MRS Studies of Human Brain Development

APA 2007 Annual Meeting

Perry F. Renshaw, M.D. Ph.D.

Young-Hoon Sung, M.D.

In Kyoon Lyoo, M.D. Ph.D.

Brain Imaging Center

McLean Hospital / Harvard Medical School

Brain Imaging Center Collaborators

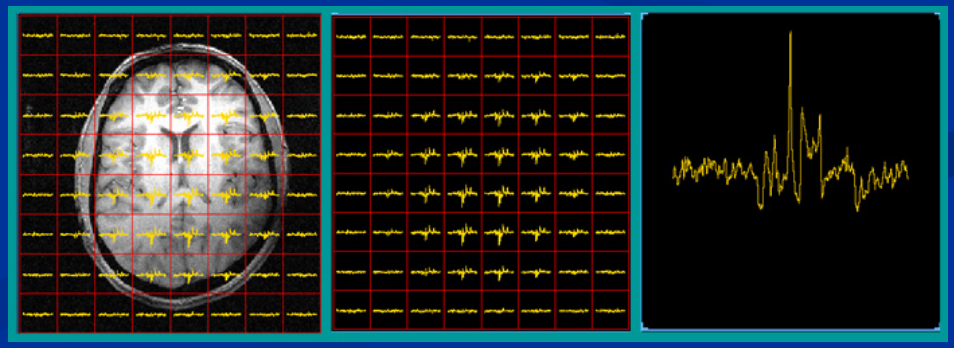
Carl Anderson
Suzann Babb
Tanya Barros
Lino Becerra
Nicolas Bolo
David Borsook
Barbara Bradley
Melanie Brimson
Kenroy Cayetano
Ashley Cerney
Chrissy Cintron
Jeanette Cohan
Sadie Cole
Melissa Daniels
Brian Dunn
Chelsea Finn
Brent Forester
Blaise Frederick
Staci Gruber
Charlotte Haws
Mike Henry
Bob Irvin
Eric Jensen
William Jones
Gen Kanayama
Mark Kaufman
Mary Knapman
Matt Lammens
Kim Lindsey
John Logue
Steven Lowen
In Kyoon Lyoo
Terry Mancini
Carissa Medeiros
Eric Moulton
Constance Moore
Susie Morris
Donna Murray
Lisa Nickerson
David Olsen
Dost Ongur
Gautam Pendse
Srini Pillay
Andrew Prescot
Perry Renshaw
Ika Rogowska
Mike Rohan
Amy Ross
Isabelle Rosso
Margaret Ricciuti
Katherine Rudich
Megan Shanahan
Marisa Silveri
Jennifer Sneider
Chris Streeter
Young-Hoon Sung
Doug Hyun Han
Kathleen Thangaraj
Jean Theberge
Rose Villafuerte
Megan Wardrop
Paul Wilson
Rinah Yamamoto
Debroah Yurgelun-Todd
Chun Zuo

Outline

- What and Why MRS in human development?
- What happens in the adolescent brain specifically?
- Examples of MRS studies for neurodevelopment
- The brief picture of metabolite changes through whole life
- Applications

Question

- Why MRS ?
  - Understanding *in vivo* Biochemistry in normal developing brains of human
  - Further, contribution to the biological knowledge and application for psychiatric disorders
- What can MR spectroscopy inform us about brain and development?
  - 1H MRS, 31P MRS, ...



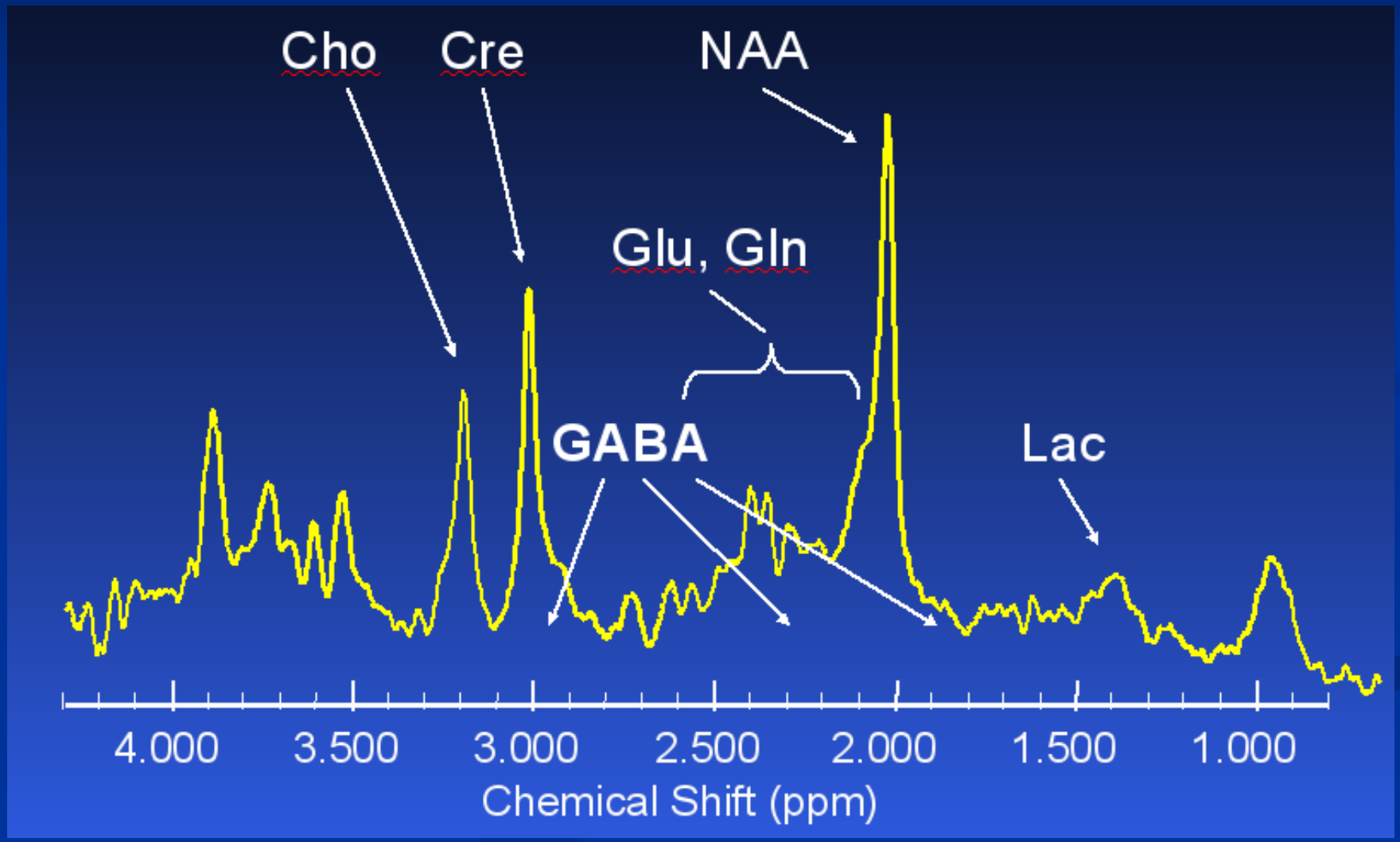
First Answer

- 1H MRS
  - NAA, Cr, Cho, mI, Glx, Lac
    - Neuronal viability/funtion
    - Glial metabolism, Neurotransmitter
- 31P MRS
  - PME, Pi, PDE, PCr, α-,β-,γ-ATP
    - Brain neuronal membrane metabolism
    - High energy phosphate metabolism

Proton MRS

- Now, let's see what NAA, Cr,.. stands for and means before going to the brain metabolites of adolescent.

The in vivo 4T ^{1}H-MRS Brain Spectrum



N-acetyl-aspartate (NAA)

- GM – neuronal viability or damage
- WM – diffuse axonal damage or loss
- Neuronal death and/or dysfunction can also cause reduced metabolite levels (Ende, 1997)

- NAA is made in mitochondria by the membrane-bound enzyme L-aspartate N-acetyltrasferase, a catalyst that is found only in the brain(Truckenmiller, 1985)
- The synthesis of NAA is energy dependent (Patel, 1979)
- Reductions in NAA are consistent with impaired mitochondrial energy production (Clark, 1998; Stork, 2005)

Creatine (Cr)

- Measure of high energy phosphate stores
- Decrease means
  - reduction of the ATP supply and high-energy phosphate pool
- The resonance arises from
  - both creatine and phosphocreatine
- Higher concentration
  - in glial cell than neurons
  - could mean glial proliferation with concurrent mI increase
- Cr is synthesized in the liver
  - hepatic pathology may affect overall conc.
- Historically used as an internal reference

Choline (Cho)

- Choline-containing compounds
  - Precursor for phosphatidylcholine (constituent of cell membrane)
  - Phosphocholine + Glycerophosphocholine
  - Related with
    - Cell membranes formation and myelination
    - Membrane turn-over
    - Marker of cellular density

Myo-inositol (mI)

- Related to intracellular sodium content
- Glial marker
  - gliosis and reactive astrocytosis
- Myoinositol (75%)
  + myoinositol monophosphate (15%)
  +α-protons of glycine (15%)
  - Ross, 1991

Lactate (Lac)

- Increases with impairments in oxidative metabolism

What happens in adolescent brain?

- Period of behavioral, cognitive and emotional reorganization/integration
  - Which means notable changes in brain
- Brain maturation may include
  - Arborization, neuritic sprouting
  - Myelination with oligodendrocyte
  - Pruning, loss of dendrite process
- Let's see how does MRS provide above pictures ?

Age-dependent Changes in Localized Proton and Phosphorus MR Spectroscopy of the Brain

Marjo S. van der Knaap, MD • Jeroen van der Grond, PhD • Peter C. van Rijen, MD • Joop A. J. Faber, PhD • Jaap Valk, MD, PhD • Kobus Willemse, MD, PhD

van der Knaap et al (1990)

- Healthy children (41 subjects)
  - Age: 1 – 16 years
- Paraventricular white matter
  - NAA/Cho, NAA/Cr
    - increase
  - Cho/Cr
    - decrease
  - Rapid change for 3 years of life
  - Continued to age 16

Development of the Human Brain: *In Vivo* Quantification of Metabolite and Water Content with Proton Magnetic Resonance Spectroscopy

Roland Kreis, Thomas Ernst, Brian D. Ross

Kreis et al (1993)

- 50 children
- 34.5 ~ 926 gestational weeks
  - 1 to 18 years
- normal and pathologic brain
- absolute quantitation
- presents normative curves for normal development
- ROI
  - occipital cortex
  - parieto-occipital lobe

Kreis et al (1993)

- NAA ↑
- Cr ↑
- Cho ↓
- mI ↓

Gestational Age

Gestational Age

- most rapid change – within first 2 years

Hashimoto et al (1995)

- Healthy 47 children and 6 adults
- Frontal, Parietal
  - NAA/Cho, NAA/Cr: increase
  - Cho/Cr: decrease
  - Rapid changes – 1 to 3 years of age
- Regional variation
  - Metabolite conc: Rt. Frontal < Rt. Parietal

Regional Age Dependence of Human Brain Metabolites from Infancy to Adulthood as Detected by Quantitative Localized Proton MRS

[Regular Manuscripts]

POUWELS, PETRA J. W.; BROCKMANN, KNUT; KRUSE, BERND; WILKEN, BERND; WICK, MARKUS; HANEFELD, FOLKER; FRAHM, JENS

Pouwels et al (1999)

- GM, WM, cerebllum, thalamus
- Subjects
  - 97 children
    - 1-18 years
    - Healthy
    - Disease brain: unaffected area
  - 72 adults
    - Healthy
    - 18-39 years

Pouwels et al (1999)

- GM, cerebellum, thalamus
  - NAA increase
- WM, thalamus
  - NAAG increase
  - Glutamine decrease
- Cr, PCr, Cho, mI, glutamate
  - remain constant after first year
- Cr: Pcr=2:1
  - regardless of age or region

Kadota et al (2001)

- 90 normal subjects
- 4 to 88 years
- WM, GM
  - ant, mid, post
- Metabolite ratios
  - NAA/Cho
  - Cr/Cho

Development and Aging of the Cerebrum: Assessment with Proton MR Spectroscopy

Tsuyoshi Kadota, Takashi Horinouchi, and Chikazumi Kuroda

Kadota et al (2001)

- WM
  - NAA/Cho
    - peak: average - 18.5 years
      - fontal 21.9 years, precentral 17.6, parietal 15.9
        - dorsal to rostral direction
    - increase
      - first decade – third
    - decrease
      - after third decade
- GM
  - NAA/Cho
    - gradual decline

Kadota et al (2001)

- Cerebral lateralization
  - Right side WM mature 1.1~4.0 years faster than left in terms of NAA/Cho levels
- Gender difference
  - Male reached maximum level of NAA/Cho 1.4 ~ 3.2 years earlier than female in WM
  - After peak, the NAA/Cho levels declined faster in male than in female
    - may be due to sex hormone difference

In Vivo Quantitative Proton MRSI Study of Brain Development From Childhood to Adolescence

Alena Horská, PhD,[1*] Walter E. Kaufmann, MD,[1–6] Larry J. Brant, PhD,[7] Sakkubai Naidu, MD,[3,4,6] James C. Harris, MD,[4,5] and Peter B. Barker, PhD[1,6]

Horska et al (2002)

- 15 healthy
- Age 3 to 19 years
- Metabolites of interest
  - NAA, Cho, Cr
- ROI from MRSI
  - GM (prefrontal, parietal, premotor/motor)
  - WM (premotor/motor, parietal)
  - Basal ganglia
  - Thalamus

Horska et al (2002)

- GM
  - NAA/Cho
    - peak around 11 years
    - decrease thereafter
- WM
  - NAA/Cho
    - increase (3 to 19 years)
- Putamen
  - NAA/Cho
    - increase until 10 years

Costa et al (2002)

Proton magnetic resonance spectroscopy: normal findings in the cerebellar hemisphere in childhood

- 37 healthy subjects
- Age 3 – 18 years
- Cerebellum, Parietal WM
- NAA/Cr, Cho/Cr
- NAA/H2O, Cr/H2O

Costa et al (2002)

- NAA/Cr
  - increasing tendency with age ($p=0.062$)
- NAA/H2O
  - increase with age in cerebellum, parietoccipital
- Topologic variation
  - NAA, Cho
    - higher in cerebellum than parietoccipital

Summary of ^{1}H metabolites[1]

- Brain metabolite profiles of life
  - Rapid change of metabolite occurs first several years in life
  - But, some maturation such as myelination continue to adolescence
- Consideration in MRS
  - Inconsistencies in studies partially due to …
    - Regional variations in each ROI
    - Different acquisition parameters for different MRS studies
  - Some conflicting MRS results but generally, ...

Summary of ^{1}H metabolites [2]

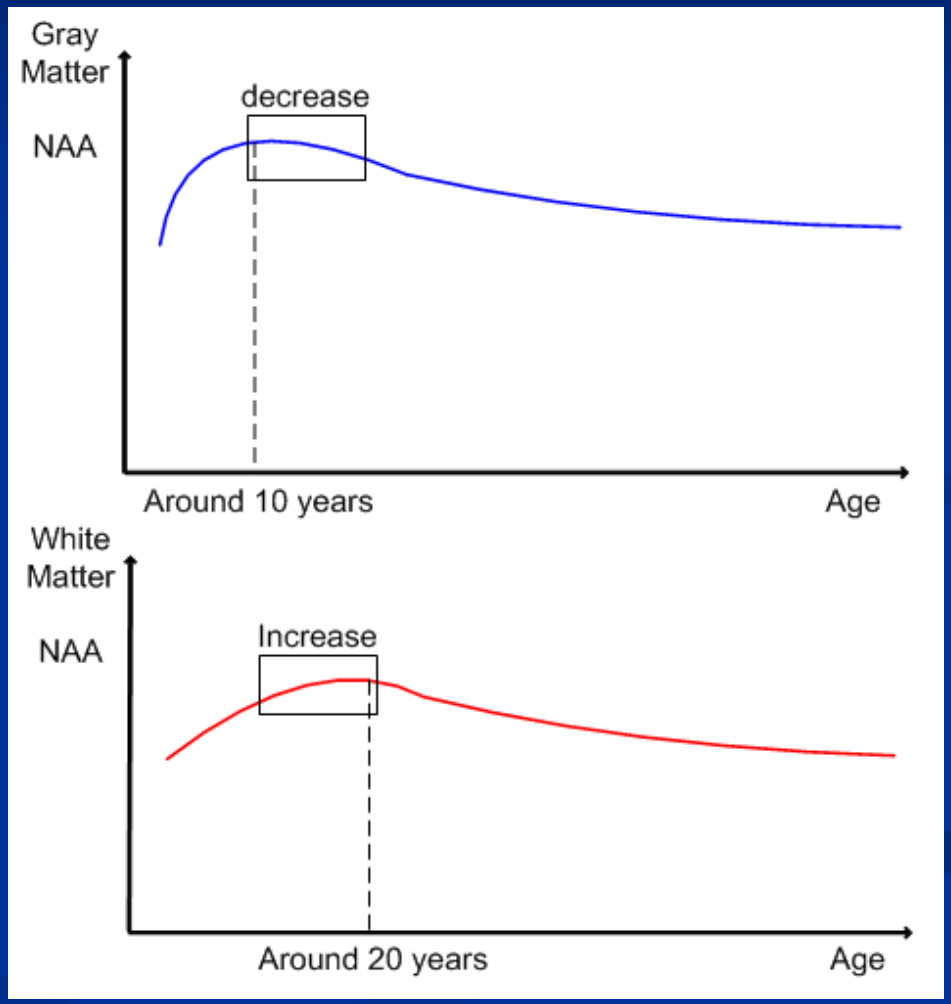
- Before maturation
  - From fetus/neonate to adults
    - NAA ↑
      - d/t increasing neuronal function/density
    - Cr ↑
      - increased energy demand
    - Cho ↓, mI ↓

Summary of ^{1}H metabolites[3]

- Aging (from adult to elderly, moore et al 1999)
  - NAA ↓ or →
    - slight decrease or stability of neuronal marker
  - Cr ↑, PCr ↑
    - Due to increased energy demand
  - Cho ↑, mI ↑
    - Due to phospholipid breakdown

Summary of ^{1}H metabolites [3]

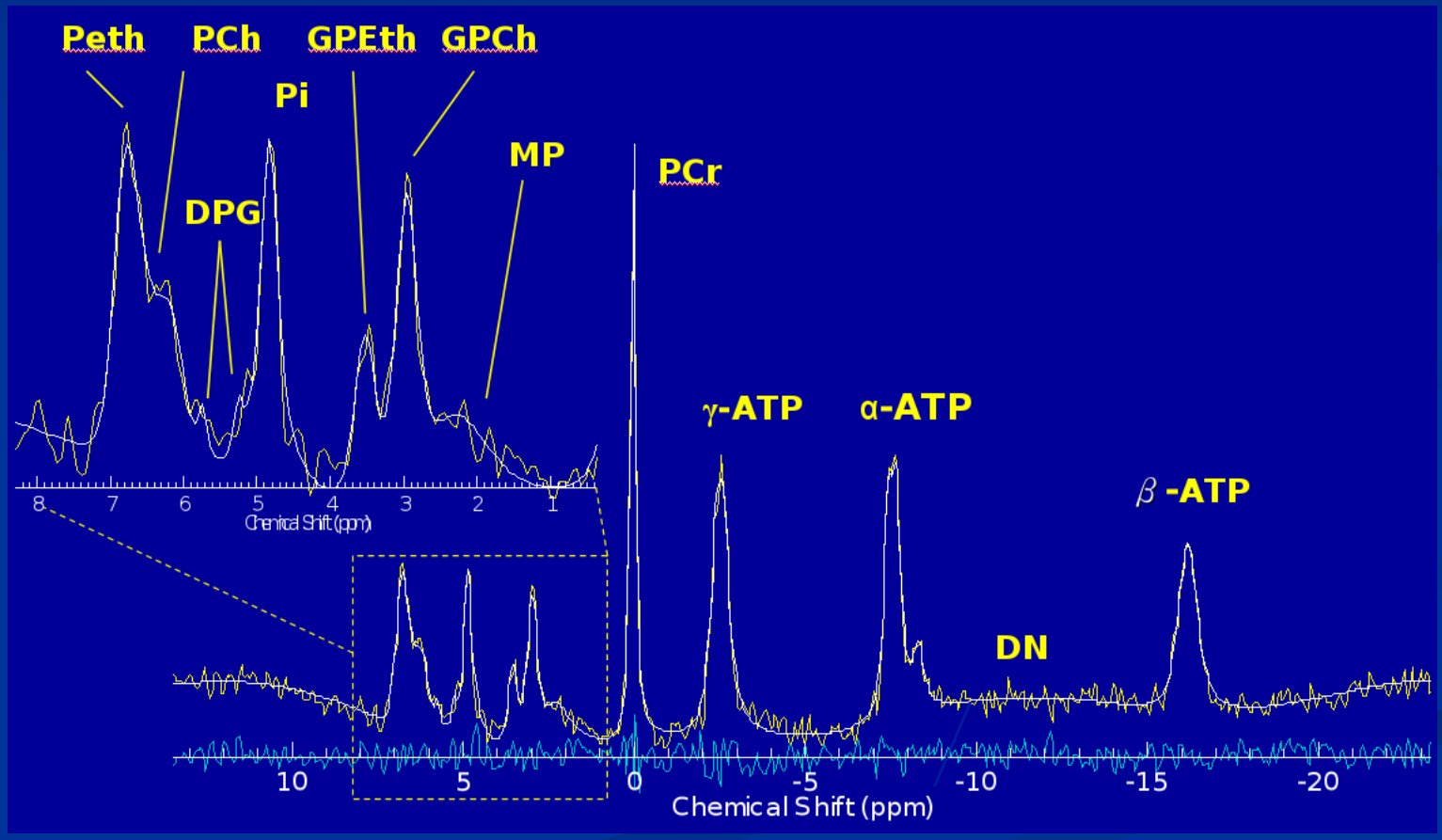
- Adolescence
  - NAA levels
  - Different profile between ..
  - GM
    - Peak – 11 years
      Horska et al (2002)
  - WM
    - Peak – 19 years
      Kadota et al (2001)
  - Could mean…pruning, loss of dendrite process in GM, myelination in WM



- Schematic diagram of NAA with age in gray and white matter

^{31}P MR Spectrum

- Typical ^{31}P MR spectrum at 4 Tesla



Phosphorus

- Lower sensitivity than proton
- Require more sophisticated hardware
- Relatively small number of studies

Phosphorus metabolites

- PME
  - Phospholipid precursor
    - phosphocholine (PCho) +phosphoethanolamine
- PDE
  - Phospholipid breakdown
    - glycerophosphocholine + glycerophosphoethanolamine
- PME/PDE ratio
    - Reflects membrane phospholipid turnover
- PCr, ATP (NTP)
  - High energy phosphate metabolism

Age-dependent Changes in Localized Proton and Phosphorus MR Spectroscopy of the Brain

Marjo S. van der Knaap, MD • Jeroen van der Grond, PhD • Peter C. van Rijen, MD • Joop A. J. Faber, PhD • Jaap Valk, MD, PhD • Kobus Willemse, MD, PhD

van der Knaap et al (1990)

- Healthy children (41 subjects)
  - Age: 1 – 16 years
- Before the age of three
  - PME/β-ATP, PME/PCr
    - decrease
  - PDE/β-ATP, PCr/β-ATP
    - increase
  - PCr/Pi
    - increase
- After the age of three
  - No change

Study of the Maturation of the Child's Brain Using ^{31}P-MRS

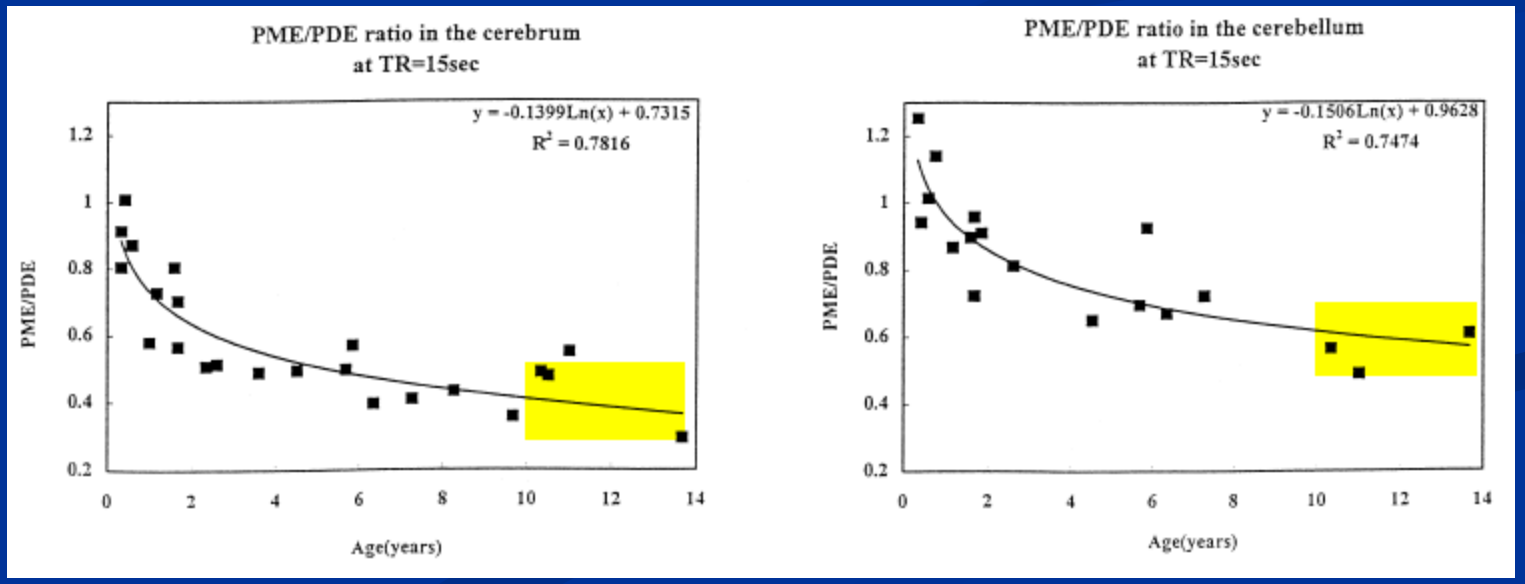
Shigeru Hanaoka, MD*, Sachio Takashima, MD†, and Keiichi Morooka, MD‡

Hanaoka et al (1998)

- 37 healthy children
- 4 month ~ 13 years
- Metabolites: PME/PDE
- TR: 3 or 15 seconds
- ROI
  - Frontoparietal region
  - Cerebellum

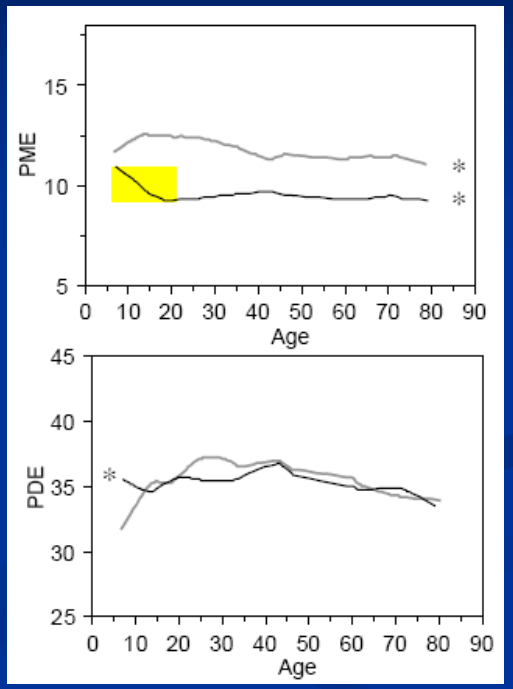
Hanaoka et al (1998)

- PME/PDE in cerebrum and cerebellum
  - Rapid decrease during first 2 years.
  - Slight decrease afterwards (adolescence)
  - Regional difference
    - Higher in cerebellum than in cerebrum



Stanley et al (2000)

- 151 healthy subjects
- 7 to 81 years
- Brain ROI
  - Prefrontal lobe
  - Centrum semiovale WM
- PME/PDE
  - Higher in adolescents compared to adults
    - Increased membrane phospholipid turnover in adolescents relative to adults



Magnetic Resonance Imaging Volumetric and Phosphorus 31 Magnetic Resonance Spectroscopy Measurements in Schizophrenia

Hinsberger et al (1997)

- P-31 MRS with MR volumetric study in schizophrenia
  - Prefrontal region
- 10 healthy subjects, 10 schizophrenics
  - PME decreased with age only in healthy subjects
  - PME of schizophrena had no correlation with age

Summary of ^{31}P metabolites[1]

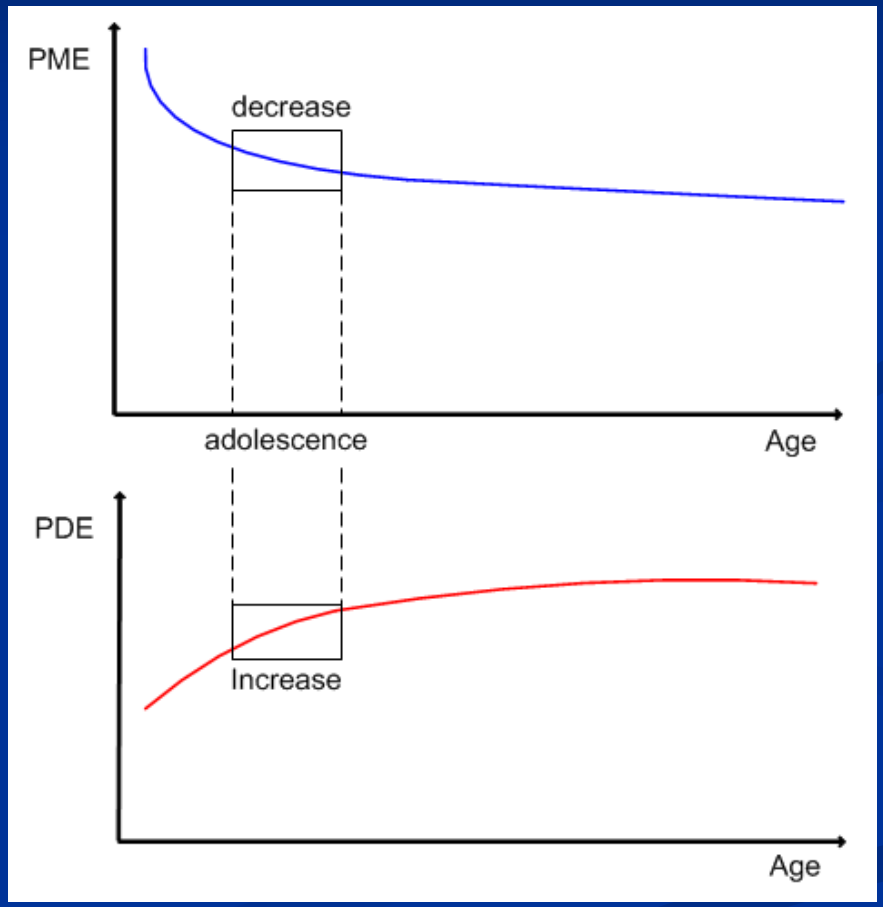
- Before maturation
  - PME – high, PDE – low in young
    - high membrane precursor, low breakdown product
    - related to increased membrane turnover
  - From neonates to adults (mmol/L), Buchli et al. (1994)
    - PME ↓ (from 4.5 to 3.5)
    - PDE ↑ (3.2 to 11.7)
    - PCr ↑ (1.4 to 3.4)
    - Pi ↑ (0.6 to 1.0)
    - ATP ↑ (1.6 to 2.9)

Summary of ^{31}P metabolites[2]

- Aging (adults to elderly, moore et al 1999)
  - PME ↓, PDE ↑
    - Due to neuronal membrane degeneration
- Excessive synpatic prunning clinical model
  - Schizophrenia
    - exaggerated normal process of neuro-development
    - PME decrease, PDE increase
    - might be related to pathophysiology of schizophrenia
      - McGlashan, 1999; Keshavan 2003, 1994

Summary of ^{31}P metabolites[3]

- Adolescence
  - PME ↓
  - PDE ↑
  - Decreasing precursor, increasing breakdown product of phospholipid of membrane



- Schematic diagram of PME and PDE with age

Conclusion

- MRS, MRSI can provide valuable information of *in vivo* adolescent brain development through neuronal chemistry and can evaluate normal or diseased brain
- The metabolite levels show different profile with maturation and topology, therefore the data of normal development provide fundamental and valuable basis for pathologic process or disorders

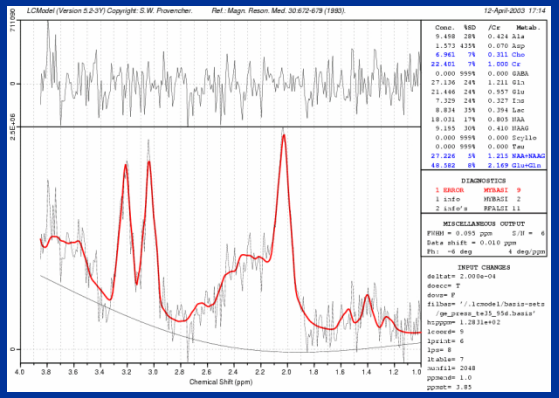
Application

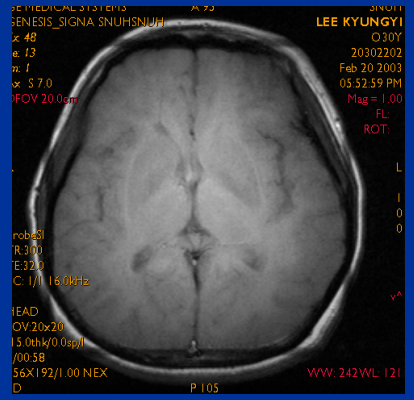
MRS
as a component of multimodal imaging studies

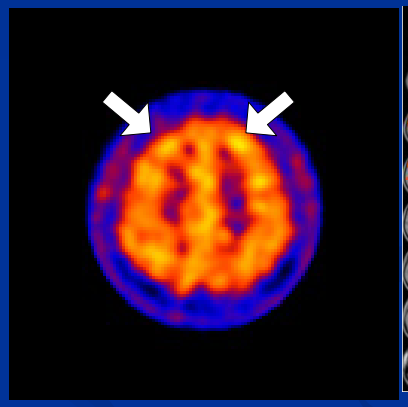
- DA09448-09S1 Results
Neuroimaging of Methamphetamine Dependent Subjects
2003-2005

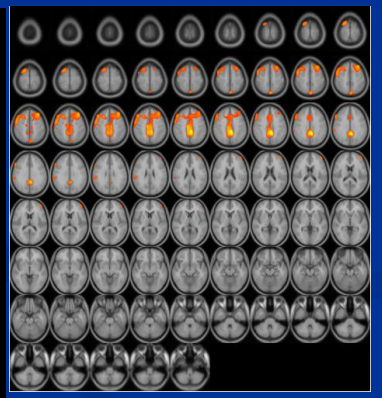
Completed studies

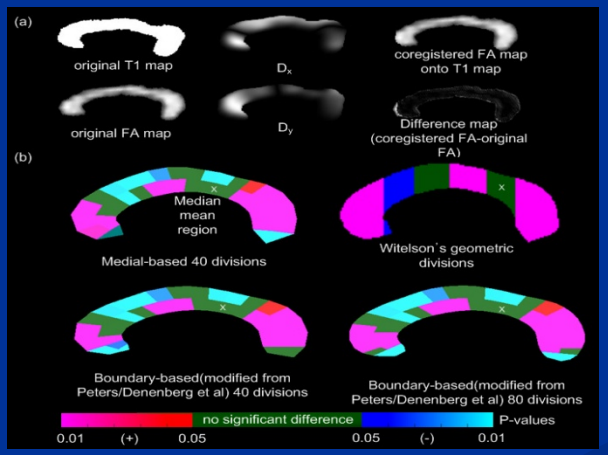
- Seven neuroimaging studies with publications
  - A multimodal brain imaging approach enables in-depth and complementary understanding of prefrontal cortical deficits and the pattern of recovery with abstinence.

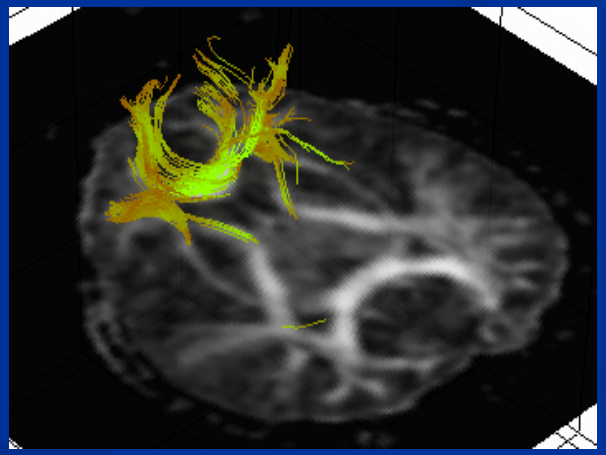


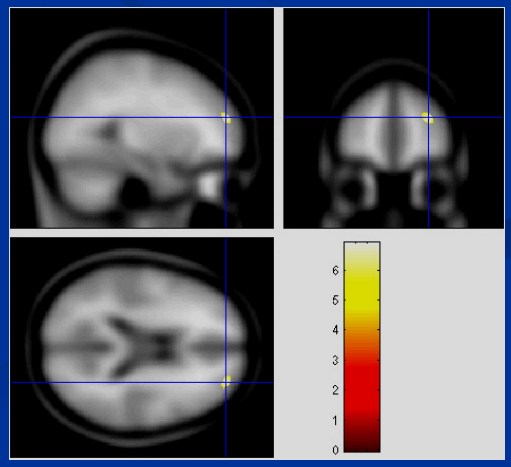








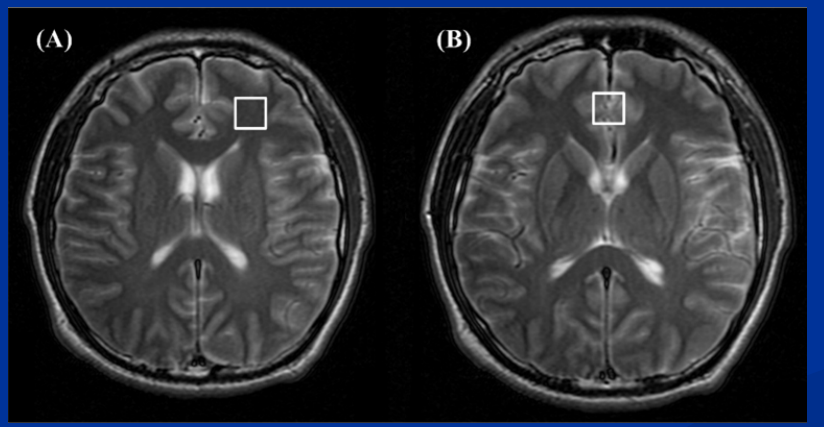


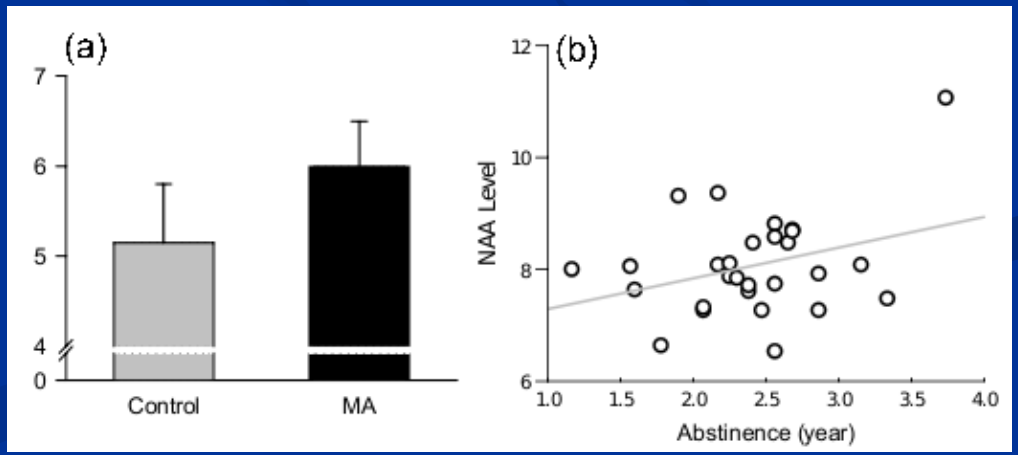


Relationship between *N*-acetyl-aspartate in gray and white matter of abstinent methamphetamine abusers and their history of drug abuse:

MRS study of brain chemistry (Sung et al, 2007)

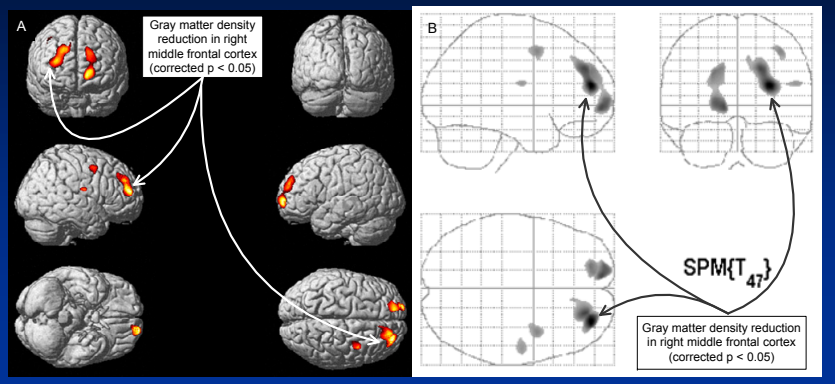
- 30 MA dependent and 20 healthy comparison subjects
- NAA concentration was lower in the frontal white matter of MA users with greater MA dose compared to a smaller dose and to healthy subjects
- *myo*-Inositol concentration in the frontal white matter was higher for the MA users compared to healthy subjects
- In MA dependent subjects, NAA concentrations correlated inversely with MA dose
- MA related abnormalities may, in part, recover with abstinence in gray matter, but not in the white matter regions



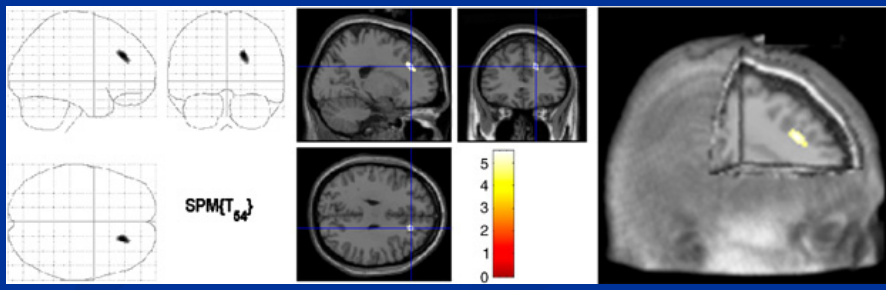


MA subjects are…

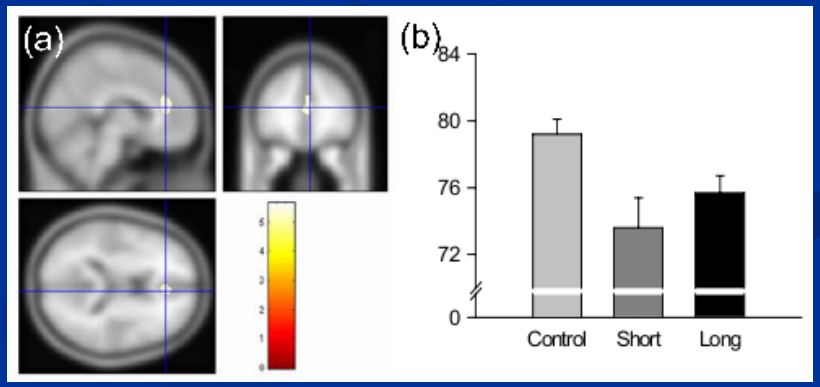
- MA dependent subjects had less gray matter density in the right middle frontal brain ; Voxel-based morphometry study (Kim et al, 2006)



- Lower cerebral glucose metabolism levels in the right superior frontal white matter ; FDG-PET study of brain glucose metabolism (Kim et al., 2005)

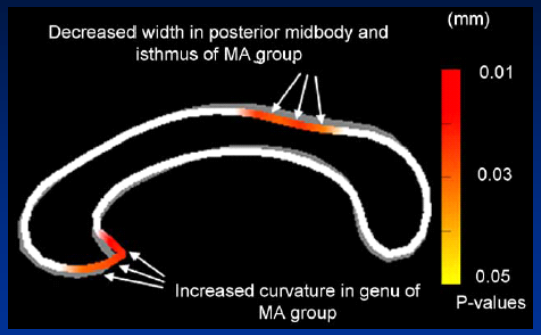


- Decreased relative rCBF in the right anterior cingulate cortex ; SPECT study of relative blood flow in brain (Hwang et al., 2006)

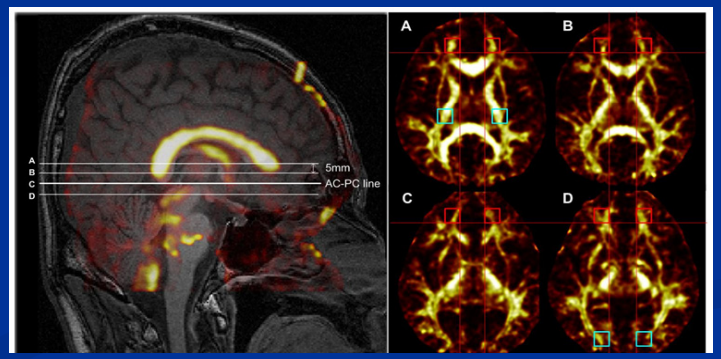


MA subjects are…

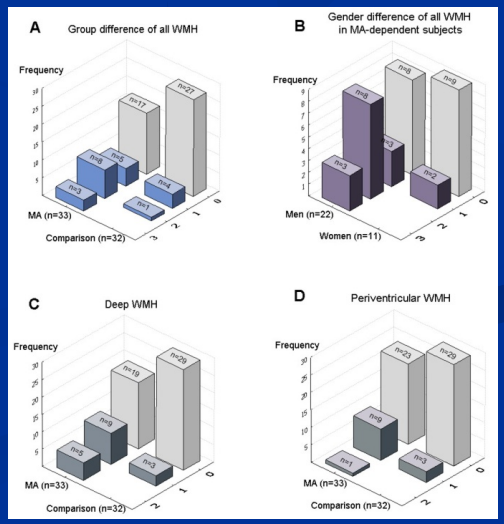
- Increased curvature in the genu; decreased width in posterior midbody; decreased width in isthmus area ; Corpus callosum shape and size analysis (Oh et al., 2005)



- MA dependent adults had lower white matter integrity values in frontal WM compared to healthy subjects ; DTI study (Chung et al., In press)



- MA users had greater severity of WMH compared to healthy subjects ; White matter hyperintensities study (Bae et al, 2006)



Pilot study

- 14 MA users (age=18.8±2.26 years; male/female=10/4) and 14 healthy comparison subjects (age=18.7±2.29 years; male/female=10/4)
  matching for age, sex, education and parent's socioeconomic status

- Months of active MA use=21.0±7.65
  lifetime cumulative number of intravenous shots=139.8±113.2.
  (One intravenous shot of 0.3 gram is typically used at a time in South Korea typically induces 3-5 hours of euphoria and 48-72 hours of excitement and hypervigilance.)

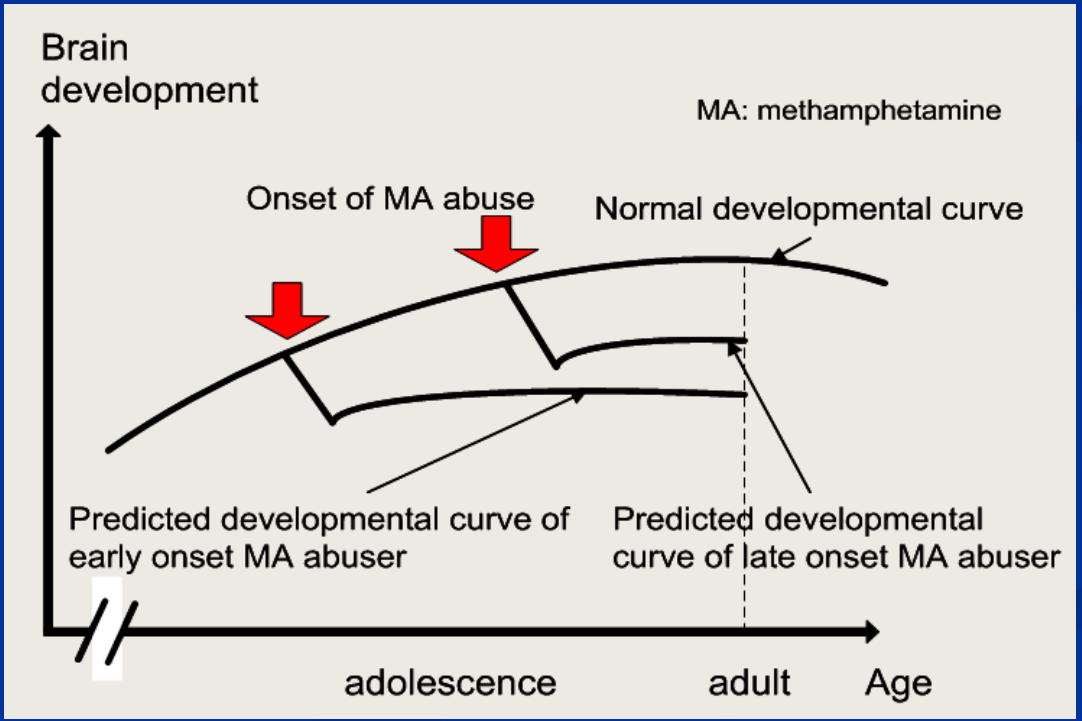
- Structural T1, DTI and 1H-MRS

- Sponsored in part by a Strategic Priority Research Grant of Seoul National University Hospital (SNUH)(21-2003-007-0), matched funds for DA09448-09S1

Hypotheses

- MA dependent adolescents will have neurobiological deficits in the frontal lobes (decreased gray matter density, white matter integrity, and neuronal viability)

- A more profound neurobiological deficit in adolescents with early-onset MA abuse will be observed when compared to those with late-onset MA abuse.



MRS study in adolescent and young adult MA users

- NAA concentrations lower in adolescent MA users (n=12) compared to healthy subjects (n=13) in frontal white matter ROI

- Age of onset positively correlated with frontal white matter NAA concentration

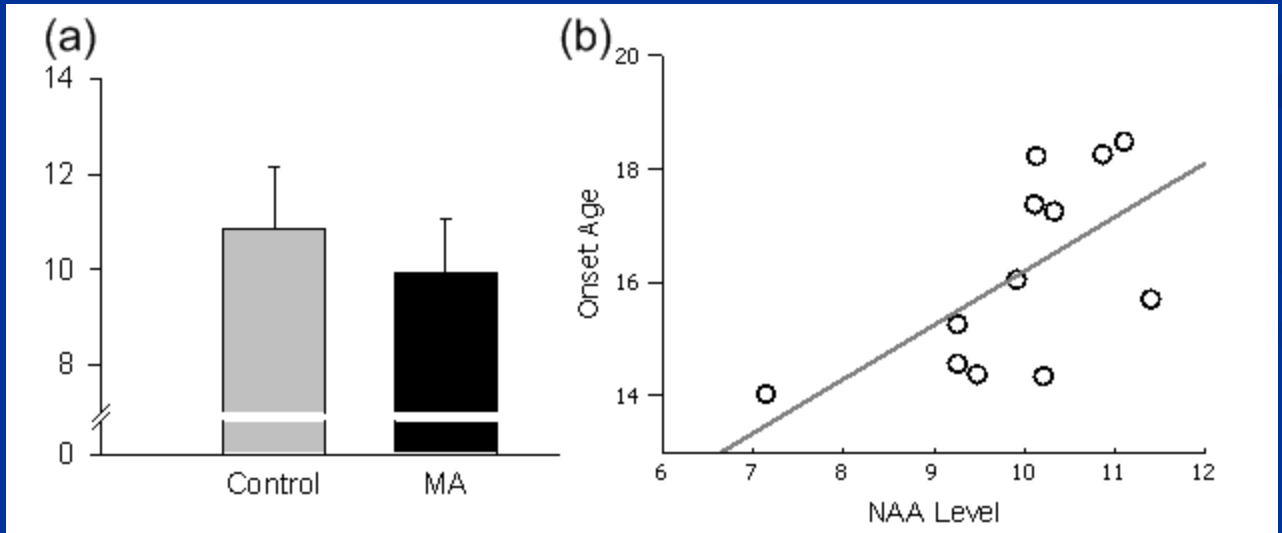
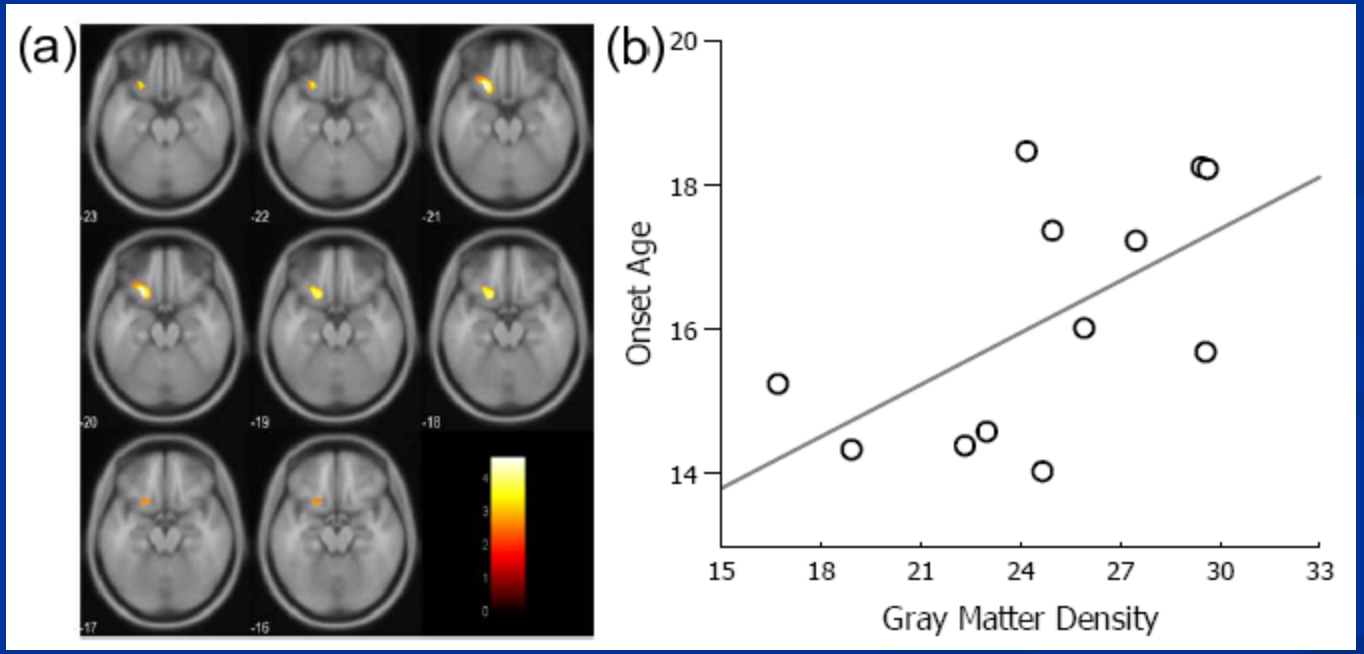


Figure. *N-acethyl-aspartate (NAA) measurement in adolescent methamphetamine (MA) users (a) Decreased N-NAA concentration of adolescent MA users relative to healthy comparison subjects (t=1.94, df=24, p=0.065), (b) Correlation between NAA concentrations in frontal white matter and onset age of adolescent MA users (r=0.63, p=0.029)*

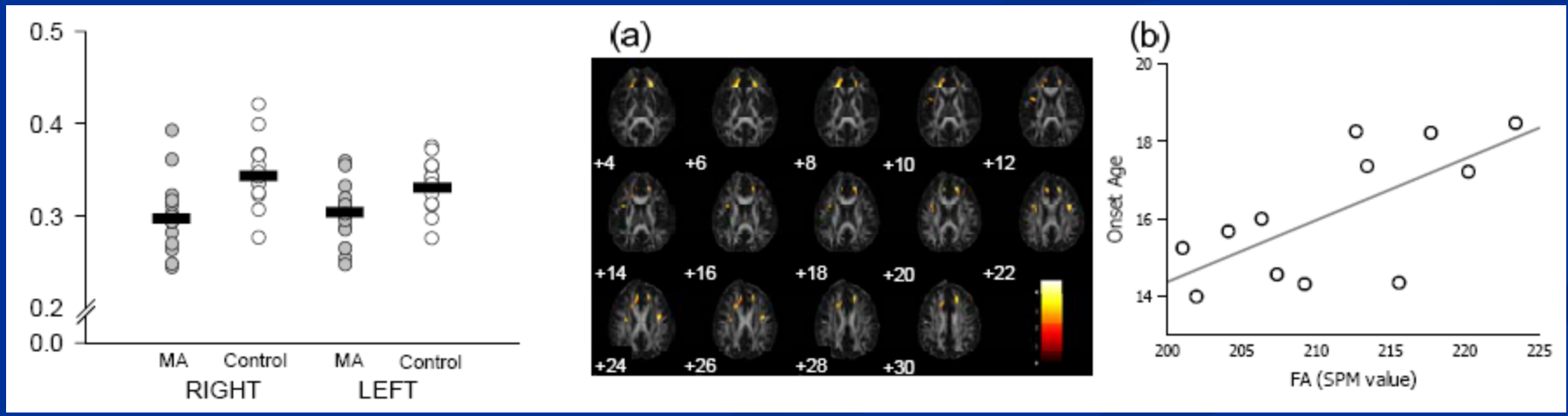
Gray matter density differences in adolescent and young adult MA users

- Adolescent MA users had decreased gray matter densities in the left orbitofrontal lobe
- Age of onset of MA exposure positively correlated with orbitofrontal gray matter densities



White matter integrity differences in adolescent and young adult MA users

- ROI analysis:
  - Adolescent MA users had smaller white matter integrity values in the frontal ROI compared to healthy subjects
- Voxel-based analysis:
  - Decreased white matter integrity values in bilateral medial frontal regions of the brain
  - Age of onset of MA abuse strongly correlated with left medial frontal white matter integrity values



Summary of pilot study

- Adolescent MA users may have neurobiological deficits in frontal regions of the brain:
  - Gray matter density decrease in orbitofrontal region
  - Neuronal viability decrease in the frontal white matter
  - White matter integrity decrease in several frontal regions of the brain
- The pattern of MA-related toxicity on the developing brain may differ from the adult brain
- Age of MA exposure seems to play an important role in MA-induced neurobiological deficit