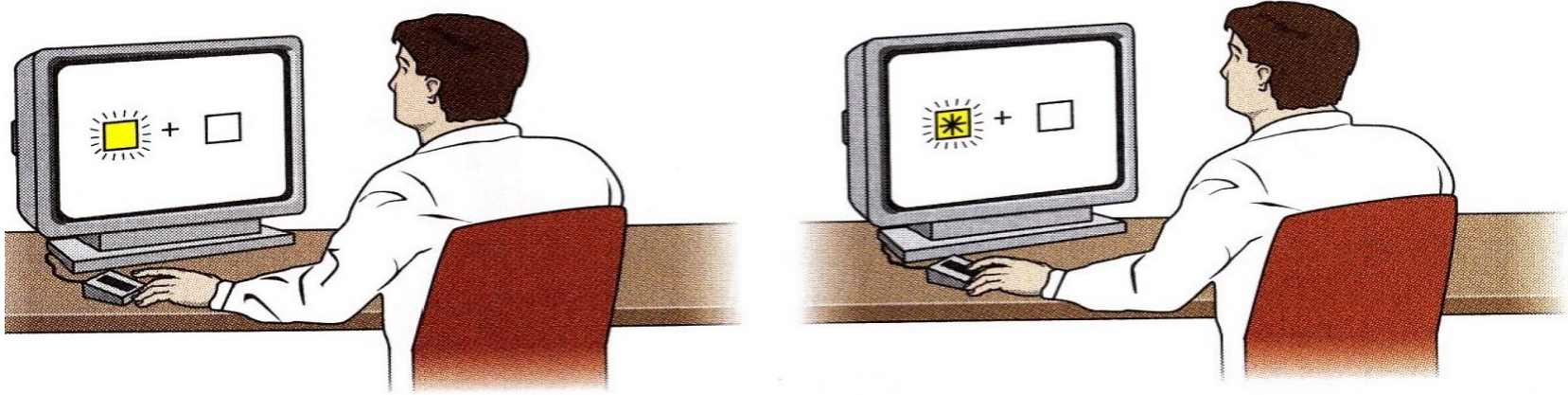


Inhibition Of Return

- Midbrain controls attention shifting, 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.
-



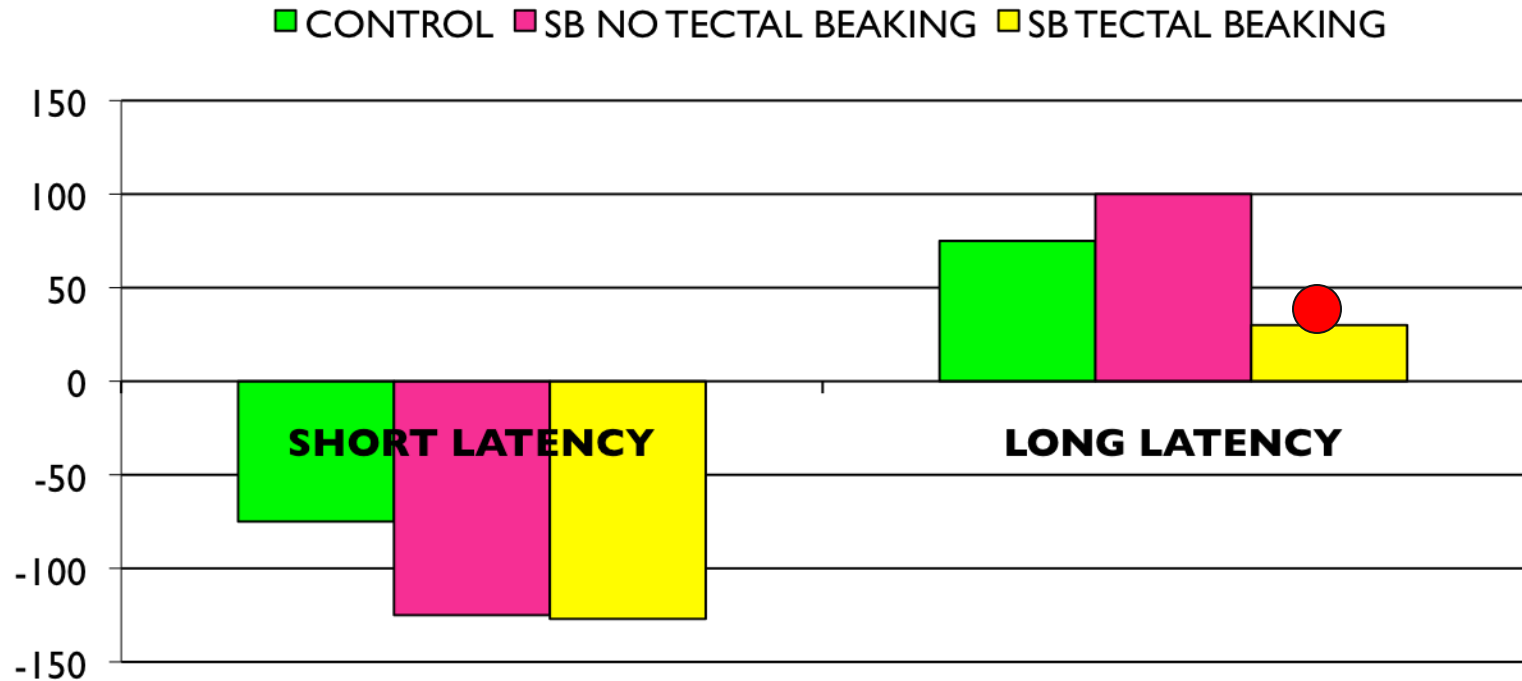
Covert Orienting Paradigm



- 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.



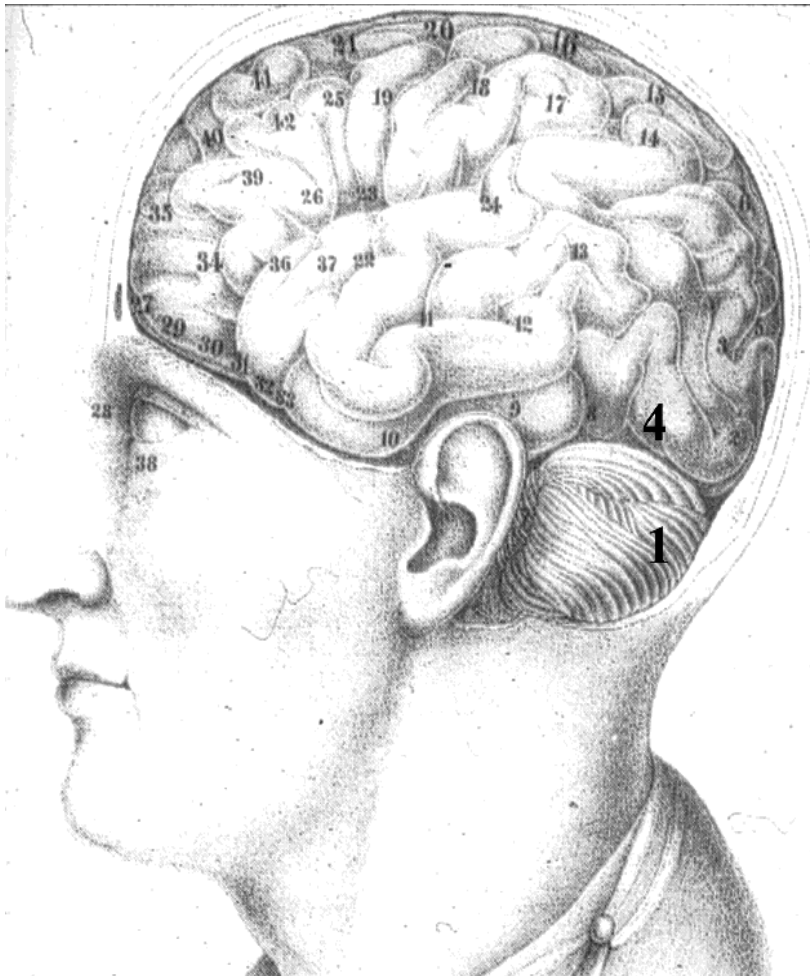
(Dennis, Edelstein, Copeland, Frederick, Francis, Hetherington, Blaser, Kramer, Drake, Brandt, Fletcher: *Neuropsychology*, 2005)

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Digression: The Cerebellum And Affect In History



Phrenology Master Plan (circa 1848)



Unusually, shows specific brain gyri locations for traits.

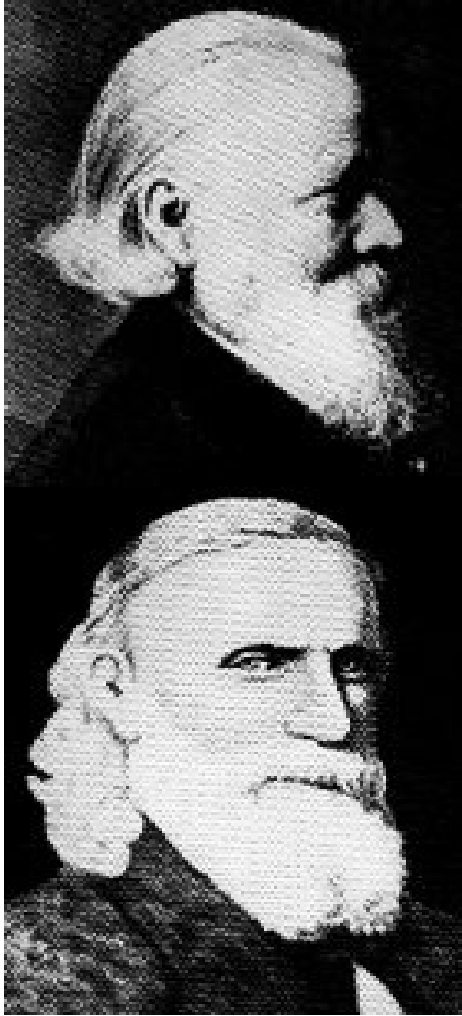
1. Sex

4. Monogamy

Prepared for Fowler's lectures (Countway Library Phrenology collection);
Reproduced in Macklis & Macklis, *Neurology*, 1992.

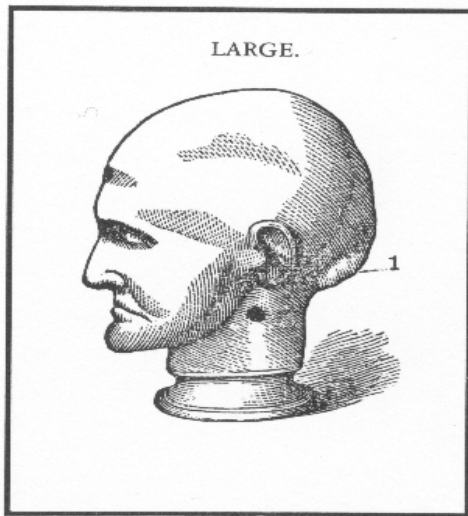


Orson (1809-98) & Lorenzo (1811-96) Fowler

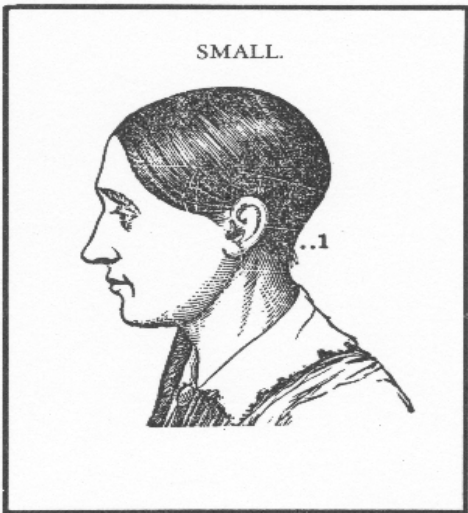


- Phrenology (English, Scottish version) spread to America in the 1830s and Fowlers were foremost American phrenologists
- Phrenological cabinet, museum and office just off Broadway in NYC
 - How-to, self-help books
 - Skull readings \$1-3
 - Public sex education
- Capitalized on expanding print industry
- Mail order business for phrenology and physical hygiene, memory enhancement, parenting, marital guides
- Pop versions of phrenology books (including cranioscopic instruments)





NO. 43. - BUST OF AARON BURR.



NO. 44. - MISS MODESTY.

Fowlers' Phrenology: A Practical Guide to Your Head

- Case Studies With Illustrative Busts and Sketches
 - politician with well hung cerebellum (Aaron Burr, upper left) is lustful, war mongering, shoots colleagues (see also Dick Cheney)
 - woman (generic, lower left) with small cerebellum ? Asexual, ? Peaceable, ? Shoots the breeze.



Affect



Affect In Spina Bifida: Clinical

- Children with SBM are warm and friendly, unlike autism spectrum disorders.
- They actively seek out social contacts and work hard to maintain them.
- BUT
- Their language (“The Cocktail Party Syndrome”) is often full of stereotyped social phrases that may serve the social function of maintaining connectedness when their language output cannot keep pace.
- The impression in the listener is that dialogue is off-target, and that conversational partners are at cross-purposes.
- While children with SBM maintain social contacts, they have difficulty terminating them, even when given socially relevant cues (“It’s been good talking to you but you need to go now.”)
- Is being excessively friendly a form of social impairment?
- How can we explain the combination of warm and friendly, on the one hand, and conversationally inappropriate, on the other?



Affect In Spina Bifida: Neurolinguistic

- *Pragmatics* is concerned with how speakers use language for communication.
- Two classes of pragmatic principles:
 - **Interpersonal rhetoric** includes principles like cooperation, turn taking, politeness, and irony, which are based on social conventions.
 - **Textual rhetoric** is oriented towards text production and interpretation, and involves issues like:
 - processability (texts should be easy to process in real time)
 - clarity (the form of a text and its meaning should be transparent and unambiguous)
 - economy (a text should be syntactically economical) and
 - expressivity (a text should be well elaborated for meaning, including inferential meaning).
- Interpersonal rhetoric seems to be largely preserved in children with SBM, who are polite and friendly, sociable, cooperative, and interested in talking.
- In conversations, they initiate as many or more turns and exchanges than controls, and take turns in narratives (Murdoch et al., 1990).
- They have a normal vocabulary to express mental states (Dennis et al, 1994).
- In contrast, children with SBM have impaired textual rhetoric with respect to ease of processing, clarity, economy, and expressivity.



Affect In Spina Bifida: Intact Or Impaired?

- The language of children with SBM is disordered with respect to pragmatic language processing
- BUT
- What does this mean for affective communication?
- We have explored this question using facial emotion as a tool to investigate two forms of affective communication in children with SBM.



Two Forms of Emotional Communication

- Facial expressions serve two types of communication (Buck, 1994).
- Emotional Communication
 - Different facial expressions convey emotional states such as happiness, sadness, anger, fear, and disgust through spontaneous facial expressions that show **what an individual feels**.
- Emotive Communication
 - Facial expressions also signal communicative intent, the conscious, strategic modification of affective signals to **show what an individual chooses to display**.
 - Emotive communication of facial expression is governed by social display rules that regulate which facial expression can be expressed, who can express them, and when they may be expressed.
 - Display rules involve **cognitive control** processes for conscious modulation of felt emotion in response to social context.



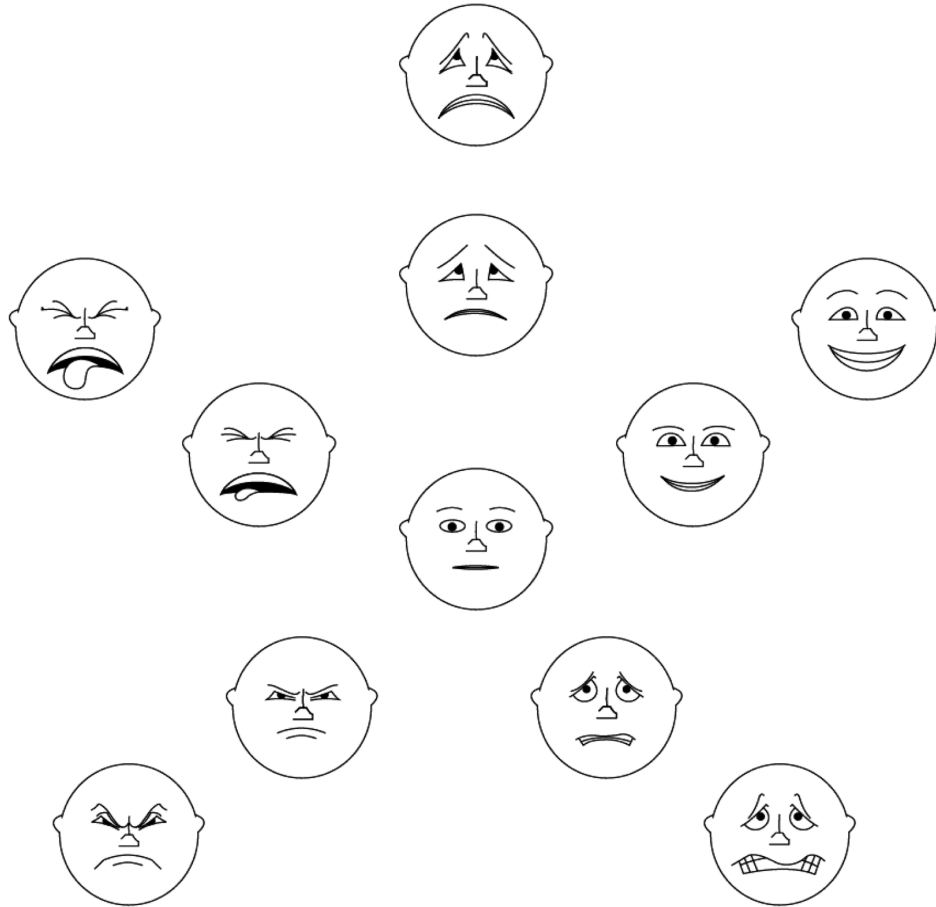
Emotional vs. Emotive Paradigm

- Pretests
 - Face emotion identification
 - Verbal emotion identification
- “Molly woke up with a tummy ache. Molly’s mom won’t let her go out to play if she know Molly has a tummy ache, so Molly hides how she feels.”
- FEEL INSIDE QUESTION: How did Molly feel inside?
- LOOK ON FACE QUESTION: How did Molly look on her face?”
- CONCEALMENT QUESTION: WHY did Molly want to hide how she felt?

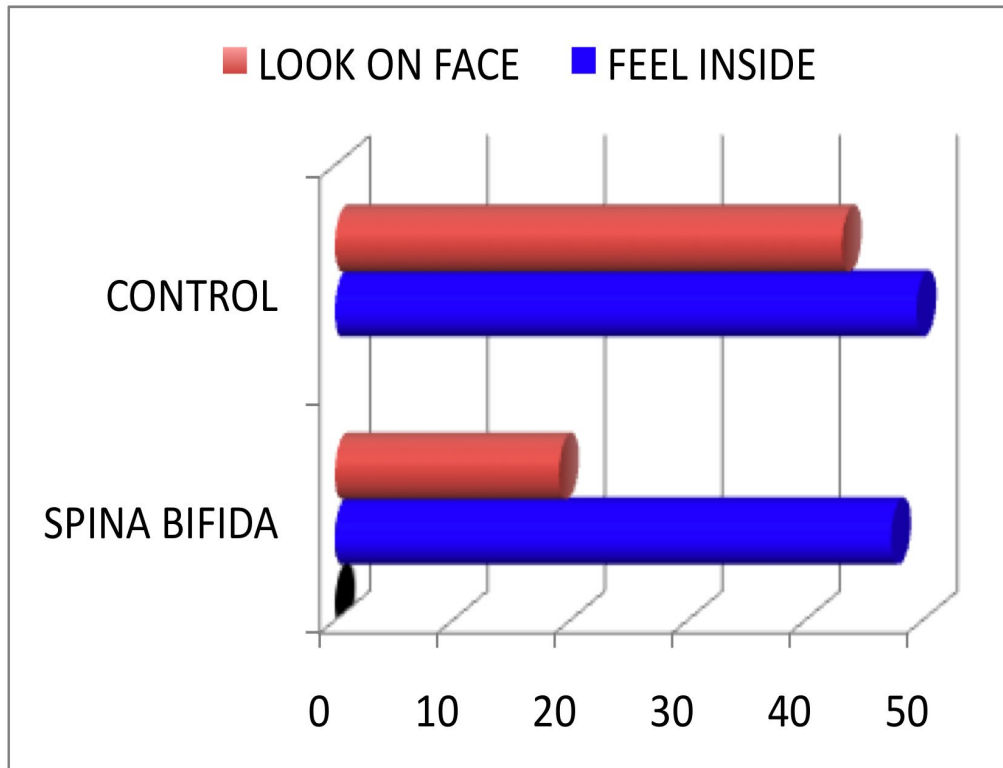


Face Display

(Happy, Sad, Angry, Scared, Yucky)



Emotional vs. Emotive Communication



- Significant interaction ($p < .01$) between group (SPINA BIFIDA, CONTROL) and QUESTION (LOOK ON FACE, FEEL INSIDE).
- Children with SB appear to have immature cognitive control: few dissimulated, only some neutralized, most minimized or changed inappropriately.
- Children with spina bifida have difficulty with the cognitive control of emotions, even those they can identify.



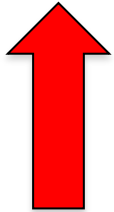
(Koval V: Master of Arts thesis, University of Toronto, 2006)

Cerebellar Structure-Function Correlations In Spina Bifida



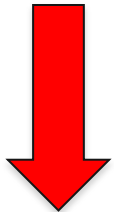
Rhythm Synchronization vs. Rhythm Entrainment in Spina Bifida

Synchronization



Rhythmic tapping in time to external beat

Entrainment

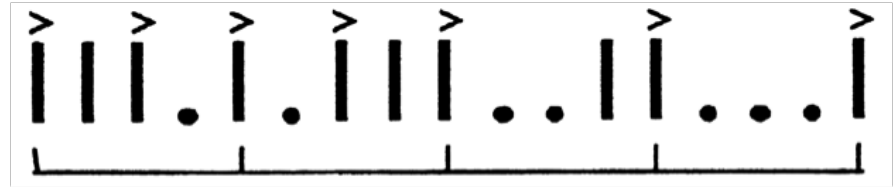


Rhythmic tapping to internally entrained beat



We Got Rhythm

- Rhythm emerges from temporal information creating perception of strong (accented) or weak (unaccented) beats at regular intervals.



- **Strong-meter rhythms**

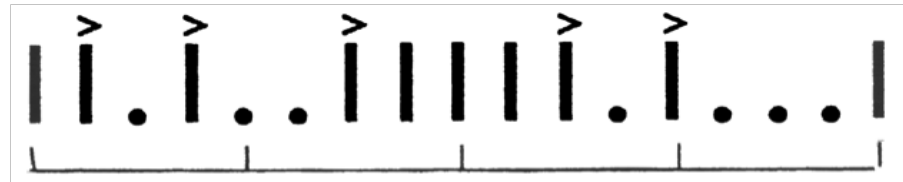
- “On the beat.”

- Strong accents coincide with strong positions in metric structure.

- Encoded as structured forms. Entrained as smooth motor act.

- **Weak-meter rhythms**

- “Off the beat” or syncopated.



- Strong accents coincide with weak positions in metric structure.

- Encoded as a series of independent units. Effortful processing.

- **The strong-meter advantage**

- Strong-meter rhythms are easier than weak-meter rhythms to discriminate, remember, and reproduce.

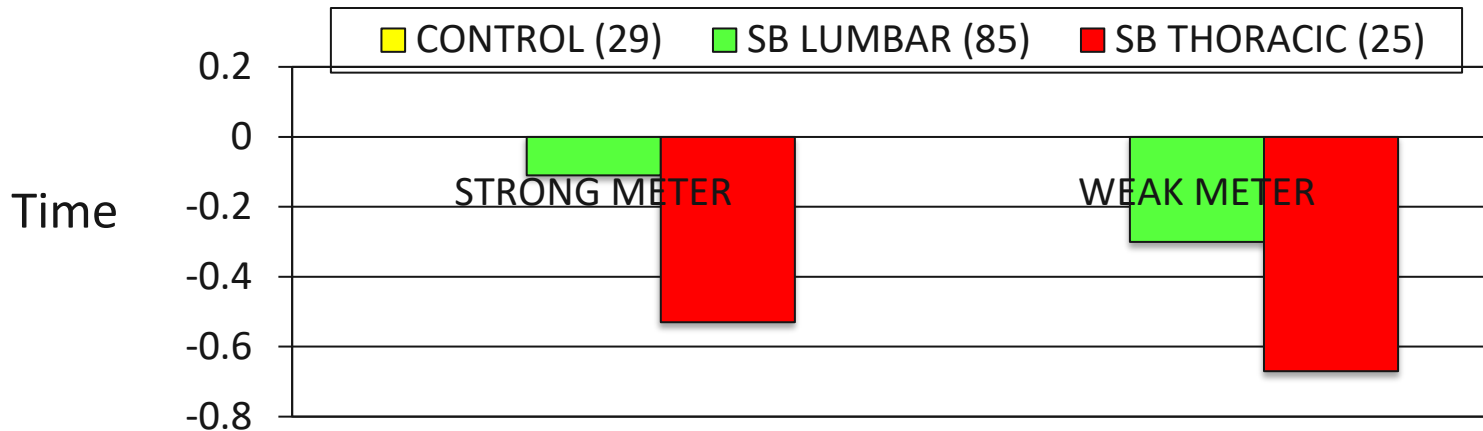
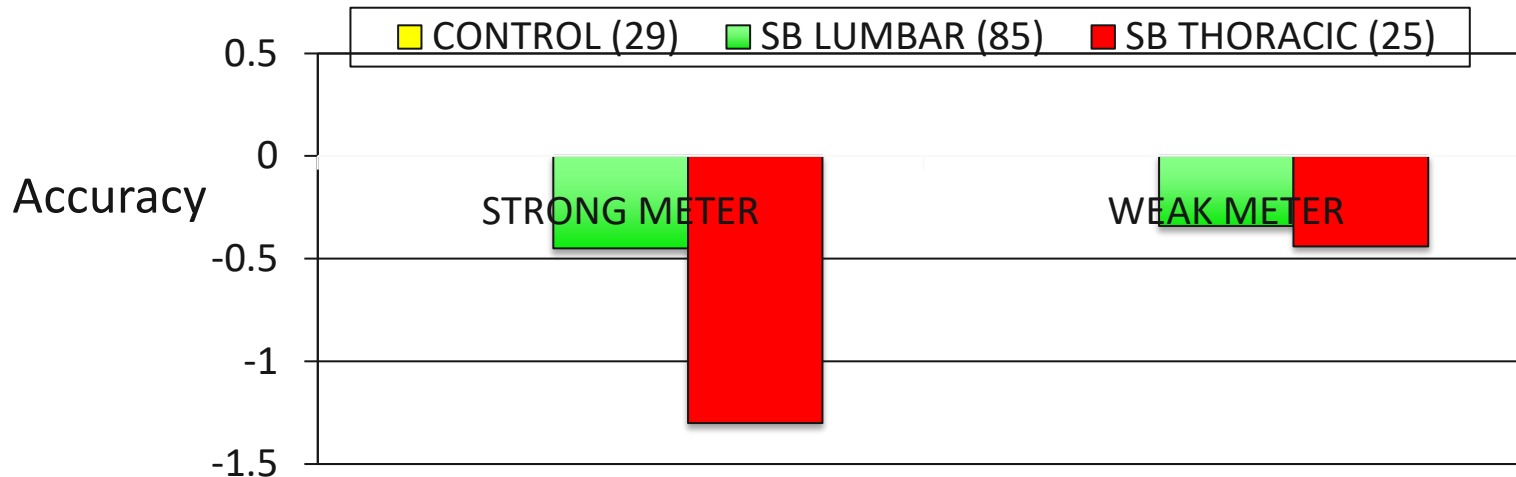


Rhythm In Spina Bifida. Results

- Accuracy (percent correct) and response times (in msec) for conditions were z-scaled based on the control group's performance (such that the mean performance in the control group received a score of 0, and higher scores denoted lower response time or higher accuracy). For strong and weak meter rhythms, the accuracy and response time z-scores were averaged, resulting in a single score, which was used as the dependent measure in analyses to follow.
- In the 3-group analysis, there was a significant group effect, and:
 - For strong meter rhythms, SBM participants with thoracic lesions were poorer than controls ($p < .0001$) or SBM with lumbar lesions ($p = .0014$).
 - For weak meter rhythms, the two SBM groups did not differ from each other, but each performed significantly below controls (upper $p = .0084$; lower $p = .0364$).
 - All children with spina bifida slower than controls even when accurate.



Rhythm In Spina Bifida



Metric Structure And The Cerebellum

- Strong-meter and weak-meter rhythms produce different cerebellar activation on fMRI.
- Strong-meter rhythm fMRI activity in premotor area and cerebellar anterior lobe (green).
- Weak-meter rhythm activity in prefrontal cortex and cerebellar posterior lobe (blue superior posterior, khaki inferior posterior).

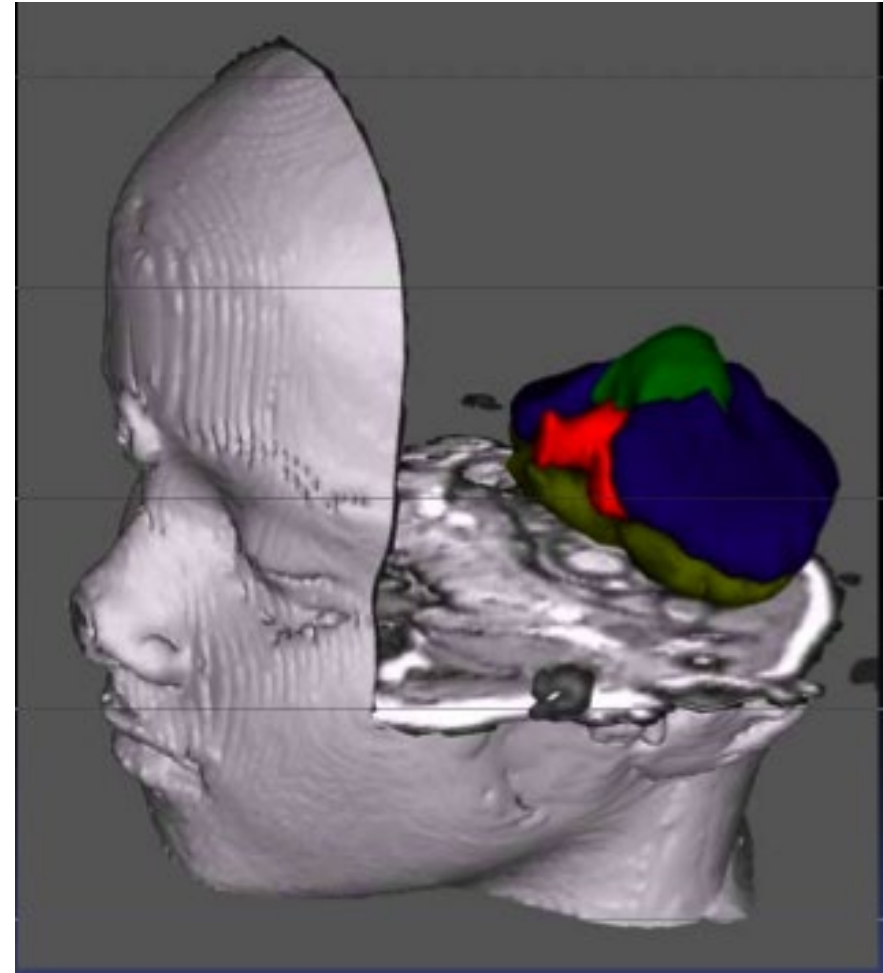


Figure courtesy J.Juranek



Dysmorphisms And Rhythm

- Individuals with SBM are inaccurate and slow to discriminate rhythms.
- Those with LUMBAR (LOWER) spinal lesions did better on STRONG METER rhythms and were able to capitalize on the predictability and entrainment strong meters allow. This group has better motor function, less brain dysmorphology in posterior fossa.
- Those with THORACIC (UPPER) spinal lesions [erfprmed poorly on STRONG METER and WEAK METER rhythms and were unable to capitalize on the predictability and entrainment strong meters allow. Thisgroup has poorer motor function, more brain dysmorphology in posterior fossa.
- Strong positive correlation of the corpus medullare with weak rhythms in the THORACIC (UPPER) group ($r=.71$, $p=.0209$), but correlations are exploratory.
- Compared to controls, spina bifida groups move dysrhythmically, are slow to entrain rhythms, and perceive rhythms poorly, so ?defective central rhythm generator related to predictive timing function of cerebellum.



Clinical Implications



What Kind of Disorder Is SBM?

- SBM is a disorder of defective feedforward models that create impairments in movement, space, time, and number, as well as cognitive-academic functions they support (reading, math).
- Associative, feedback operations are intact.
 - Learning
 - Semantic activation
 - Categorical perception
- Assembled, feedforward operations are impaired.
 - Inferencing
 - Entrainment
 - Coordinate perception.



What Can We Explain?

- Deficits in some functions are related to the cerebellum.
 - Timing
 - Movement regulation
 - Ataxic dysarthria
 - Rhythm
- Whether and how other functions are related to the cerebellum is not clear.
 - Cocktail Party Speech
 - Emotive communication.



Associative vs. Assembled Processing

- *Associative Processing* is based on the formation of associations, enhancement, engagement, and categorization. It includes adaptive changes in response to stimulus repetition, as well as the activation and categorization of stimulus information.
- *In individuals with SBM, strengths in associative processing facilitate temporal synchronicity, endogenous attention, adaptive movement, categorical perception, retrieved language, word-level literacy, and numeration and calculation procedures.*
- *Assembled Processing* is based on on-line iterative cycles of activation, disengagement, and integration; it includes the creation of internal feed-forward models to guide performance over time.
- *Weaknesses in assembled processing disrupt temporal entrainment, exogenous attention, predictive movement, coordinate perception, constructed language, text-level literacy, and most types of mathematical problem solving.*



Clinical Implications: No Diagnosis by Domain, or Modality

- Individuals with SBM have functional assets in timing, attention, movement, perception, language, literacy, and numeracy, as well as functional deficits in the same domains. It is misleading to classify or diagnose by domain (“Perceptual Deficit,” “Motor Deficit”) because each domain has assets as well as deficits.
- Individuals with SBM have functional assets in audition and vision, as well as functional deficits in the same sensory modalities, so assets and deficits cannot be classified according to sensory modality (“Visual Processing Deficit”); the fact that the auditory modality has core deficits (in timing, above) and the visual modality has both assets and deficits in perception means that the cognitive phenotype of SBM cannot be explained by a simple dichotomy between intact auditory and deficient visual perception.



Clinical Implications: No Simple Label

- No generic problem in “Perceptual Integration.” because they perceive wholes and gestalts.
- No generic problem in “Temporal Sequencing Deficit” because children with SBM have good ordinality (sense of what comes first, second, etc) but poor temporal motor regulation, which we believe is one cause of their functional difficulty with movement control, drawing, and handwriting.



Clinical Implications: Non-Verbal Learning Disability

- Individuals with SBM have functional assets and deficits involving verbal and non-verbal content, so no “Non-Verbal Learning Disability”.
- If we actually compare SBM and Non-Verbal Learning Disability on some key domains, the profile of function is quite different.
 - categorical perception specifies discrete spatial relations of visual primitives for categories (objects), feature groupings (faces), or verbal locatives (e.g., above, below, left, right)
 - coordinate perception specifies precise spatial relations of visual primitives by coordinate metrics (e.g., “the line and the dot are 2 cm apart”).
- In a virtual reality task, children with SBM can navigate by landmarks (intact categorical perception) but not by spatial coordinates (Wiedenbauer & Jansen-Osmann, 2006) (impaired coordinate perception).
- Children assessed as having a Non-Verbal Learning Disability are impaired in both categorical and coordinate perception (Mammarella et al., 2009).



Clinical Implications: Remediation

- Better delineation of assets and deficits emerging from experimental studies largely unexploited in motor, cognitive, and academic remediation programs.
- That children with SBM have relatively good spatial orientation when they use landmarks (compared to coordinates) provides an avenue for improving extrapersonal orientation and ability to navigate in environment and community.
- Clinical motor deficits are obvious in individuals with SBM, but extent of the relatively well developed ability for motor adaptation and learning in eye, arm, and hand in SBM has been underestimated and has not formed an explicit component of programs to improve coordination and handwriting.
- Cross-domain training is an underexplored area of rehabilitation in individuals with SBM. In children with SBM, training in physical rotations improves mental rotation skill.



Clinical Implications: Tailoring Treatments

- In children with SBM, there is some preliminary evidence suggesting that:
 - tailoring interventions to assets and deficits may be effective (e.g., for math)
 - basing treatments on an incorrect and incomplete understanding of the core deficit may be ineffective (e.g., for attention).



Clinical Implications: Treating Math Deficits

- Executive function consists of *representations*, structured event complexes (Grafman, 2002) that are the basis of skills like metacognition and planning, and *capacity-limited processing resources* like working memory (Dennis, 2006).
- Children with SBM have executive dysfunction their executive representations are more intact than their executive processing resources
- Children with SBM exhibit metacognitive control over their academic skills (English et al., in press). Like typically developing children, they take more time to read when the situation requires it (e.g., for study rather than for fun) and they are accurate judges of their own understanding. They have poor working memory.
- Representations like metacognition may be sufficiently functional to scaffold forms of cognitive-academic rehabilitation.
- In a case series of adolescents with SBM, Coughlin and Montague (in press) showed that a math word problem intervention that involved **learning and implementing executive strategies** led to improved problem solving both post-intervention and at long-term follow-up, as well as improving self-efficacy in math.



Clinical Implications: Treating Attention Deficits

- Approximately one-quarter of children with SBM have reported difficulties in attention although they are not hyperactive.
- Specifying the attention phenotype of SBM with experimental tasks has helped to understand how it overlaps with, and diverges from, the cognitive-behavioral phenotypes in other conditions.
 - For example, individuals with SBM have difficulties with midbrain attention orienting tasks, such as inhibition of return, that are performed well by those with ADHD.
- A better understanding of the attention phenotype in SBM helps make sense of some of the treatment outcome data.
- Children with SBM respond more poorly than children with ADHD to stimulant medication treatment.
- SO
- Standard medication treatments for ADHD may be suboptimal for individuals with SBM, whose attention profile does not include the response control deficits that respond well to stimulant medication.

(Dennis, Sinopoli, Schachar, Fletcher, JINS, 2009)



End of Part 1



Acquired Posterior Fossa Tumors: Cerebellar Medulloblastomas and Astrocytomas



Childhood Cerebellar Tumors

Two most common childhood cerebellar tumors are astrocytomas and medulloblastomas.

Cerebellar Astrocytomas are pathologically benign and are treated with neurosurgical resection with no adjuvant therapy.

Cerebellar Medulloblastomas are malignant tumors requiring surgical resection and adjuvant therapy, including chemotherapy and craniospinal radiation or high dose chemotherapy with autologous stem cell rescue/bone marrow transplant in children younger than three years old.



Childhood Cerebellar Tumors: Treatment

Table 11.2 Treatment-related injury

Treatment	Nature of injury
Surgery	Removal, section, or traction of nerve tissue
Radiation	Damage to vascular endothelium, demyelination. Effects are progressive, dose-related, and related to fields of treatment
Chemotherapy	
IV	Limited evidence of functional toxicity
RT + IV	Cerebral calcification, vascular damage, demyelination, multifocal white matter
RT + IT ± IV	Further enhanced neurotoxicity

IT, intrathecal; IV, intravenous; RT, radiotherapy.

- In survivors of childhood brain tumors, craniospinal radiation is consistently associated with significantly lower cognitive and neurobehavioral functioning.
- Chemotherapy, especially agents like methotrexate, have additive effect on toxicity and morbidity.
- Treatment effects interact with age, gender, and time since treatment.

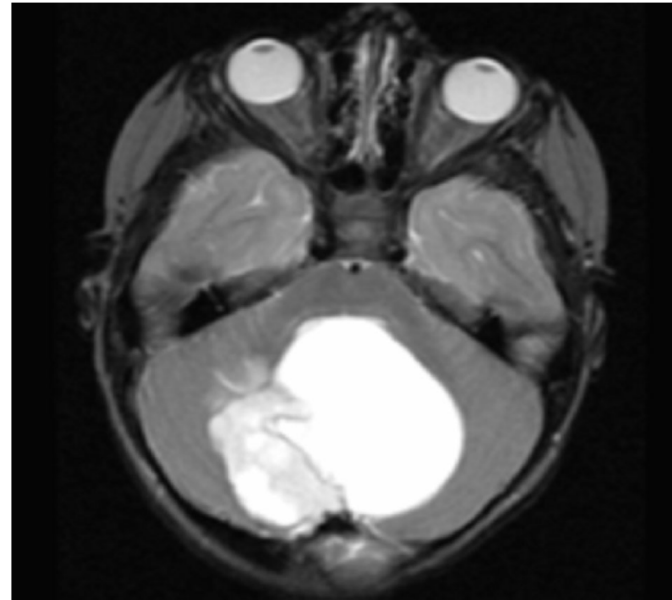


(Dennis, Spiegler, Riva, MacGregor: In: *Brain And Spinal Tumors Of Childhood*, 2004.)

Childhood Cerebellar Tumors



MEDULLOBLASTOMA



ASTROCYTOMA

(Pre-surgical MRI axial images)

Note. As is typical, both tumors have a midline cerebellar vermis location.



Movement



Cerebellar Signs: Acquired cerebellar lesions

- Children with cerebellar tumors exhibit:
 - Dysmetria
 - Ataxia
 - Dysarthria
- These deficits persist before and after treatment.



Ataxic Dysarthria

- Motor speech deficits associated with cerebellar lesions, termed *ataxic dysarthria*, are characterized by:
 - motor slowing
 - imprecise articulation
 - altered prosody of speech
 - monotonous vocal pitch, monoloudness, and harsh voice quality.
- Cerebellar lesions also influence the fluency of speech production, resulting in repetition of syllables and individual phonemes as well as prolonged intervals between words and syllables.



Ataxic Dysarthria in Cerebellar

Tumors

- Video-taped speech samples from cerebellar tumor survivors (mean age 13) and controls were analyzed by two speech pathologists for ataxic dysarthria, dysfluency, and speech rate.
 - Medulloblastoma (n=25; 6 children and 19 adults)
 - Astrocytomas (N=29, 15 children and 14 adults)
 - Controls (n=40; 20 children and 20 adults).
- Medulloblastoma survivors had more ataxic dysarthria than either astrocytoma survivors or controls, who did not differ.
- Both tumor groups were more dysfluent than controls, and did not differ.
- Neither tumor group improved speech rate from childhood to adulthood.
- Dysfluent and slow speech occur in cerebellar tumor survivors, regardless of tumor type and whether radiated or not.
- Childhood cerebellar tumors slow speech rate development.



(Huber-Okraïneç, Dennis, Bradley, Spiegler : Neuro-Oncology, 2001)

Mutism With Subsequent Dysarthria (MSD)

- A severe motor speech complication following childhood cerebellar tumor resection is a transient period of complete loss of motor speech production, commonly referred to as “transient cerebellar mutism.”
- Because mutism progresses into dysarthria, the condition often called “mutism with subsequent dysarthria” (MSD).
- MSD occurs in approximately 7.5% of patients and is more prevalent in childhood than adulthood.
- Following surgical resection, a postoperative period of normal well-preserved speech production lasts from 24 hr to 6 days before mutism ensues and lasts for days to up to 4 months.



MSD: Two Unresolved Issues

- Do children with postoperative transient cerebellar mutism after cerebellar tumor resection show very long-term motor speech disorders?
- Are long-term motor speech disorders in these children greater than those in children with cerebellar tumors without transient cerebellar mutism?
- Using a triplet match methodology, studied motor speech in three groups:
 - Childhood cerebellar tumors who had developed postoperative TCM
 - Childhood cerebellar tumors who had not developed postoperative TCM
 - Typically developing age peers.
- Hypothesized
 - long-term survivors of childhood cerebellar tumors followed by transient cerebellar mutism would show chronic motor speech deficits that persisted as a milder form of ataxic dysarthria.
 - survivors with a history of transient cerebellar mutism would have more severe motor speech deficits than those who had not developed the syndrome.



(Huber, Bradley, Spiegler, Dennis: Child's Nervous System, 2006)

MSD: Long-Lasting If Not Permanent

- Compared to either controls or cerebellar tumor survivors with no transient cerebellar mutism, those survivors with a history of transient cerebellar mutism had:
 - significantly more ataxic dysarthric speech
 - slower speech
 - more speech dysfluencies.
- Motor speech disorders in the form of ataxic dysarthria are a chronic if not permanent sequel of transient cerebellar mutism.



(Huber, Bradley, Spiegler, Dennis: Child's Nervous System, 2006)

Adult Survivors of Childhood Cerebellar Tumours Have Subsecond Timing Deficits

- Participants

- 20 medulloblastomas
- 20 astrocytomas
- 20 controls

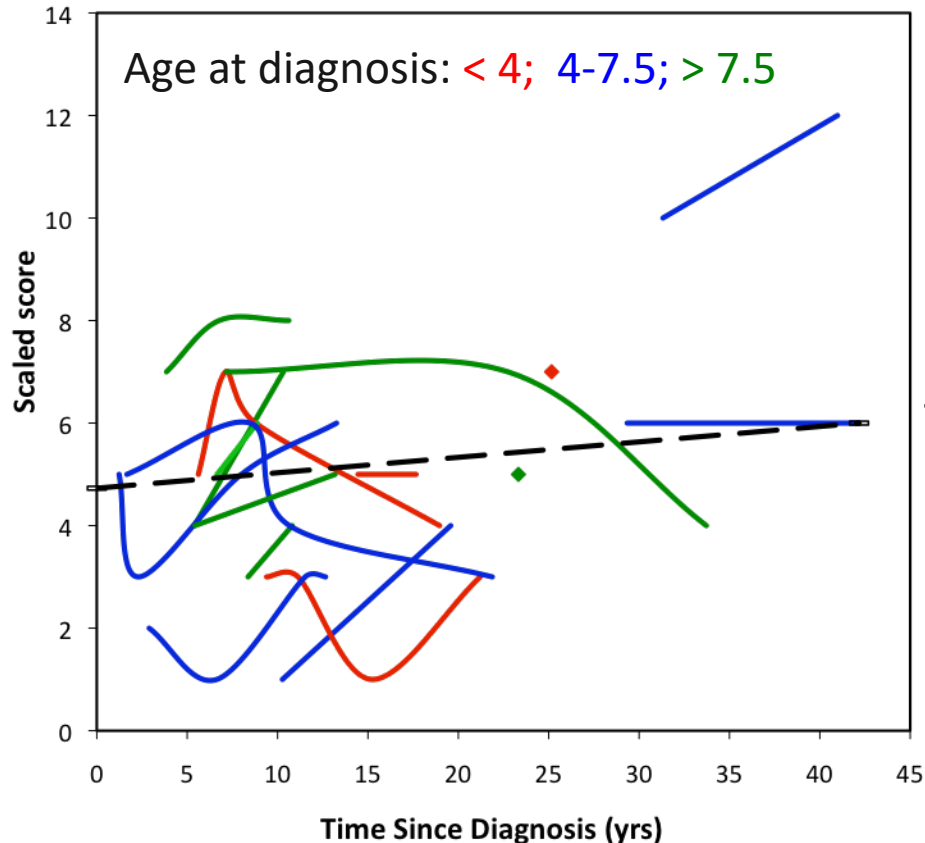
- Subsecond (sensory-motor) timing deficits

- Impaired thresholds for perception of duration (around 400 ms)
- Normal thresholds for perception of frequency (around 3000Hz)
- Preserved ability to estimate longer durations (30 min)



(Hetherington, Dennis, Spiegler: *J Int Neuropsychol Soc*, 2000)

Speeded Motor Control Does Not Improve Up To 40 Yr After Diagnosis



- Long term survivors of childhood medulloblastoma (N=17).
- Solid (colored) lines represent individual cases.
- Dotted black line is the trend line from the growth curve model.
- No change over time in survivors many years since diagnosis.
- [Little data from the initial 5 years after diagnosis, can't model the initial decline).

(Edelstein, Spiegler, et al: manuscript in preparation; INS presentation 2009)



Cognition



Cognitive Functions & Cerebellar Tumors

- Many cognitive functions are impaired in child and adult survivors of childhood cerebellar tumors
 - Intelligence
 - Language
 - Visual perception
 - Executive planning, metacognition, prospective time estimation)
 - Executive resources (working memory, inhibitory control)
- Problems Interpreting Deficits
 - Specificity vis-à-vis cerebellum?
 - Primary vs. secondary deficit?
 - Cerebellar function vs. cerebro-cerebellar circuit?



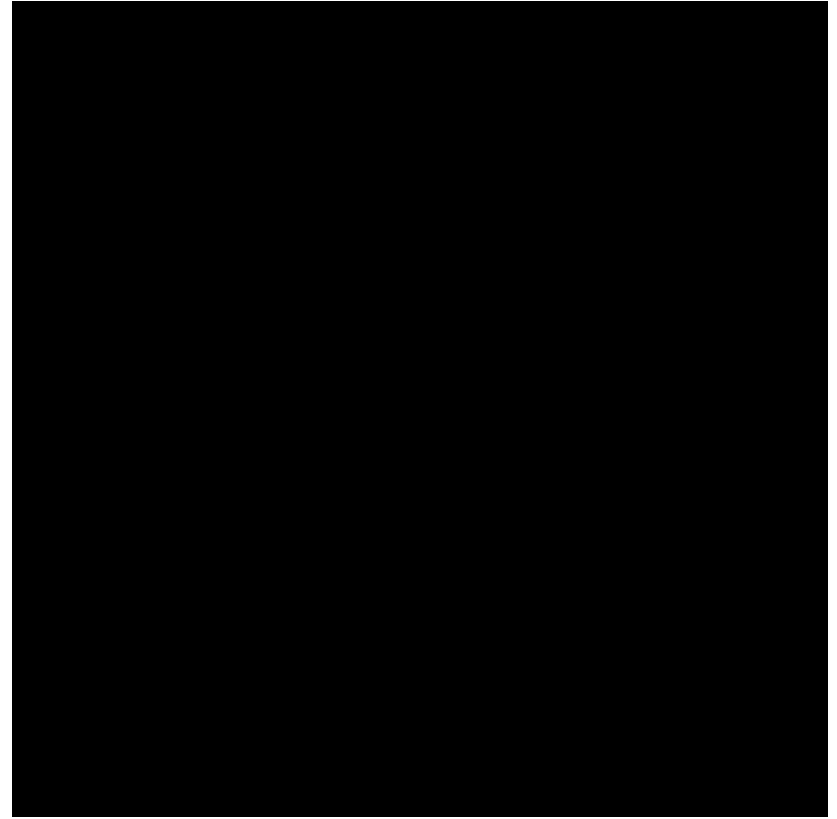
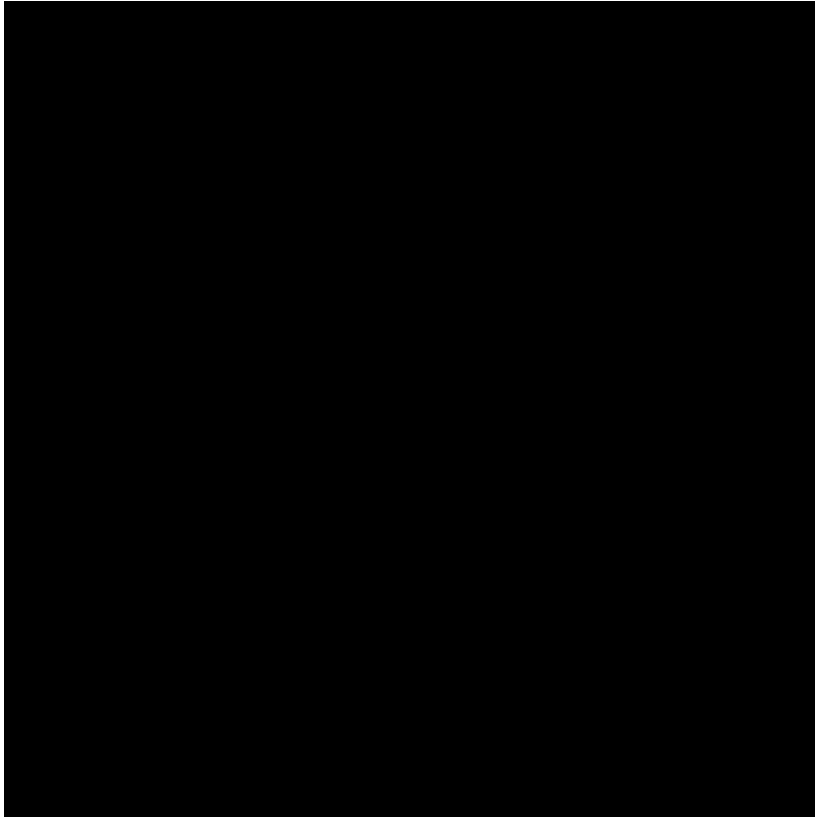
Study Of DTI Tractography And Working Memory

- Can a cerebellum-DLPFC pathway be identified in children with posterior fossa tumors and controls?
- Is integrity of this pathway compromised in patients relative to controls as measured by DTI indices (FA, MD, and radial and axial diffusivity).
- Are deficits in working memory present and, if so, are deficits related to integrity of cerebellum-corsolateral prefrontal cortex (DLPFC) ?
- medulloblastoma, astrocytoma, control (mean age 10.5yr).

(Mabbott, Rockel, Scantlebury, Law, & Bouffet. Probabilistic tractography of cerebellar-cerebral connections in paediatric brain tumor patients: *Proc. Ann Mtg Int Soc. Mag. Res. Med*, 3408, 2009).



Cerebello-thalamo-cortical Pathway



Tracts were produced that clearly replicated the cerebello-thalamo-cortical pathway that has been delineated in prior animal models (Schmahmann, 1996) for both patients (LEFT) and control (RIGHT). Tracts cross over to contralateral side from cerebellar seed in red nucleus, from where they extend into the thalamus and then into the dorsolateral prefrontal cortex.

(Mabbott, Rockel, Scantlebury, Law, & Bouffet. Probabilistic tractography of cerebellar-cerebral connections in paediatric brain tumor patients: *Proc. Ann Mtg Int. Soc. Mag Res. Med*, 3408, 2009).



Regional Pathway Integrity

A statistically significant main effect for region (i.e. cerebellum, pons, mid regions, frontal) was evident across all DTI indices.

-For FA and radial diffusivity, main effects were qualified by a region by group interaction.

For medulloblastoma relative to astrocytoma or controls ($p < 0.01$), and for cerebellar regions across tracts:

- Radial diffusivity (mm^2/sec) significantly higher, indicating reduced myelin integrity of axons
- FA was significantly lower, indicating possible breakdown of myelin and axonal fibre degeneration.



(Mabbott, Rockel, Scantlebury, Law, & Bouffet. Probabilistic tractography of cerebellar-cerebral connections in paediatric brain tumor patients: *Proc. Ann Mtg Int. Soc. Mag Res. Med*, 3408, 2009).

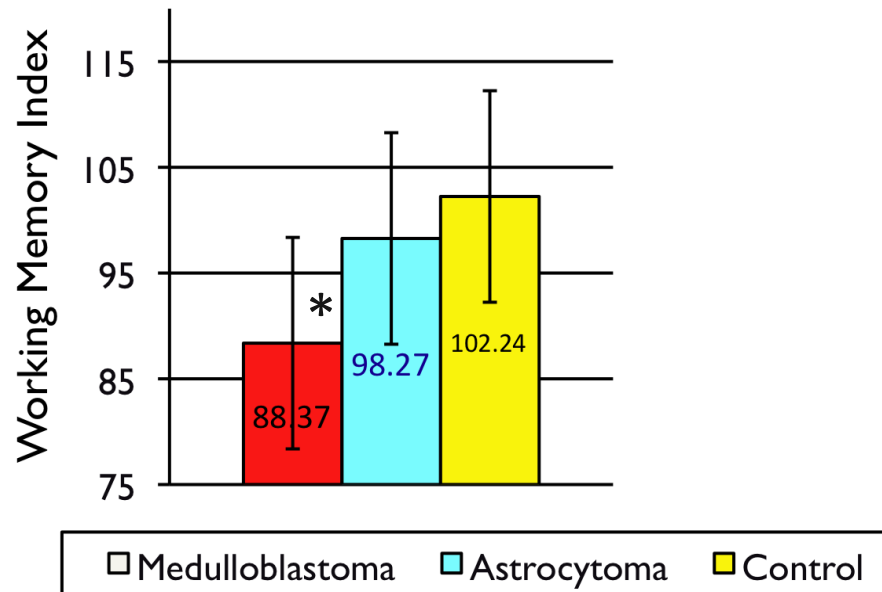
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Group Differences In Working Memory

- Significant group effect [$F(2, 59) = 4.012, p = 0.02$]
- Tumor groups performed more poorly than controls ($p = 0.02$).
- Astrocytomas had better working memory than medulloblastomas ($p = 0.04$).



(Law: Masters of Arts thesis, University of Toronto, 2009)



White Matter Integrity Of Cerebellum-DLPFC Pathway And Working Memory

- For tract connecting the right cerebellar hemisphere to the left DLPFC via the left thalamus, FA and radial diffusivity were correlated with WMI ($r = 0.334$, $p = 0.008$ and $r = -0.312$, $p = 0.014$, respectively).
- For the tract linking left cerebellar hemisphere to the right DLPFC via the right thalamus, only FA was correlated with WMI ($P = 0.262$, $p = 0.04$).

(Law: Masters of Arts thesis, University of Toronto, 2009)



Symptom Variability And Functional Outcome After Childhood Cerebellar Tumors



Outcome Variability: Cerebellar Tumors

- Children treated for cerebellar tumors experience pre-, peri-, and postoperative medical events.
- Conflicting evidence about relation between medical events and long-term neurobehavioral outcome, so we developed an index of medical events based on retrospective coding, clustering, and weighting of information obtained from records.
 - The first aim was to document the incidence and natural history of adverse medical events throughout the course of PF tumor diagnosis, treatment, recovery, and long-term survival.
 - The second aim was to examine whether medical events occurring perioperatively and in the short- and long-term survival periods predicted long-term neurobehavioral outcome.



(Roncadin, Dennis, Greenberg, & Spiegler: *Child's Nervous System*, 2008)

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Pre- Peri- Postoperative Medical Events

Time periods:

- diagnosis (at presentation)
- perioperative (initial in-patient hospital stay)
- short-term survival (during first 5 years post-initial hospitalization)
- long-term survival (beyond 5 years post-initial hospitalization).

Table 1 Descriptive statistics for each tumor group

Parameter	MBL (N=29; 18 males/11 females)	AST (N=29; 18 males/11 females)	<i>t</i>	<i>p</i> (two-tailed)
Age at diagnosis	7.30 (3.35; 1.17–15.00)	6.35 (3.82; 1.17–15.92)	1.01	0.318
Survival years	16.29 (7.21; 5.17–31.42)	11.06 (6.10; 4.83–22.17)	2.98	0.004
Age at testing	23.54 (8.33; 9.75–36.00)	17.43 (7.11; 7.50–31.33)	3.01	0.004

Roncadin, Dennis, Greenberg, & Spiegler: *Child's Nervous System*, 2008)



Symptom Profile & Cognitive Outcome

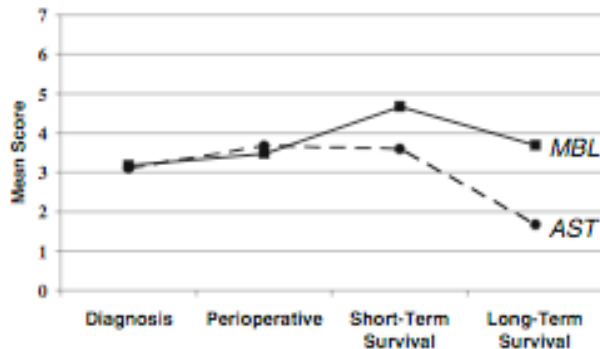


Fig. 1 Mean overall cluster scores by time period for each tumor group

Clusters	Events	Diagnosis		Perioperative		Short-term survival		Long-term survival	
		MBL	AST	MBL	AST	MBL	AST	MBL	AST
Cerebellar/bulbar	Head tilt	7	8	5	3	4	0	1	0
	Ataxia	26	29	20	23	29	27	19	10
	Mutism	0	0	5	2	0	0	0	0
	Bulbar signs	1	4	3	9	6	2	6	0
	Fine motor coord.	11	7	8	7	11	12	8	4
	Oculomotor	24	17	18	15	18	18	15	9

Table 3 Neurobehavioral outcome at long-term follow-up by tumor group

Outcome measure	MBL	AST	Test statistic	P (two-tailed)
Intelligence	79.38 (12.02)	98.52 (15.64)	t(56)=-5.22	<0.001
Memory	79.72 (15.71)	93.41 (17.28)	t(56)=-3.16	0.003
Functional independence	74.03 (23.30)	89.83 (20.50)	t(56)=-2.74	0.008
Health-related quality of life	0.85 (0.11)	0.89 (0.16)	Z(56)=-2.32	0.020

Values represent means (SDs).

MBL Medulloblastoma, AST astrocytoma



(Roncadin, Dennis, Greenberg, & Spiegler: *Child's Nervous System*, 2008)

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Are Symptoms Related To Outcome?

Long-term outcome is related to the occurrence of time-dependent medical events in astrocytoma survivors.

Neuroanatomical variables have been associated with functional outcome in astrocytoma survivors.

Greater perioperative and short-term medical adversity contributes to lower IQ in the long term.

Poorer memory, within the impaired range for individual AST survivors, is associated with a younger age at diagnosis, more perioperative events, and more events in the first 5 years postsurgery.

Lower functional independence is associated with more perioperative and short-term survival events.

Radiated medulloblastoma survivors experience marked changes in the trajectory of neuropsychological development.



Affect



Cerebellar Cognitive-Affective Syndrome

- Reported in adults and children post cerebellar lesions.
- Consensus that the CCAS exists, but less agreement about its definition and measurement.
- Term implies failure of emotion identification and/or disturbed emotion-cognition interface, but one or both?
- Some CCAS reports describe deficits in the awareness of emotions, others identify deficits in cognitive control.
- Cognitive control of emotion involves the ability to modify, inhibit, or delay emotional expressions.



CCAS In Music

- Emotion identification and the cognitive control of emotion..
- 37 children (7-16 years) treated for cerebellar tumors
 - 19 benign astrocytomas (AST)
 - 18 malignant medulloblastomas (MB)
 - 37 matched typically-developing controls (CON).
- Emotion Identification Task: how well do children recognize emotions and which features of music do they use to do so?
- Affective Music Stroop Task: can children focus on emotion in music when emotion in the lyric and music is either congruent or incongruent.

(Hopyan, Laughlin, Dennis: Emotions and Their Cognitive Control in Children with Cerebellar Tumors, submitted).



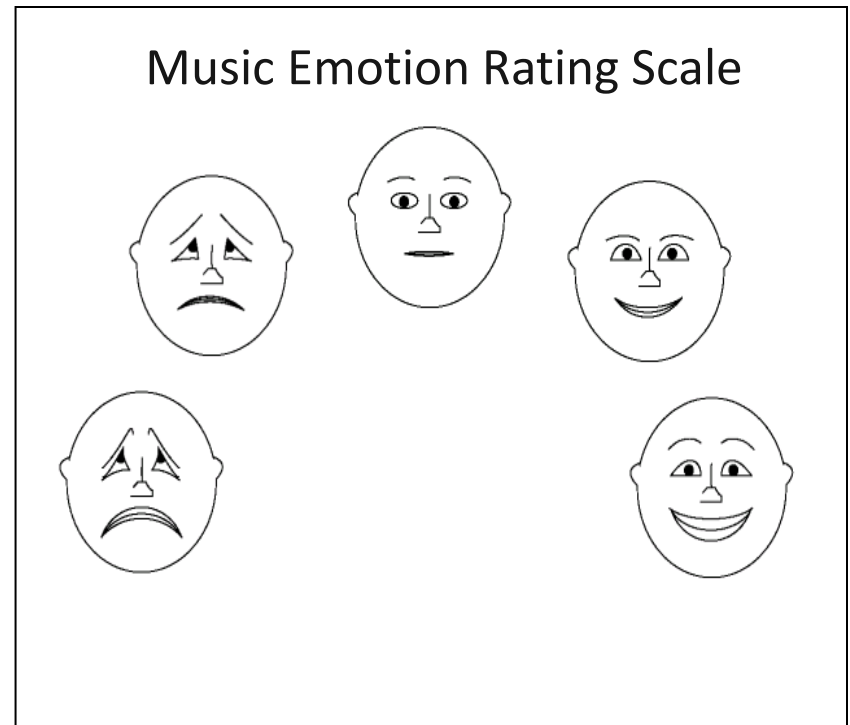
How Music Encodes Emotion

- Music encodes emotion by
 - **mode** (the specific subset of pitches used to write a given musical excerpt, e.g., major and minor modes) and
 - **tempo** (the number of beats per minute).
- Mode and tempo may be independently varied to elicit different emotions.
 - Fast tempi evoke a happy tone, slow tempi a sad tone.
 - Music played in a major mode is perceived as happy and music played in a minor mode is perceived as sad.
 - Children as young as 6 to 8 years of age are as accurate as adults at identifying emotions in music; like adults, they vary their judgments of emotion in music with changes in both tempo and mode, and they can identify unfamiliar music as being happy or sad.



Emotion Identification Task

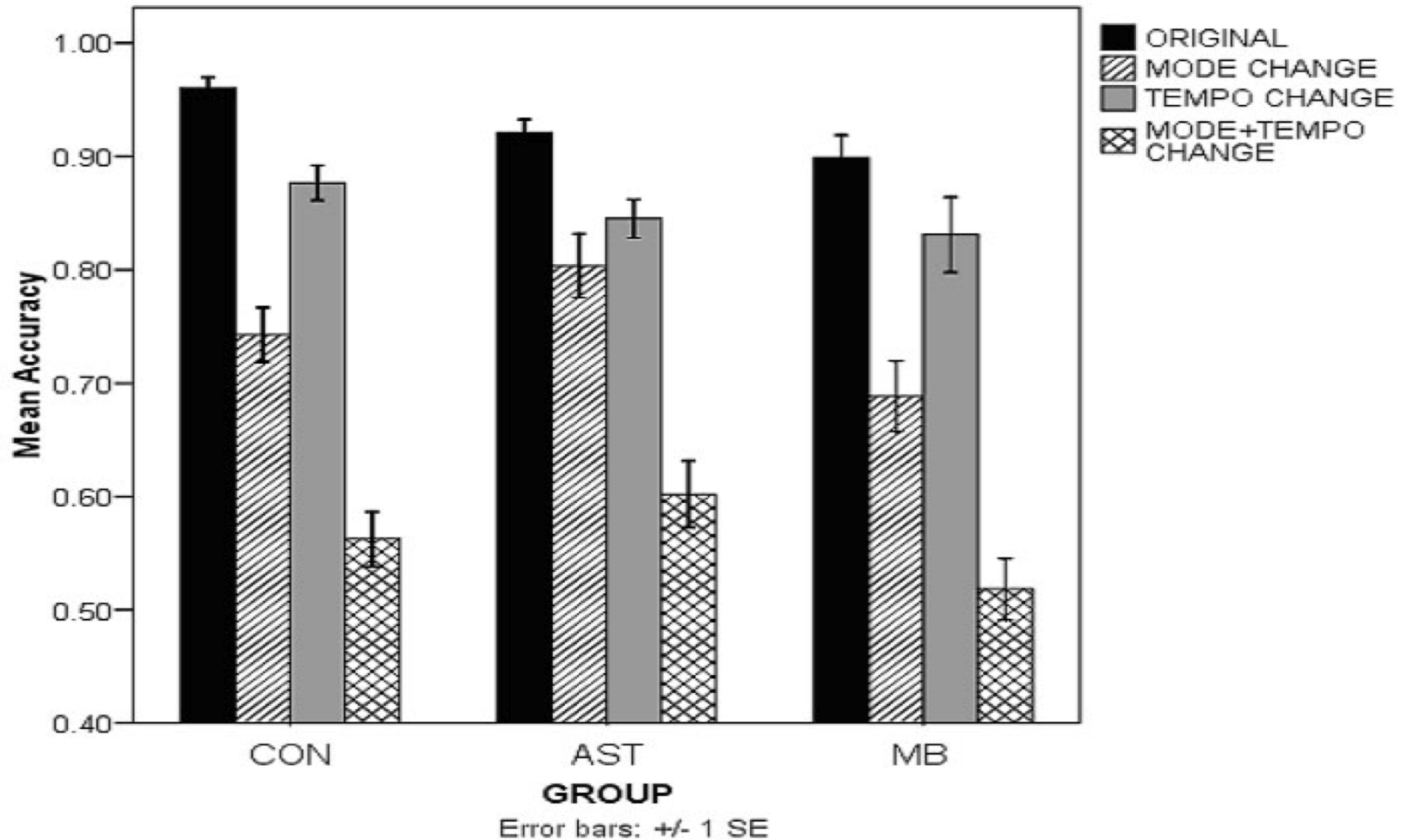
- 96 brief piano excerpts reliably rated as either happy or sad by adults and children 6-8 years of age.
- In *Original* condition, excerpts were in canonical form.
- In *Mode Change* condition, excerpts were mode transcribed from major to minor, or from minor to major.
- In the *Tempo Change* condition, tempi were set to median of original tempi.
- In the *Mode+Tempo* change, excerpts were transcribed to opposite mode of the original song and all tempi set to the median of the original tempi (this manipulation essentially neutralizes the emotion).



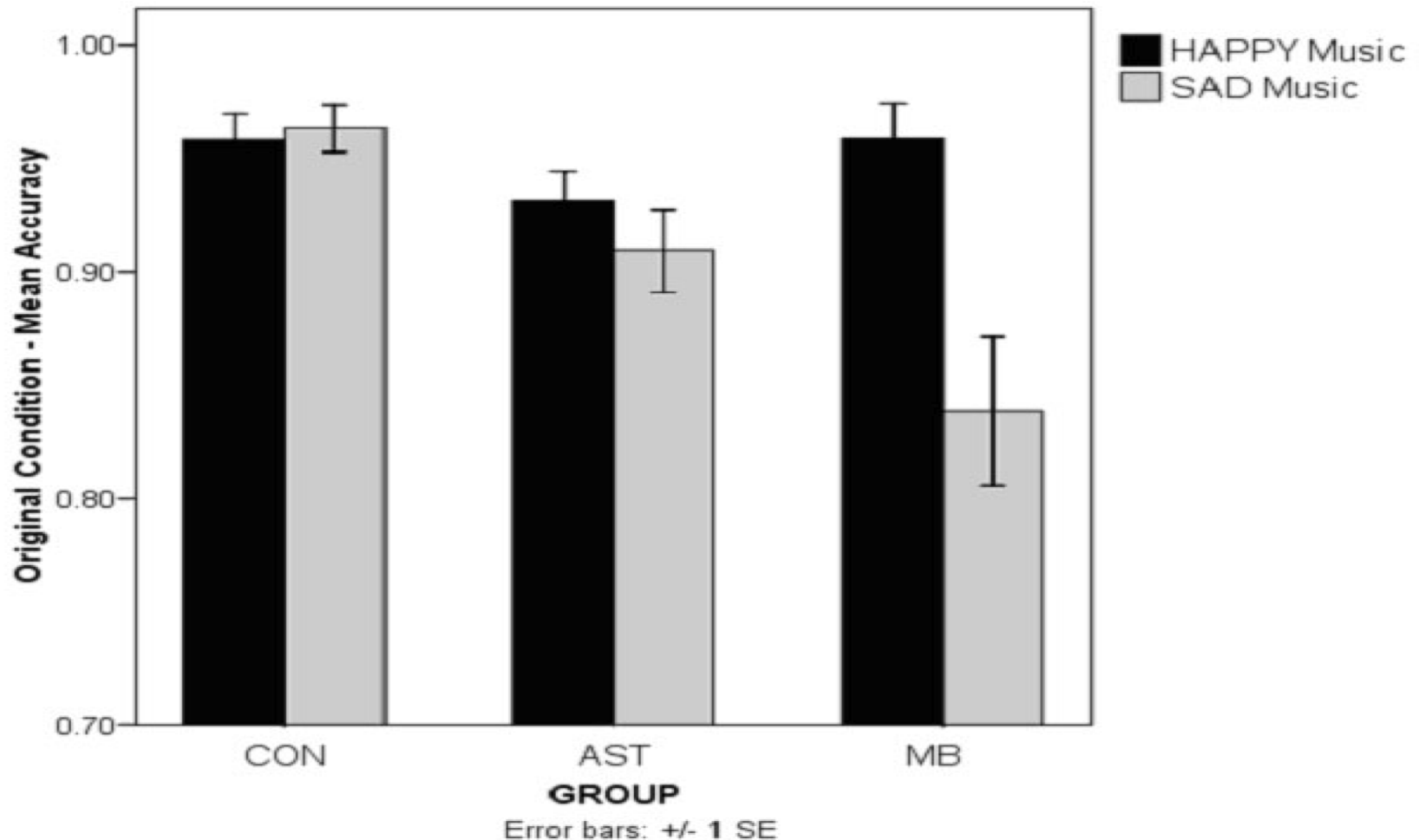
(Hopyan, Laughlin, Dennis: Emotions and Their Cognitive Control in Children with Cerebellar Tumors, submitted).



Emotion Identification: Results



Medulloblastoma And Sad Emotions



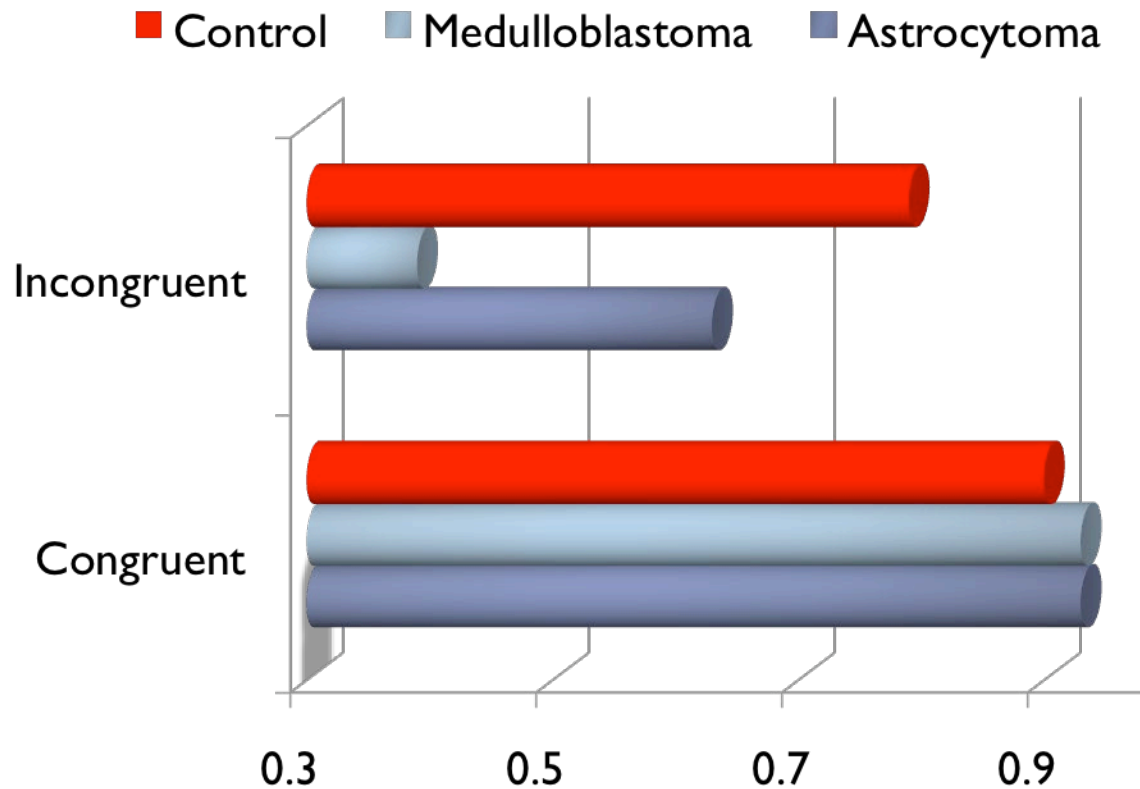
Cognitive Control Of Emotion

“Music Stroop” Task

- 48 original musical excerpts from Emotion Identification task.
- *a cappella* female voice sang the lyric *happy* or *sad*, which either matched or mismatched the emotion in the music.
- In *Congruent* condition, lyrics matched music (happy music sung with lyric *happy*, sad music with lyric *sad*).
- In *Incongruent* condition, lyrics mismatched music (happy music sung with lyric *sad*, sad music with lyric *happy*).
- Task: Attend to and rate emotion in the music.



Cognitive Control of Music Emotion: Results



(Hopyan, Laughlin, Dennis: Emotions and Their Cognitive Control in Children with Cerebellar Tumors, submitted).



Affect And Cerebellar Tumor Location



Pre-operative MRI tumor location

	MEDULLO BLASTOMA (N=17)	ASTRO CYTOMA (N=19)
Anterior lobe	8 (47%)	6 (32%)
Posterior-superior lobe	4 (24%)	14 (74%)
Inferior-posterior lobe	12 (71%)	16 (84%)
Corpus medullare	4 (24%)	11 (58%)
Hemisphere Right	5 (29%)	10 (53%)
Hemisphere Left	2 (12%)	8 (42%)
Vermis	15 (88%)	15 (79%)

- Vermis tumor involvement both groups.
- Hemispheric tumor involvement more frequent in AST group ($X^2 = 4.48, p = 0.02$), especially in left cerebellar hemisphere ($X^2 = 3.60, p = 0.05$).
- More tumor involvement in superior - posterior lobe in AST group ($X^2 = 5.56, p = 0.01$).
- Cerebellar tumor location more similar in MB and AST groups than suggested in the literature.



Cerebellar Tumor Location & Emotion

- Emotion Identification not significantly related to tumor location in either group.
- In AST group, Cognitive Control (Musical Stroop) positively related to right hemisphere tumor location, $r = .53, p = .02$.
- In MB group, Cognitive Control positively related to anterior lobe tumor location, $r = .52, p = .03$.
- Results are exploratory, but support idea of cerebellar role in Cognitive Control of Emotion rather than in Emotion Identification.



Clinical Implications: Not psychometrics

- Impairments in emotion and the cognitive control of emotion are dissociable from psychometric test performances.
- Despite differences in performance across psychometric tests between the tumor groups and controls, children in the astrocytoma group performed as accurately and as quickly as controls on the emotion identification task, children in the medulloblastoma group generally performed similarly to controls, and both tumor groups were impaired on the cognitive control task.



Clinical Implications: Cerebellar Cognitive Affective Syndrome

- Children with cerebellar tumors were able to identify emotions, and they used the same features (mode, tempo) as typically developing children to do so.
- Nevertheless, they had difficulty with the cognitive control of emotion.
- This suggests that the Cerebellar Cognitive Affective Syndrome in children is a disorder of the regulation of emotion, rather than of emotion identification.



Clinical Implications: Speech Prosody

- Recent hypotheses have proposed that the right cerebellum differentially processes high pass filtered information (segmental properties) and the left cerebellum differentially processes low pass filtered information, including the prosodic information important for speech prosody, affect, and singing (Callan et al., 2007).
- The fact that astrocytoma tumor involvement in the right cerebellar hemisphere preserved cognitive control of emotion may mean that the left cerebellar hemisphere is more important than the right for cognitive control in music, which is the key component of language prosody.



Clinical Implications: Astrocytomas

- Clinical reports focus on the major neurocognitive deficits of children with radiated cerebellar tumors, with less attention being paid to the astrocytoma group in terms of planned follow-up and monitoring.
- Nevertheless, recent data suggest non-trivial cognitive morbidity in astrocytoma survivors, especially in the long-term, and our data show that the cognitive control of emotions is significantly impaired in this group.
- Children treated for astrocytoma need planned follow-up, because they are at some individual risk for cognitive deficits and at group risk for cognitive-affective deficits.



Where Are We With Studies Of Cerebellar Structure and Function In Neurodevelopmental And Childhood Acquired Cerebellar Disorders?

There is GOOD NEWS and BAD
NEWS....



The Good News: # 1

- There is a burgeoning data base on the effects of both developmental perturbations of the cerebellum and childhood acquired cerebellar disorders.
- Because so many childhood disorders involve some form of cerebellar structural or functional anomaly, this is a GOOD THING.



The Good News: # 2

- We are beginning to move away from purely descriptive analyses of the cerebellum towards a more quantitative approach:
 - Cerebellar volumetrics
 - Cerebellar parcellations
 - Just beginning cerebellar tractography.
- This will grow to form the basis of a corpus of knowledge about developmental perturbations of the cerebellum and childhood acquired cerebellar disorders, so this is a GOOD THING.



The Good News: # 3

- In an earlier era, the only thorough analyses of cerebellar disorders involved descriptions of post-mortem material.
- For example, we know a vast amount about the post-mortem features of the cerebellum in Dandy-Walker syndrome and variants but relatively little about living children with this condition.
- Now, children living with cerebellar disorders can be imaged in vivo and their imaging correlated with measures of motor, cognitive, and affective function, which is also a GOOD THING.



The Good News: # 4

- Because there is now a consensus that the cerebellum is important for more than movement, clinical researchers are increasingly willing to look at functions that are actually interesting:
 - From a neurocognitive perspective
 - From an ecological, real-world perspective.
- This is also a GOOD THING.



The Bad News: # 1

Many cerebellar disorders are still understudied, which is a BAD THING.

- Developmental cerebellar dysmorphology
 - ~~Spina bifida meningocele~~
 - 22q11.1 Deletion Syndrome
 - Autism
 - Asperger syndrome
 - Williams syndrome
 - Down Syndrome
 - Fragile X
 - Dandy-Walker syndrome & variants
 - Joubert syndrome
- Acquired cerebellar lesions
 - ~~Cerebellar medulloblastoma~~
 - ~~Cerebellar astrocytoma~~
 - Cerebellar strokes
 - Traumatic brain injury
 - Prematurity
 - Alcohol & drug use



The Bad News: # 2

- Most information comes from psychometric, omnibus outcome measures, which are not designed to target the unique issues of the cerebellum.
- Many relevant constructs targeting what is uniquely wrong about the cerebellum are insufficiently or incorrectly parsed by standard psychometric tests
- For example, there are really no psychometric measures useful in identifying and diagnosing the Cerebellar Cognitive Affective Syndrome.
- We don't yet have a workable coalition of psychometric and cognitive measures, which is a BAD THING.



The Bad News: # 3

- Some of the clinical research effort in cerebellar tumors seems incorrectly focused, which is a BAD THING.
- For example, several articles reject the idea that medulloblastomas are of theoretical interest because of radiation effects, without recognizing that there is a natural comparison group in benign cerebellar tumors rather than in a random collection of “extra-cerebellar” tumors.



The Bad News: # 4

- A number of research studies of cognitive function in childhood cerebellar disorders attempt to ‘parcel out’ or ‘control for’ motor impairments.
- Of course, studies should have control of the motor demands of the task
BUT
- *We are* movement (some of us even believe that there is no cognition that is not motor) so dysmetria and dysrhythmia cannot be ‘extracted’ from cognition.
- Thinking that motor and cognitive issues are subtractive is a BAD THING.



The Bad News: # 5

- In some neurodevelopmental disorders, cerebellar involvement becomes the brain insult *du jour*, *causally* invoked to explain broadly defined functions.
- ADHD as timing disorder caused by cerebellar disorder BUT
- Time perception may involve different timescales.
 - Subsecond interval timing requires the cerebellum
 - Suprasecond timing involves a more distributed network including basal ganglia.
- ADHD deficit in executive control (suprasecond estimation) rather than subsecond timing that is the output of the olivo-cerebellar system, which generates temporal patterns in the inferior olive to time intervals (~hundreds of ms) using oscillations to keep track of time (Jacobson et al., 2008).
- Appealing randomly to cerebellar disorder as an explanation of dysfunction without being able to tie the function to the cerebellum theoretically and empirically is a BAD THING.



Does the Cerebellum Exhibit Age- Based Plasticity, Structural And/Or Functional?



What Does Age-Based Plasticity Mean?

- Plasticity is not an aberrant state; it is what the brain is designed to do, and what it does normally.
- A pop version of plasticity has it that a “Kennard Principle” based on work in the 1930s-1940s showed that early brain insult has fewer, and more transient effects than damage to the mature brain.
- Before considering the issue of plasticity in relation to children with neurodevelopmental disorders and childhood acquired lesions of the cerebellum we will digress to discuss the “Kennard Principle,” which is
 - neither Kennard’s
 - nor a principle.



Digression: The “Kennard Principle”



Margaret Kennard (1899–1975)

- The supposed ‘Kennard Principle’ asserts a negative linear relation between age at brain injury and functional outcome: Other things being equal, the younger the lesioned organism, the better the outcome.
- But other things are never equal, and the ‘Kennard Principle’ is neither Kennard’s nor a principle.
- Kennard sought to explain factors that predicted outcome (age, to be sure, but also staging, laterality, location, and number of brain lesions, outcome domain) and the neural mechanisms that altered the lesioned brain’s functionality.



Fig. 1 - Headshot of Margaret Kennard extracted from her medical school graduating class photograph (1930). Courtesy of Medical Center Archives of New York-Presbyterian/Weill Cornell.

Dennis M. Margaret Kennard (1899–1975): Not a ‘Principle’ of brain plasticity but a founding mother of developmental neuropsychology, *Cortex* (2009), doi:10.1016/j.cortex.2009.10.008



Age Not Sole Predictor Of Early Lesion Outcomes

- Kennard's overarching interest was how functionality was effected in the lesioned brain.
 - Even had she sought to identify a single principle for recovery of function – and I believe she did not – age at lesion would not have been that principle.
 - For Kennard, early brain damage did not consistently spare function or optimize functional outcome, but could be more, less, or equally disabling than later-onset injury depending on the features of the injury, post-injury neuroanatomical reorganization, the staging of the lesion, how and when outcome was assessed.
-



Plasticity of Motor Function: Neurodevelopmental

- Despite congenital onset, children with spina bifida have:
 - Dysmetria
 - Ataxia
 - Dysarthria
- We believe that their motor deficits involve defective feed-forward, predictive motor control coupled with intact feedback-adaptation learning.
- Current models of adult cerebellar motor function stress disorders of predictive control, which is what we see in spina bifida, so there is little plasticity for core cerebellar motor functions.



Plasticity of Motor Function: Acquired Lesions

- Children with acquired cerebellar lesions continue to have motor deficits long after their tumor treatment, including:
 - Dysmetria
 - Ataxia
 - Dysarthria
- Malignant tumors and their treatment result in poorer long-term adaptive and motor function than do non-malignant tumors treated by surgery alone.
- There have been no clinical research studies that study the kind of theoretical issues in motor control that have been addressed in adult lesions so we currently cannot characterize the nature of the motor impairment in childhood cerebellar acquired lesions.



The Special Case Of Eye Movements

- Cerebellum has important role in control of eye movements.
 - visual fixation
 - vestibulo-ocular reflex
 - binocular alignment
 - saccade accuracy and adaptation
 - smooth pursuit.



Plasticity of Eye Movements?

- Eye movements correlated with midsagittal vermis expansion (lobules VI-VII).
- Midsagittal vermis expanded in children with spina bifida with normal eye movements.
- Dymorphic vermis expansion preserves ocular functions of vermis (saccadic accuracy, adaptation, smooth pursuit).
- Eye movements are better with expanded cerebellar tissue, but is this functional plasticity?

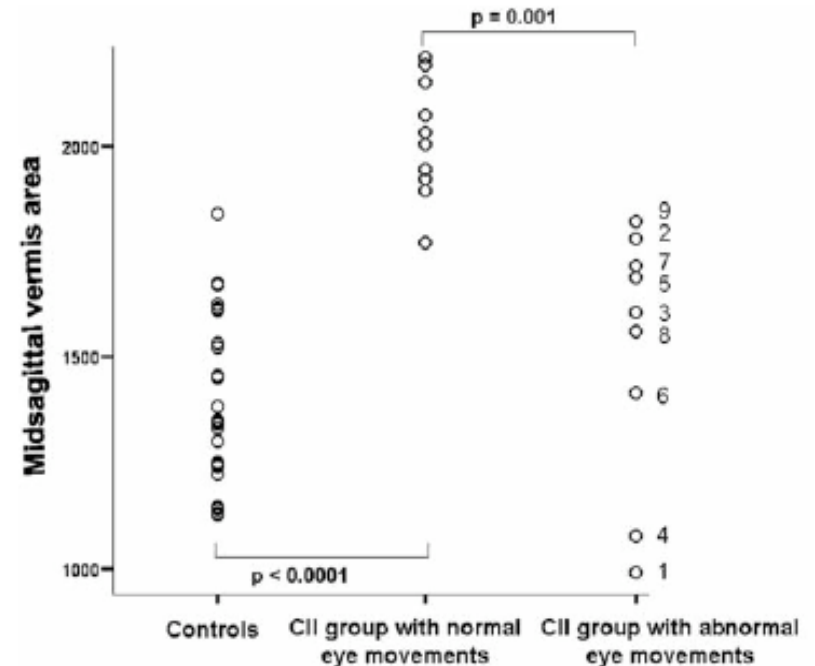


Figure 1: Midsagittal vermis areas (mm²) are shown in the controls, patients with CII who had normal eye movements, and patients with CII who had abnormal eye movements. The vermis is significantly expanded in patients with CII who had normal eye movements (the numbers 1-9 on the right correspond to the participants' number as presented in Table 3).



Salman, Dennis, & Sharpe: *Canad J Neurol. Sci.*, 2009

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Plasticity of Affective Function

- The Cerebellar Cognitive Affective Syndrome occurs in both children and adults with cerebellar disorders.
- In spina bifida, this co-occurs with excessive sociability.
- In cerebellar tumors, it co-occurs with more autistic spectrum symptoms.
- [In cerebellar tumors, it is unrelated to the presence of the Posterior Fossa Syndrome, i.e., to mutism with subsequent dysarthria]
- Despite the fact that spina bifida is a neurodevelopmental disorder and cerebellar tumors are acquired conditions, both groups have difficulty in the cognitive control of affect.
- Little age-based plasticity for cerebellar affective dysregulation, but some important differences between neurodevelopmental and acquired childhood conditions.



Knitting It All Together

These days, even knitted brains include the cerebellum.....



Knitted by Dr Karen Norberg, Cambridge, Massachusetts.

<http://www.telegraph.co.uk/news/newstoppers/howaboutthat/4245919/Psychiatrist-knits-anatomically-correct-woolly-brain.html>



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