Anterior Cerebellar Vermis Blood Flow: Neurobehavioral Correlates in Child Abuse and ADHD

C.M. Anderson, A.M. Polcari, C.E. McGreenery, L.C. Maas, P. Renshaw & M.H. Teicher. Consolidated Dept. of Psychiatry, Harvard Med. Sch., Developmental Biopsychiatry Research Program & The Brain Imaging Center, McLean Hospital, Belmont, MA.

INTRODUCTION: The Paleocerebellum and Emotional Dysfunction

• This poster presents unique findings suggesting a role for the cerebellar vermis (CV) in the enduring effects of child abuse and the psychopharmacology of methylphenidate in ADHD children.

• Historically, the cerebellar vermis has long been implicated in varous kinds of psychopathology. A wide range of basic, clinical and brain imaging studies support a role for the midline cerebellar vermis in **aggression** (Berman 1997), (Heath 1977), **depression** (Beauregard, Leroux et al. 1998), **hyperactivity** (Berquin, Giedd et al. 1998),(Mostofsky, Reiss et al. 1998), (Altman 1987) , **psychosis** (Heath 1977) (Lauterbach 1996) and the enduring effects of **early trauma** (Kling, Steinberg et al. 1979).

• The anterior cerebellar vermis (ACV) bilaterally influences dopamine release in the basal ganglia, amygdala and accumbens (Snider and Maiti 1976; Snider, Maiti et al. 1976; Supple and Kapp 1994) via fastigial nucleus projections (Heath and Harper 1974) to pontine and mesencephalic nuclear groups (see CENTRAL DIAGRAM ->).

• The role of the vermis in bimanual and bipedal coordination (Ouchi, Okada et al. 1999) may provide theoretical insights into the role of ACV dysfunction in psychopathology.

OUR WORKING HYPOTHESES:

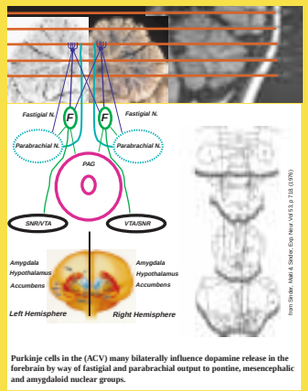
1) The ACV may function in emotional motor -- visceral coordination through bihemispheric switching of the forebrain limbic regions.

2) Abnormally elevated resting blood flow in the ACV may be a marker of neural dysfunction in this cerebellar area.

3) Impaired hemispheric shifting (for example, as observed for binocular rivalry in bipolar disorder [Pettigrew and Miller 1998]) may represent a functional trait common to both survivors of early child abuse and hyperactive ADHD children.

4) Psychopharmacological interventions may restore normal switching function by reducing resting blood flow in the ACV as is observed with methylphenidate administration in hyperactive ADHD children (OTHER SIDE).

Note: The findings reported in this poster represent "**work in progress**" and may be modified with further analysis.



Purkinje cells in the (ACV) many bilaterally influence dopamine release in the forebrain by way of fastigial and parabrachial output to pontine, mesencephalic and amygdaloid nuclear groups.

Methylphenidate Dose-Dependently Decreases Blood Flow in the Cerebelluar Vermis of Childern with ADHD:

• Recent evidence from animal and human research suggests that developmental pathology of the cerebellum may be particularly relevant to understanding childhood attention deficit hyperactivity disorder or ADHD.

• For example, Altman observed that selective x-ray irradiation of the cerebellum in infant rats during a critical granule cell migration period results in enduring morphological alterations and a period of behavioral hyperactivity during adolescence which declines in adulthood.

• Findings from several recent studies employing magnetic resonance imaging-based morphometric analysis of the cerebellum in ADHD children implicate a midline region of the cerebellum called the "inferior posterior lobe" of the vermis in the pathophysiology of motor and cognitive defects (Berquin et al. 1998).

• Schmahmann has proposed that cerebellar pathology, which typically results in motor dysmetria (the term derived from the Greek (dys) "bad" and (metron) "taking a measure of time and/or space") may also contribute to a "cognitive dysmetria" in adults characterized by defects in the "...[the] speed, capacity, consistency and appropriateness of mental or cognitive processes" (Schmahmann, 1998) -- a description consistent with behavioral deficits observed in ADHD.

Behavioral Measures:

Activity and attention data were collected as previously described (Teicher et al 1996). Children sat in front of a computer and were evaluated using a continuous performance attention task (CPT) based on the MCA and TOVA (Greenberg 1987). This is a simple GO/NO-GO vigilance task in which the subject responds to visual presentation of a target and withholds response to non-target stimuli that appear in the center of the screen at a fixed intertrial interval. The stimuli are simple geometric shapes that can be distinguished without right/left discrimination, and are designed to allow children with dyslexia to perform as well as normal controls. Three 5 minute test sessions were recorded during a 30 minute test period while an infrared motion analysis system (Qualisys, Glastonbury CT) recorded the movement of small reflective markers attached to the child head, shoulder, elbow and back. The motion analysis system stored on a computer the precise vertical and horizontal position of the centroid of each marker 50 times per second to a resolution of 0.04 mm.

SUBJECTS:

Thirty seven young adults **(9M/28F; 18-22 yr)** participated, including **17 (3M/14F)** with a history of sexual or verbal child abuse exclusive of physical trauma. All subjects were recruited by advertisement and were not using illicit substances or medications.

Exclusion factors: History of DSM-IV axis I psychiatric disorder in first degree relative or history of known neurological disease or insult or history of maternal substance abuse or viral infection during pregnancy, and any of a series of complications during delivery or perinatal period (e.g., permaturity, eclampsia, fetal distress, high forceps delivery, labor greater than 24 hours, emergency Cesarian section, low birth weight, hyperbilirubinemia, respiratory distress, etc.). Also subjects with verified or suspected seizure disorders were excluded if the seizure disorder predated the abuse, or was related to known CNS disease or trauma. Subjects with head injuries were excluded if the injury resulted in loss of consciousness for more than 2 hours, or fractured the skull.

Inclusion criterium: Satisfactory completion of the following assessment tests:

Abuse Trauma Questionnaire (ATQ), Parental Bonding Instrument (PBI), Dissociative Experience Scale (DES), Limbic System Check List (LSCL-33), and Medical History-Birth Questionnaire.

Subject procedures: On the first visit, subjects received a brief screening interview to confirm the data collected to date, to explain the purpose and nature of the study, and to obtain informed consent. Eligible subjects underwent a EEG coherence assessment and a structured clinical interview (SCID) supplemented by clinical ratings of depression and anxiety, and a toxicological screen. During the second visit they underwent phlebotomy at 10:00 a.m. ± 30 min for a2 and glucocorticoid receptors, as well as neuropsychological tests, complete self-report ratings. They then underwent fMRI study and regional Cerebral Blood Volume determinations,at the McLean Hospital's Brain Imaging Center. Patients received payment of $15 for the assessment tests and $250 after completing the study.

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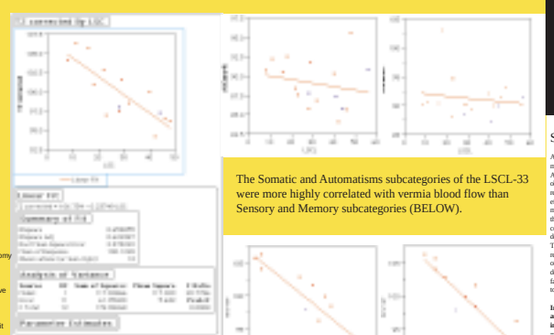
LIMBIC SYSTEM CHECKLIST-33 (LSCL-33)

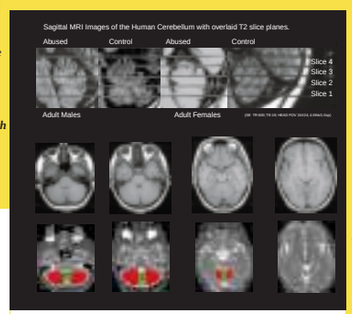
The LSCL-33, was designed to measure somatic, sensory, behavioral, and memory symptoms suggestive of temporal lobe epilepsy. Child abuse can be likened to a kindling phenomena (Teicher, Ito et al. 1997).

In a study of over 250 outpatients (Teicher, Glod et al. 1993), physical abuse was found to be associated with a 38% increase in LSCL-33 scores ($P < 0.01$), sexual abuse with a 49% increase ($P < 0.02$), and combined abuse with a 113% increase ($P < 0.0001$). ***Physical or sexual abuse alone was associated with elevated LSCL-33 scores only if the abuse occurred before age 18.***

A strikingly robust correlation (BELOW) was observed between blood flow in the midline vermis (but not the cerebellar hemispheres) and LSCL-33 scores.



The Somatic and Automatisms subcategories of the LSCL-33 were more highly correlated with vermia blood flow than Sensory and Memory subcategories (BELOW).



Steady-State fMRI

A novel fMRI procedure, steady-state fMRI (Teicher, in prep.), was used to derive steady state blood flow measures and to test for enduring effects of childhood sexual abuse and methylphenidate in ADHD children. Although conventional Blood Oxygenation Level Dependent (BOLD) fMRI is a valuable technique for observing brain activity changes between baseline and active conditions, it fails to provide insight into possible resting or steady-state differences in regional perfusion between groups of subjects, and can not delineate effects of chronic drug treatment on basal brain function. Steady-state fMRI, like BOLD, hinges on the para-magnetic properties of deoxyhemoglobin. However, the mismatch between blood flow and oxygen extraction that occurs as an acute reaction to enhanced neuronal activity in BOLD does not persist under steady state conditions. Instead, regional blood flow is regulated to appropriately match perfusion with ongoing metabolic demand, and deoxyhemoglobin concentration becomes constant between regions in the steady-state. Therefore, regions with greater continuous activity would be perfused at a greater rate, and these regions would receive, over time, a greater volume of blood and a greater number of deoxyhemoglobin molecules per volume of tissue. Thus, there should be an augmentation in the paramagnetic properties of the region that would be detectable as a diminished T2 relaxation time. This method uses a TE (Time-to-Echo) stepping procedure to factor T2* from the estimate of T2 decay. One of the advantages of measuring T2 relaxation time, as opposed to a change in image signal intensity during a single scanning session, is the higher signal to noise ratio.

Images were aquired using a 1.5-T GE Signa system equipped with a whole-body echo planar gradient set and a quadrature head coil. Values of T2 were estimated from a series of 32 TE stepped echo planar imaging (EPI), spin echo images collected in 10 axial slices (TE = 32 msec, TR = 10 msec, Slice thickness = 7mm with a 3mm skip, in-plane resolution = 3.125 mm,FOV = 200 mm).

For cerebellar regions, a median regional decay curve was generated by taking the median pixel intensity within the region of interest (ROI) at each value of TE examined. An estimate of T2 decay time was then computed by linear least square fitting of the log-transformed median time course. Use of median values provides greater immunity from partial volume contamination due to bordering regions, white matter and CSF. Images were corrected for frame-to-frame motion with the DART registration algorithm (Maas, 1997).

Please see: **Http://remfractal.mclean.org:8080/vermis.html** for a PDF version and further developments.

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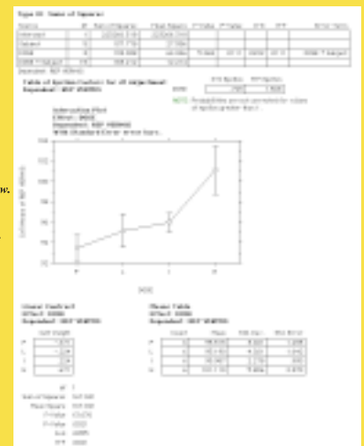
SUBJECTS:

Six healthy control boys (10.2 ± 1.5 yr) and 11 boys with ADHD (9.3 ± 1.6 yr) served as subjects in this study, which was approved by the McLean Hospital Institutional Review Board. The healthy controls were screened using structured diagnostic interview (K-SADS-E) and were free of any major psychiatric disorder, and had no more than 3 out of 9 possible symptoms of either inattention or hyperactivity-impulsivity by DSM-IV criteria. Children with ADHD were included if they met criteria for ADHD on structured diagnostic interview, and had at least 6 of 9 symptoms of inattention or hyperactivity-impulsivity. Normal controls were studied once. Children with ADHD took part in a triple blind (parent, child, rater), randomized, placebo-controlled study of effects of methylphenidate (0, 0.5, 0.8, 1.5 mg/kg in divided dose) on activity, attention and fMRI. Children with ADHD were treated continuously for one week with placebo or specific dose of methylphenidate and at the end of the week were tested for drug efficacy using objective measures of attention and activity (Teicher et al 1996), and fMRI within 1 - 3 hours of their afternoon dose. Time between dose and testing was held constant for each subject throughout the four treatment conditions. Activity and attention were evaluated in healthy controls using the same procedure as children with ADHD, and fMRI followed within the same time frame.

RESULTS:

An overall dose-dependent resting blood flow decrease in the vermis was observed [$F_{1,5} = 5.261$, $p < .01$]. Trend analysis supported a dose-dependent linear decline in perfusion [$F_{1,5} = 13.676$, $p < .001$].



SPECULATIONS AND CONCLUSIONS:

• ***The LSCL-33 appears to provide an indirect assessment of vermial blood flow.***

• ***The use of chronic electrical stimulation of the ACV to treat human epilepsy is consistent with our findings and with the kindling hypothesis of child abuse.***

• ***The extended postnatal development of the vermial cortex (Isumi, et al. 1997) could increase its susceptibility to early environmental insults.***

• ***Dynamic studies of vermial blood flow in association with measures of bihemispheric activity in psychiatric patients over the course of treatment could potentially provide insights into cerebellar coordination of cortical-striatal-thalamic loops.***

• ***Psychopharmacological theories and models of psychiatric drug action in depression, PTSD, borderline personality disorder and ADHD may need to be reevaluated in light of the emerging role of the cerebellum in the underlying pathophysiology of these disorders.***

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