Lifespan Brain Institute of CHOP & UPenn

Session on Modern Tools in Neuroscience and Tumor Immunogenicity Research

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Neuroscience Graduate Group
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The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Developing a Long-Term Strategy for Low-Dose Radiation Research in the United States
Tuesday, November 16, 2021

Lifespan Brain Institute of CHOP & UPenn

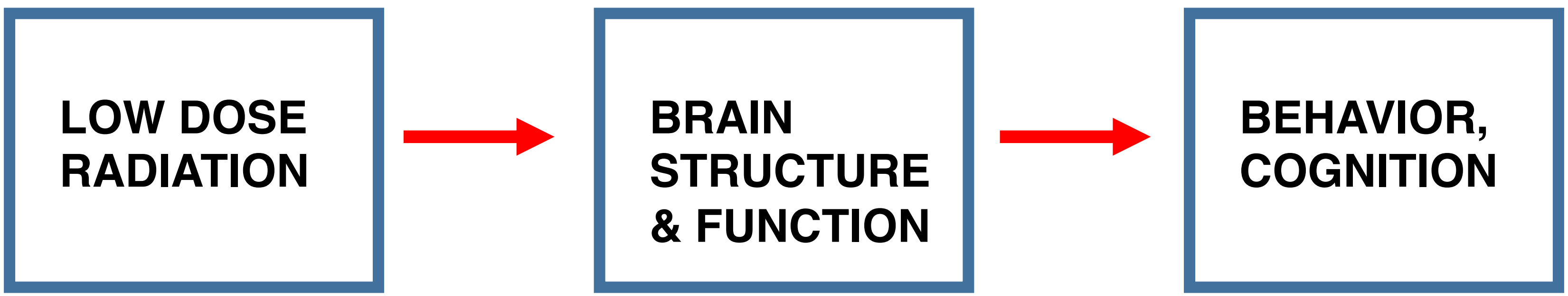
Tools for structural and functional neuroimaging

- ☐ Application of these tools following radiation exposures (with examples)

- ☐ Opportunities and challenges to use these techniques in low dose radiation exposures.

- ☐ Views on research priorities

Understanding effects of low dose radiation requires linking radiation to brain aberrations as they relate to behavioral domains



THE NEUROIMAGING REVOLUTION

Neuroimaging made available a plethora of tools for studying brain structure and function

STRUCTURAL

X-ray CT

MRI

- **Volumetric**
- **Structural Connectivity (DWI/DTI)**
- **Spectroscopy**

FUNCTIONAL

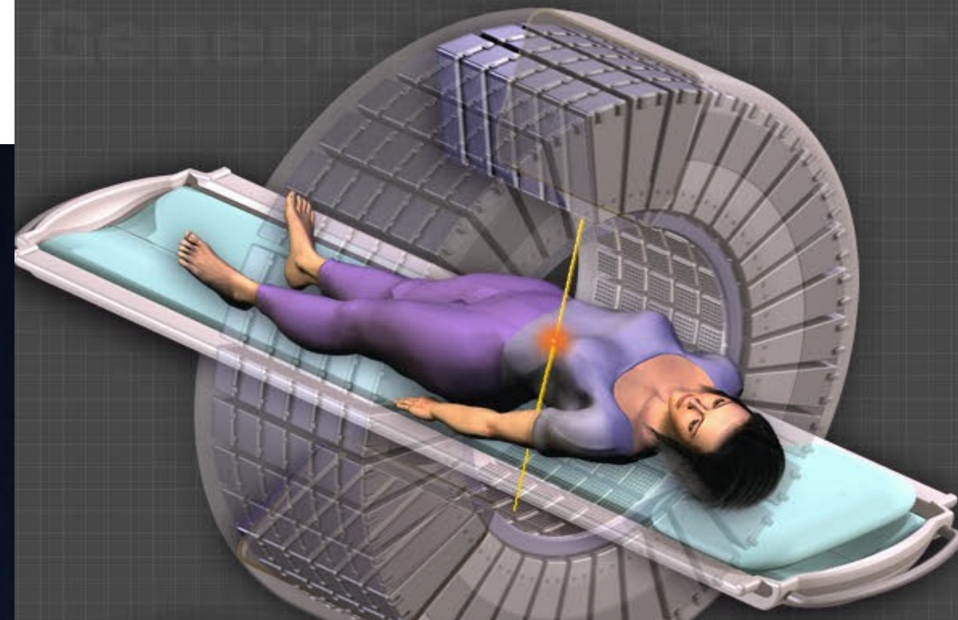
PET

- **Cerebral glucose metabolism**
- **Cerebral oxygen metabolism**
- **Cerebral blood flow**
- **Receptor availability**

Functional MRI (fMRI)

- **BOLD fMRI**
    - **Task Activated**
    - **Resting State Functional Connectivity**
- **ASL Quantitative CBF**

Positron Emission Tomography (PET)



Clockwise from bottom left, images from:
www.robinsonimaging.org/TICK_photos/online_tour/Pet2.jpg
www.griffwason.com/pet_scanner.htm, and img2.timeinc.net/health/images/health-news/positron-emission-tomography-200.jpg (accessed 12/4/09).

PET images of Mr. XX's brain.

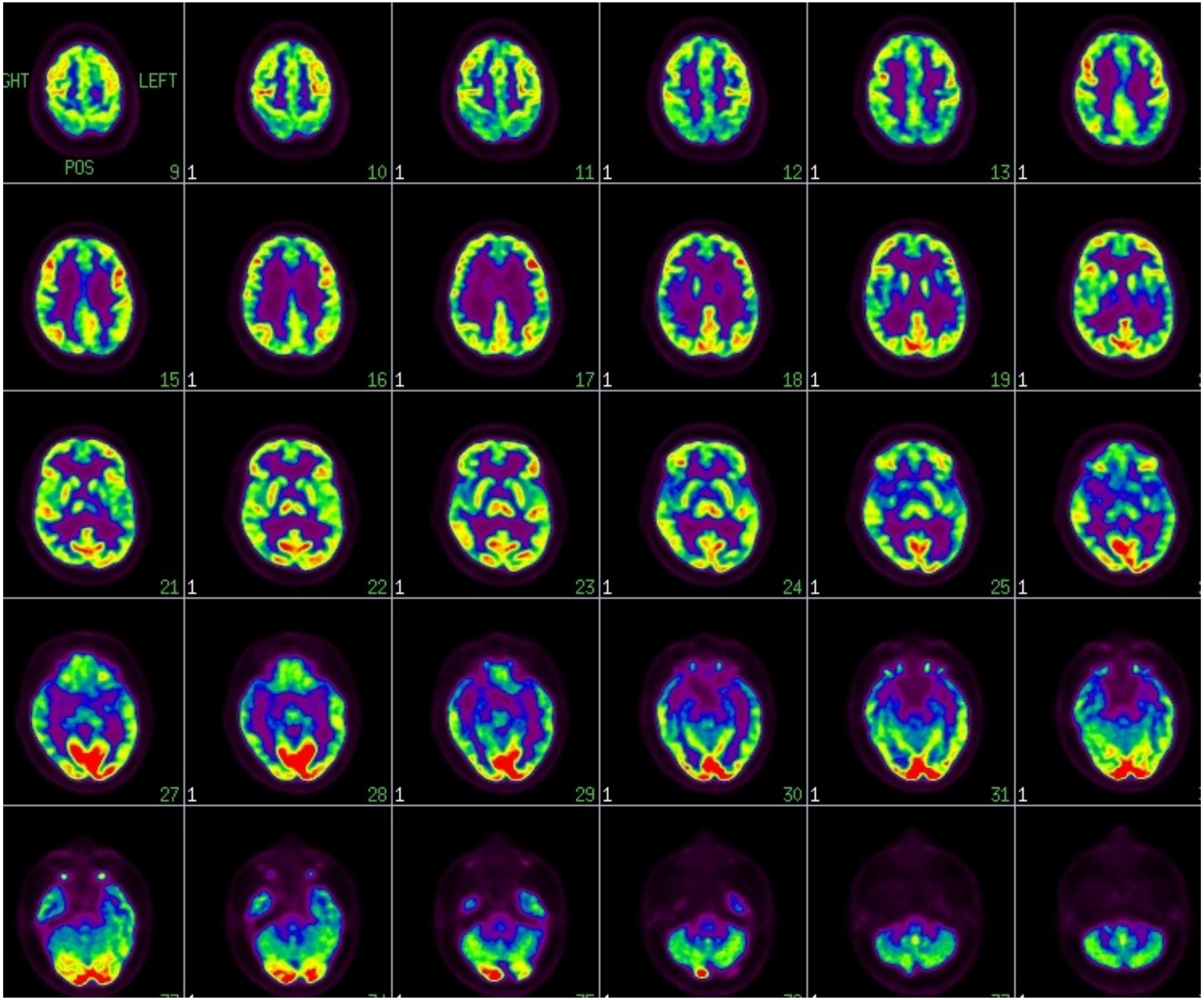
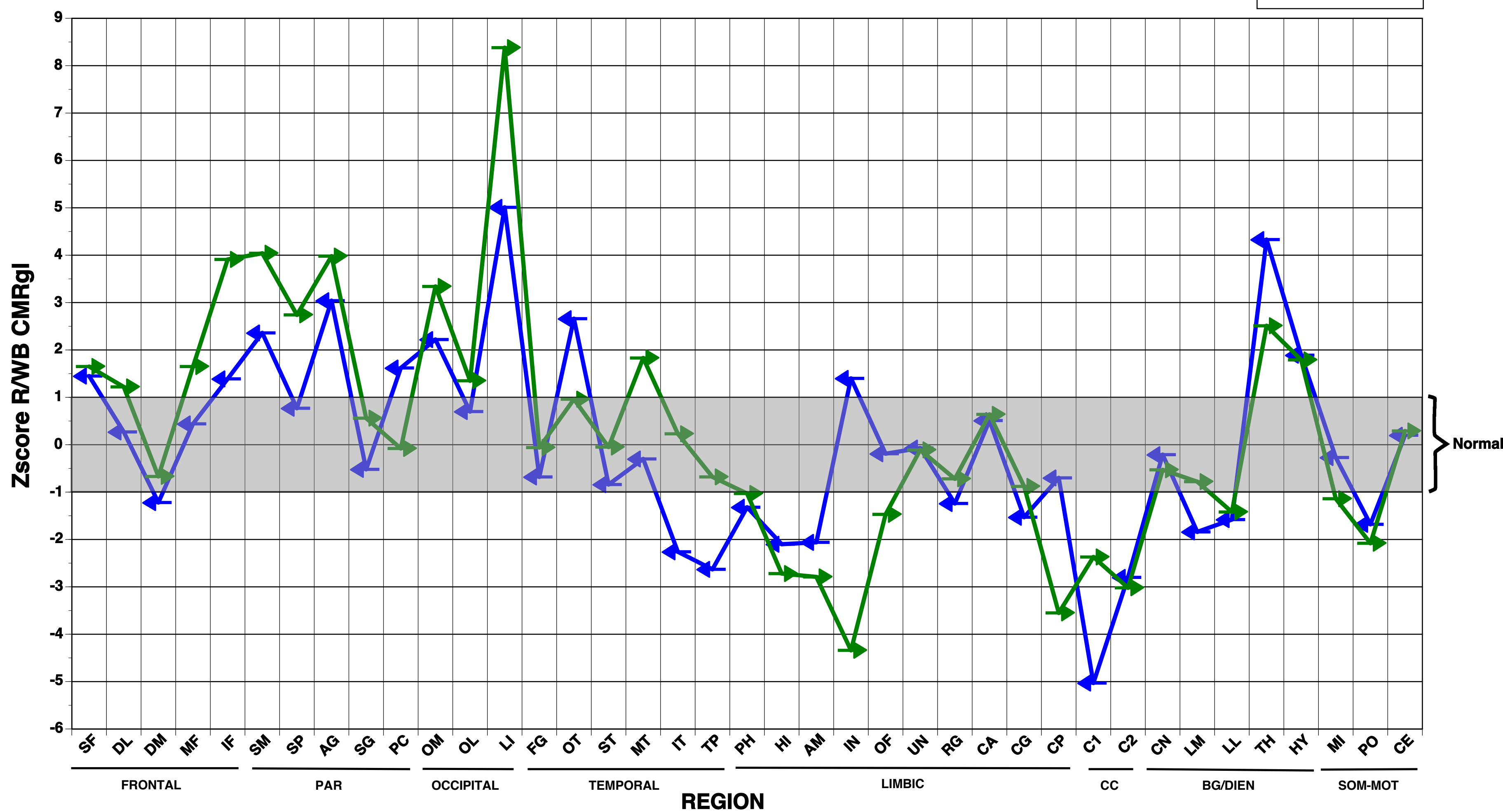
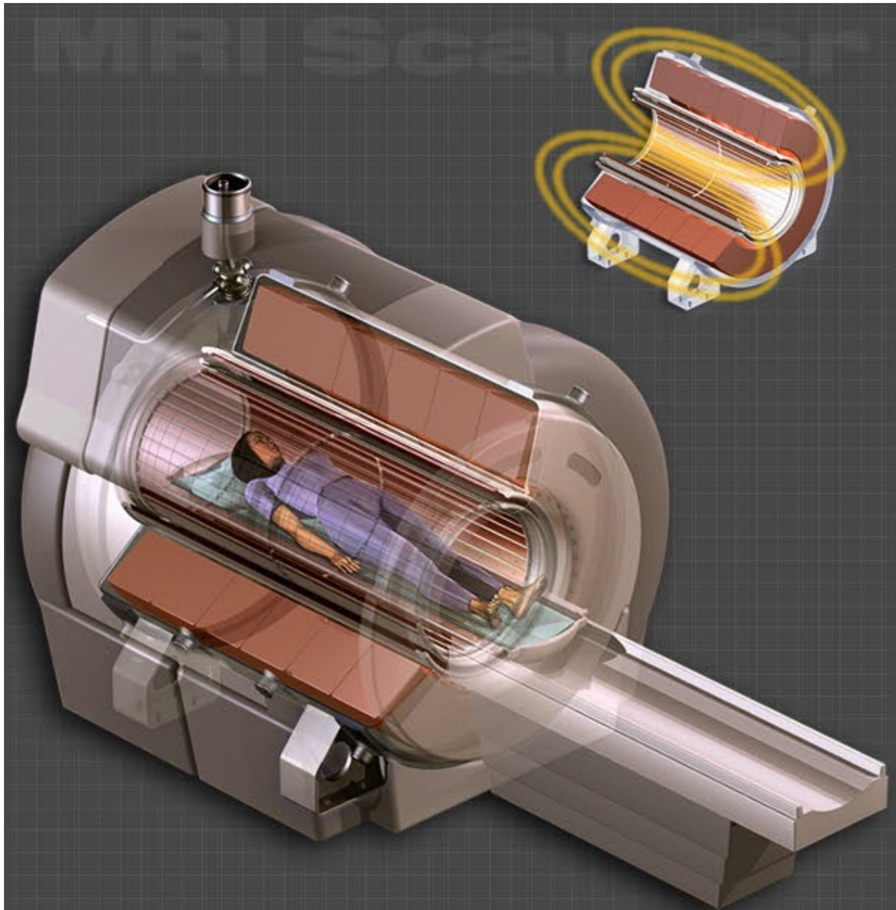


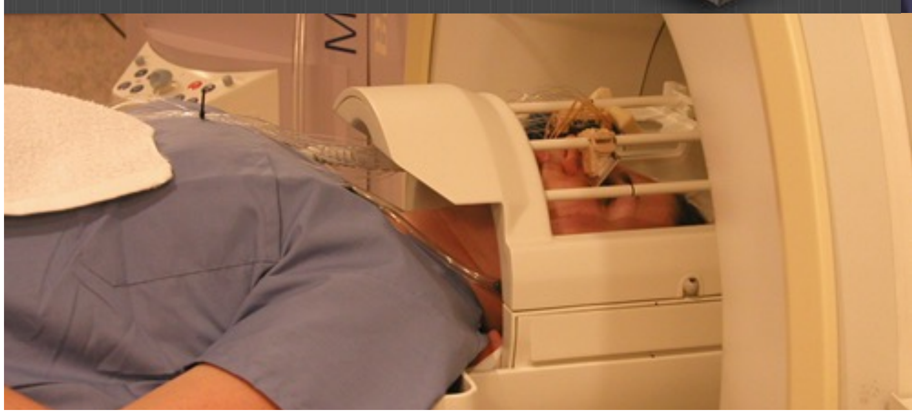
Figure 3: PET region-whole brain ratio (R/WB) results for cerebral metabolic rates for glucose (CMRgl) in Mr. [redacted] Results are expressed as Z-scores relative to a comparison group of healthy people.



SF = Superior Frontal; DL = Dorsal Prefrontal - Lateral; DM = Dorsal Prefrontal - Medial; MF = Mid-Frontal; IF = Inferior Frontal; SM = Sensorimotor; SP = Superior Parietal; AG = Angular Gyrus; SG = Supramarginal Gyrus; PC = Precuneus; OM = Occipital cortex, Medial; OL = Occipital cortex, Lateral; LI = Lingual Gyrus; FG = Fusiform Gyrus; OT = Occipital Temporal; ST = Superior Temporal; MT = Mid-Temporal; IT = Inferior Temporal; TP = Temporal Pole; PH = Parahippocampal Gyrus; HI = Hippocampus; AM = Amygdala; IN = Insula; OF = Orbital Frontal; UN = Uncus; RG = Rectal Gyrus; CA Cingulate Gyrus = Anterior; CG = Cingulate Gyrus - genu; CP = Cingulate Gyrus - Posterior; C1 = Corpus Callosum - Anterior; C2 = Corpus Callosum - Posterior; CN = Caudate Nucleus; LM = Lenticular - Medial [Globus Pallidus]; LL = Lenticular - Lateral [Putamen]; TH = Thalamus; HY = Hypothalamus; MI = Midbrain; PO = Pons; CE = Cerebellum.

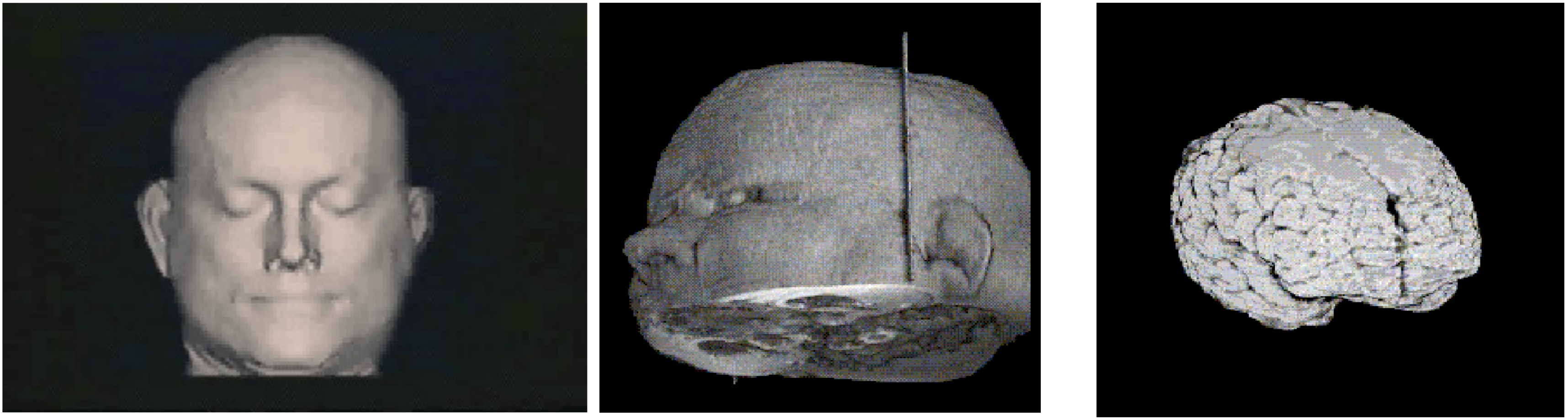
Magnetic Resonance Imaging (MRI)

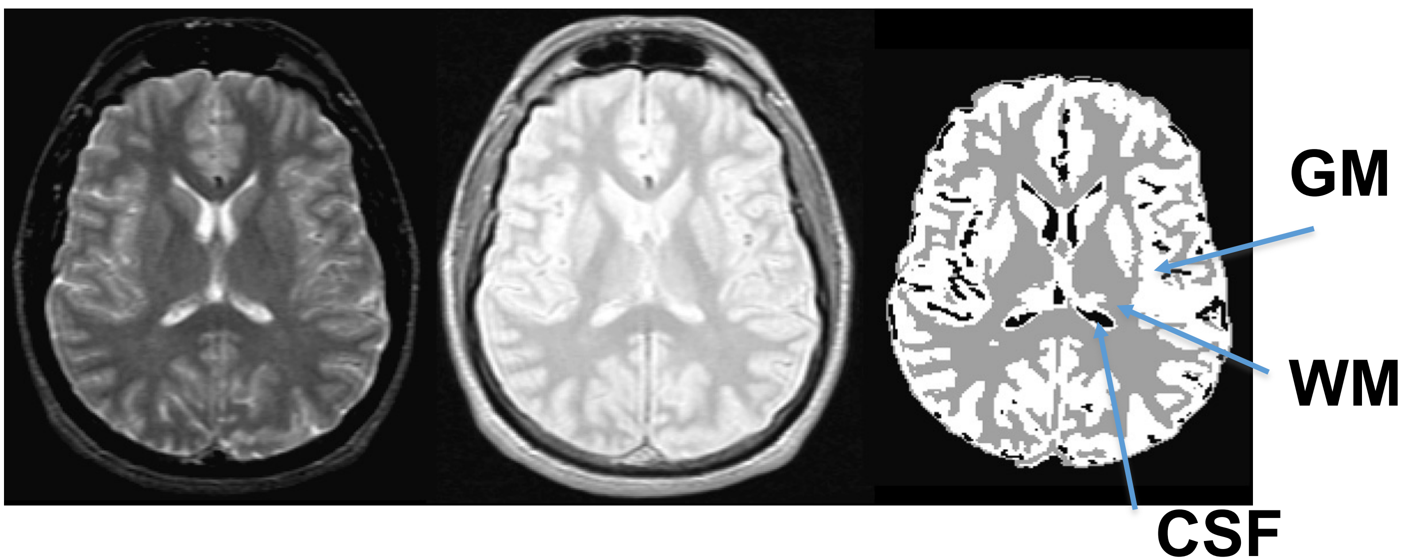




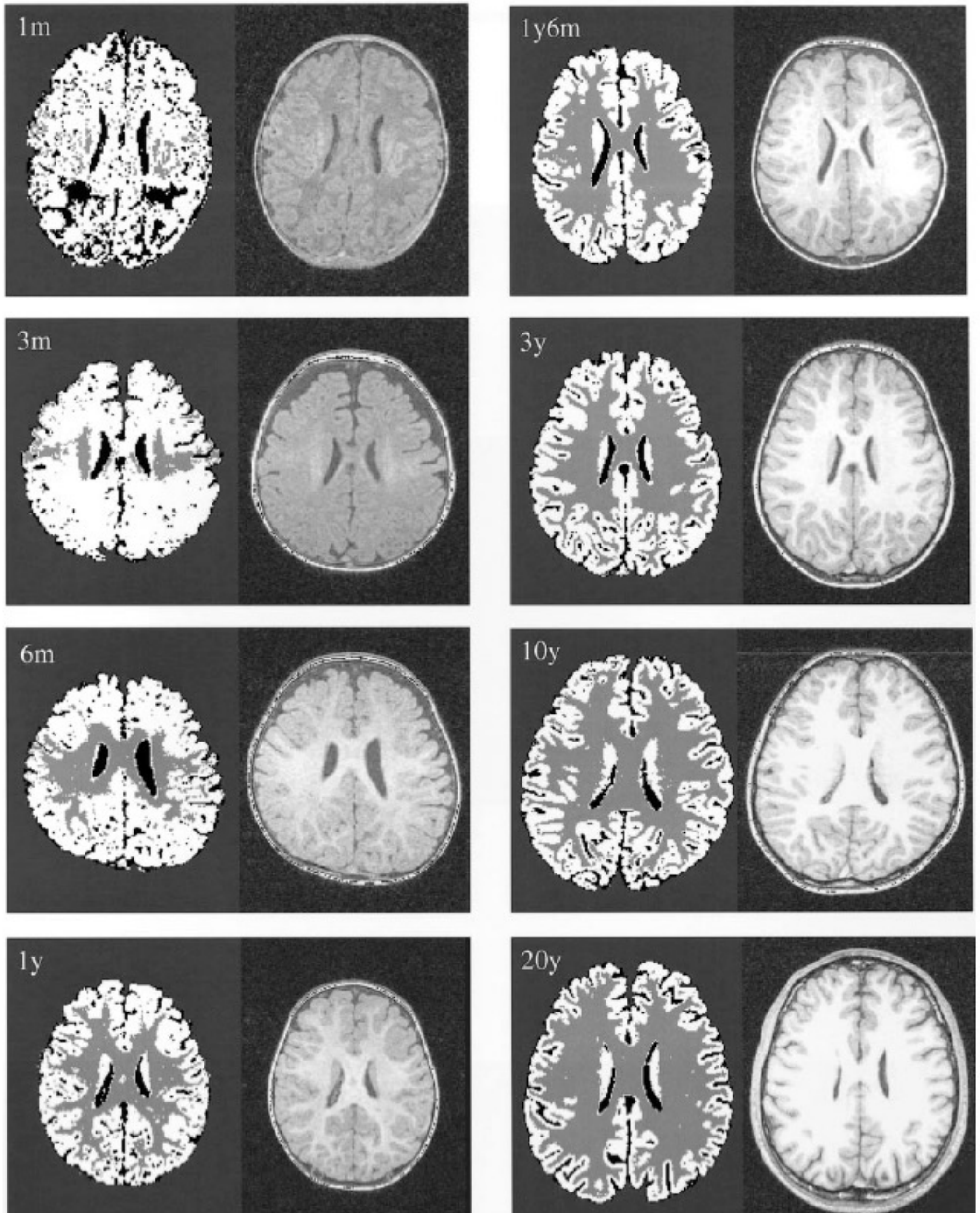
Clockwise from bottom left, images from:
lcni.uoregon.edu/images/gallery/Machine1500x375.png,
www.griffwason.com/mri_scanner1.htm, and
biologybiozine.com/images/tech_09.jpg (accessed 12/4/09).

MRI Segmentation





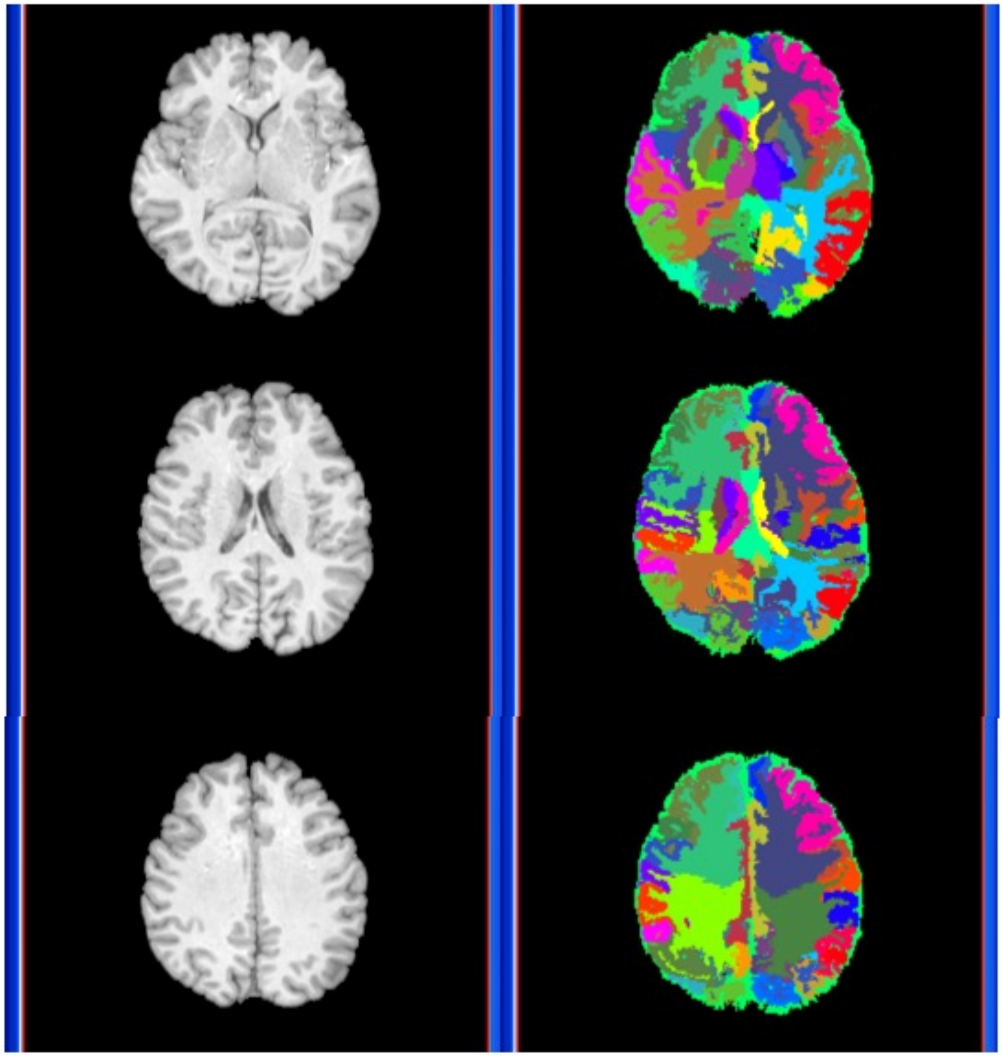
Gur et al., J Neurosci 1999



Neuroanatomic measures in healthy development

Matsuzawa et al., Cerebral Cortex, 2001

Regions of Interest



Original image

(skull removed)

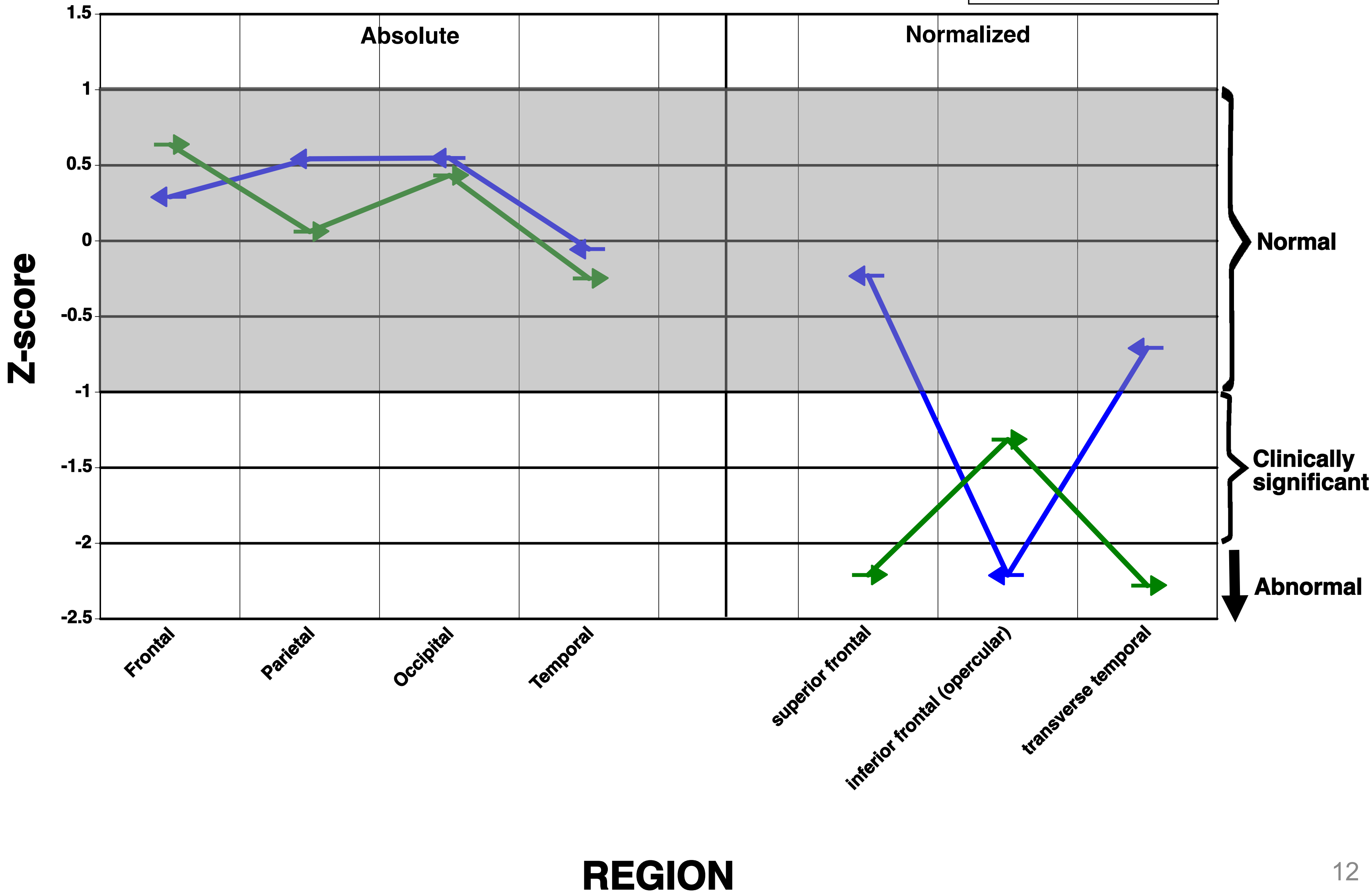
Labelled Image

(each color represents a Region of Interest)

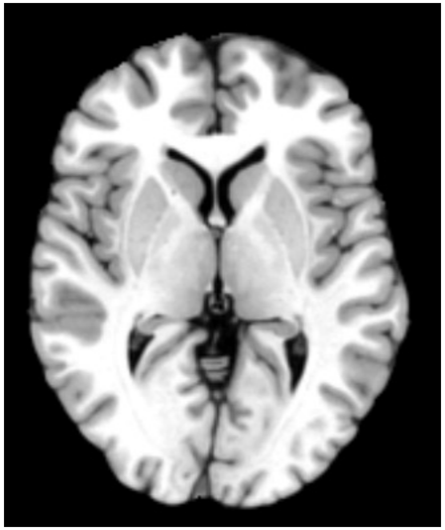
Neurologic convention
Pt. Left is on left

Courtesy Christos Davatzikos

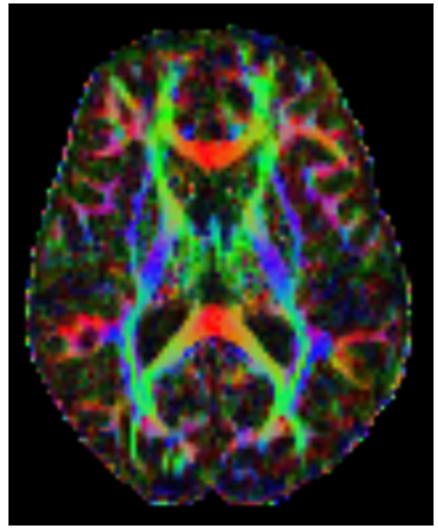
Figure 1: Volumetric analysis of Mr. [redacted]'s MRI. Volumes are expressed as absolute z-scores (SDs from the mean) relative to healthy individuals.



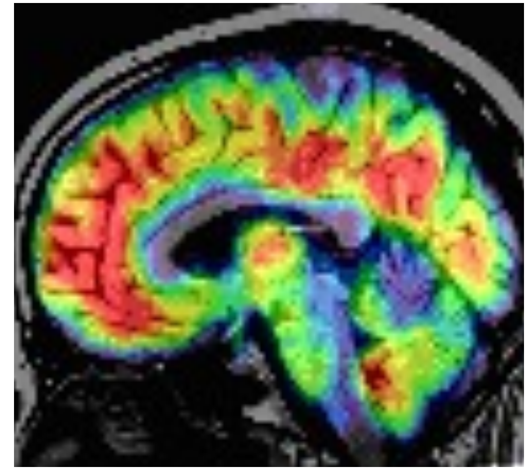
MRI Protocol - Overview



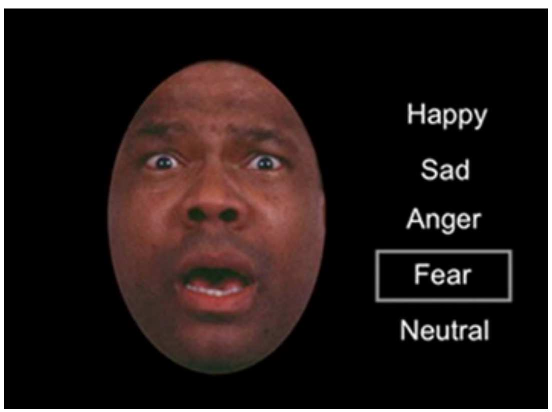
T1-weighted structural (3:28)



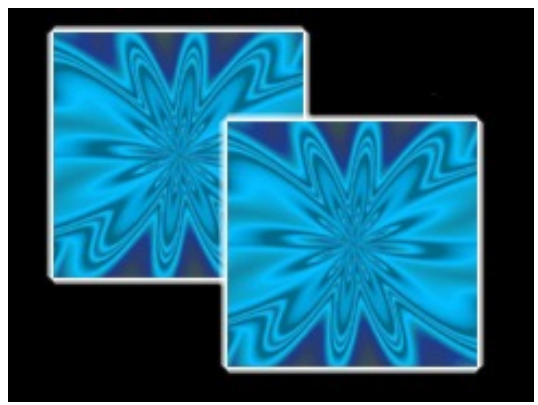
Diffusion Tensor imaging (10:56)



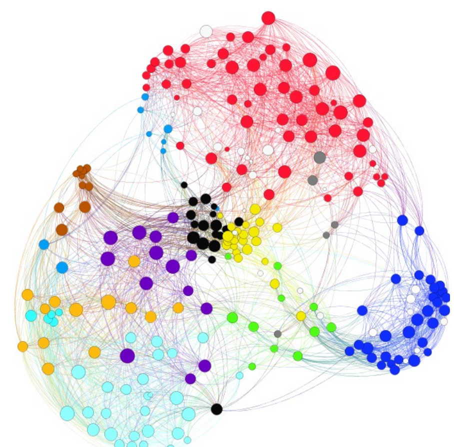
ASL Perfusion (5:32)



fMRI: Emotion Identification (10:36)



fMRI: Fractal *n*-Back (11:39)



fMRI: Resting State (6:18)

Total scan time : 50 minutes

Satterthwaite et al., Neuroimage 2013

Volume vs GMD

Gennatas et al. • Gray Matter Development in Adolescence

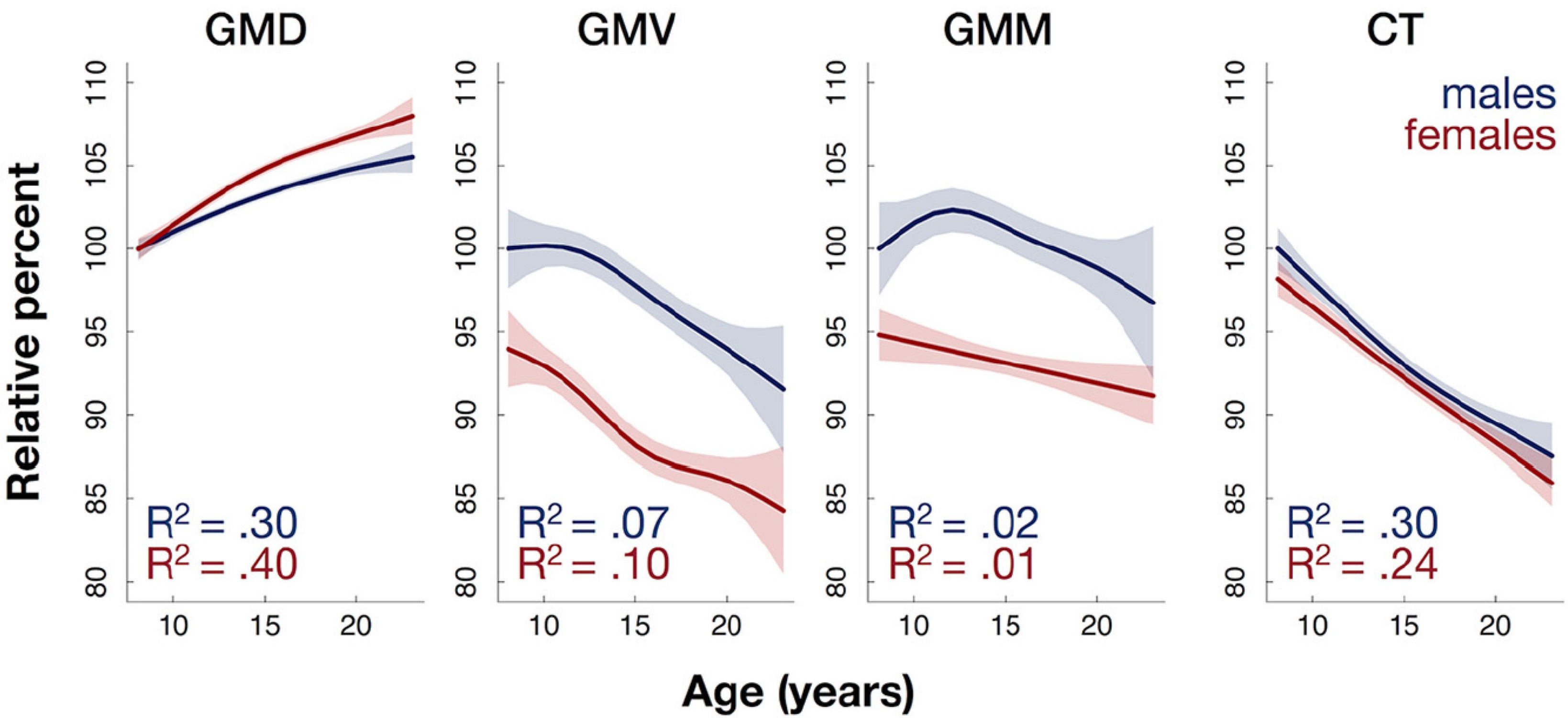


Figure 2. Density increases in adolescence while other measures largely decrease. Females have higher density and lower volume. Plots show fitted values of whole-brain gray matter measures against age for the two sexes. GMD and CT were averaged across the brain (weighted by *N* voxels in each parcel), and GMV and GMM were summed. To make results comparable across measures, they are plotted as percentages: 100% is defined as the fitted value for males at 8 years of age. Shaded bands correspond to $\pm 2 \times$ SE of the fit ($\sim$95% confidence interval).

Gennatas et al., J Neurosci, 2017

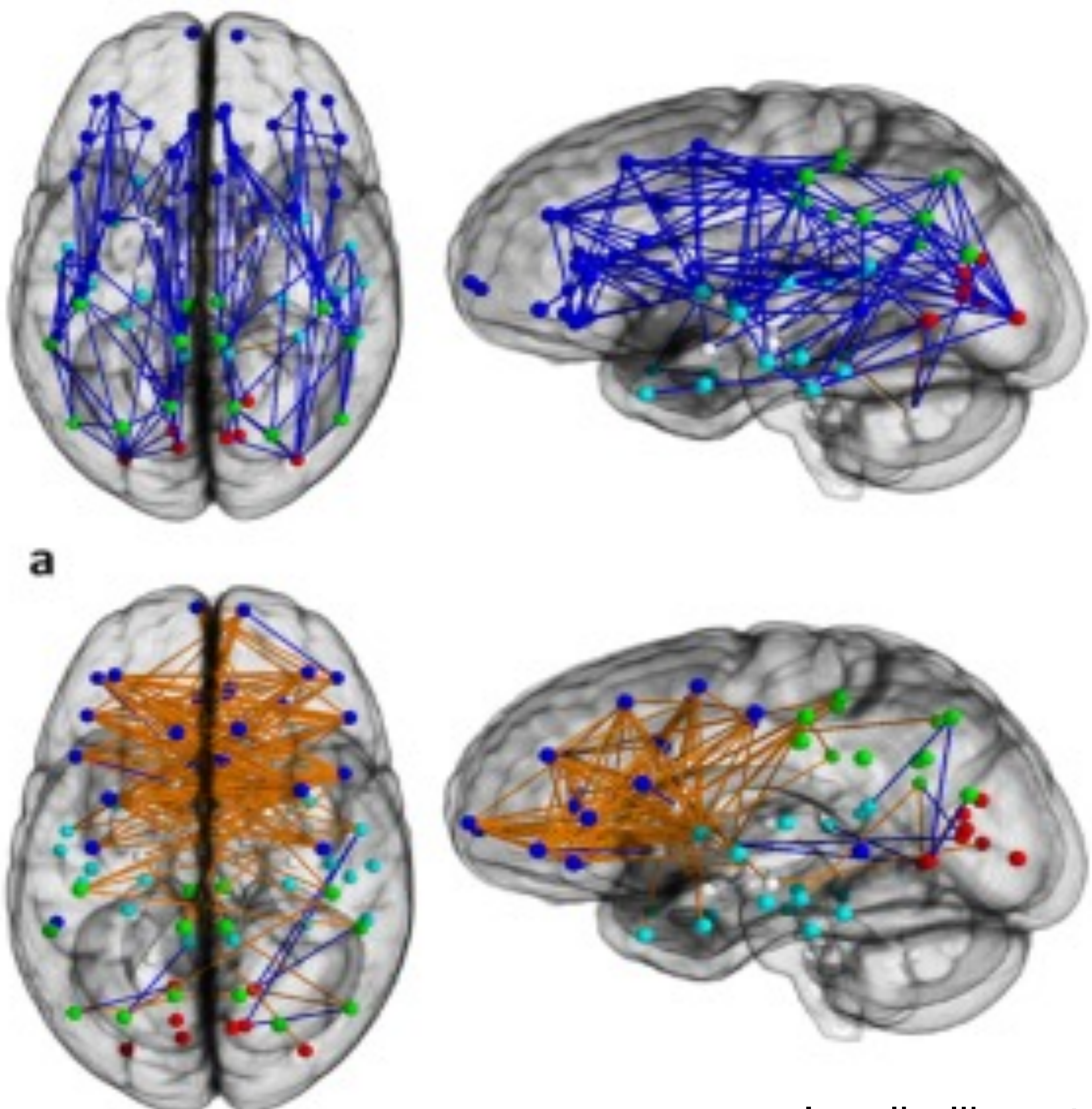
SEX DIFFERENCES IN CONNECTIVITY

INTRA-HEMISPHERIC

INTER-HEMISPHERIC

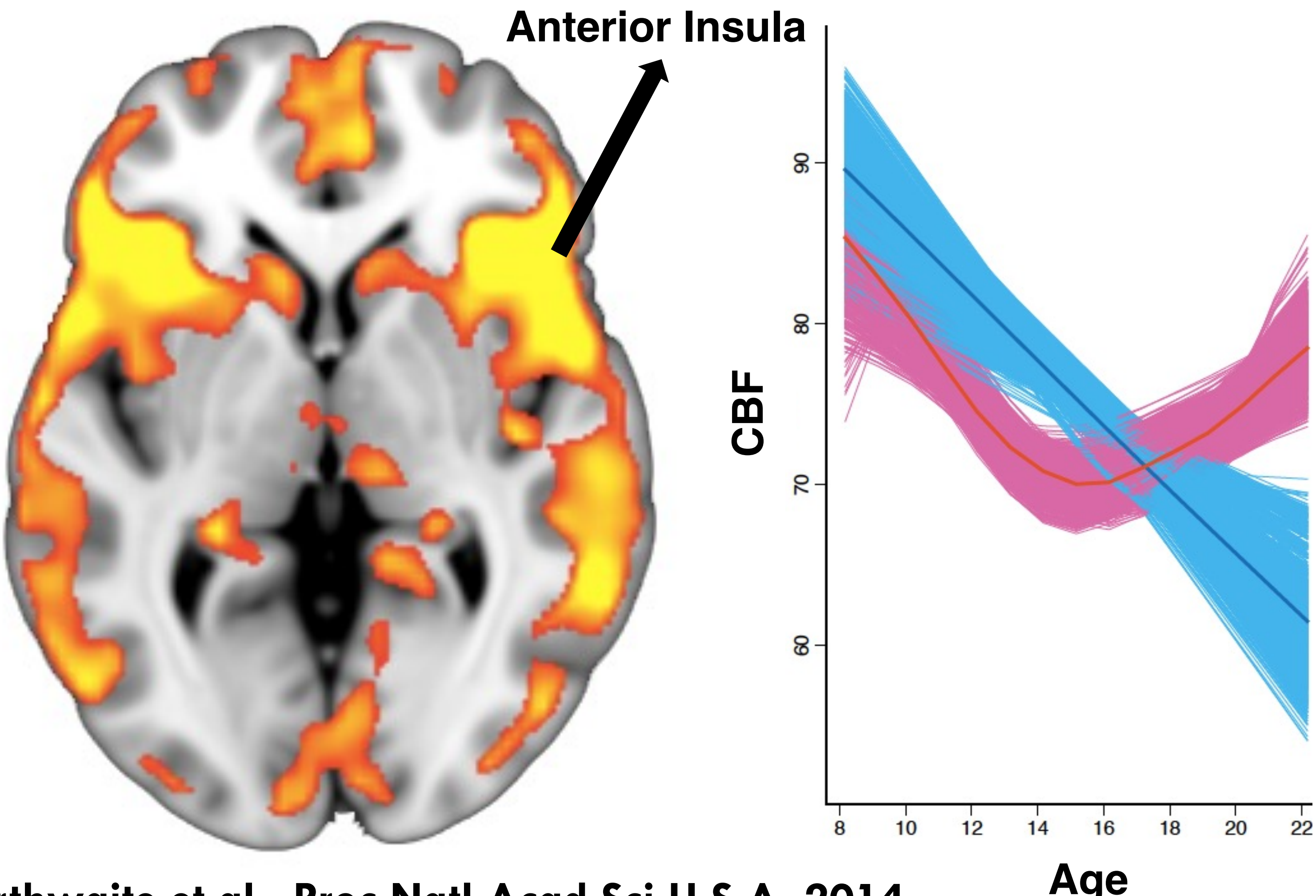
MALES

FEMALES



Ingalhalikar et al., PNAS 2014

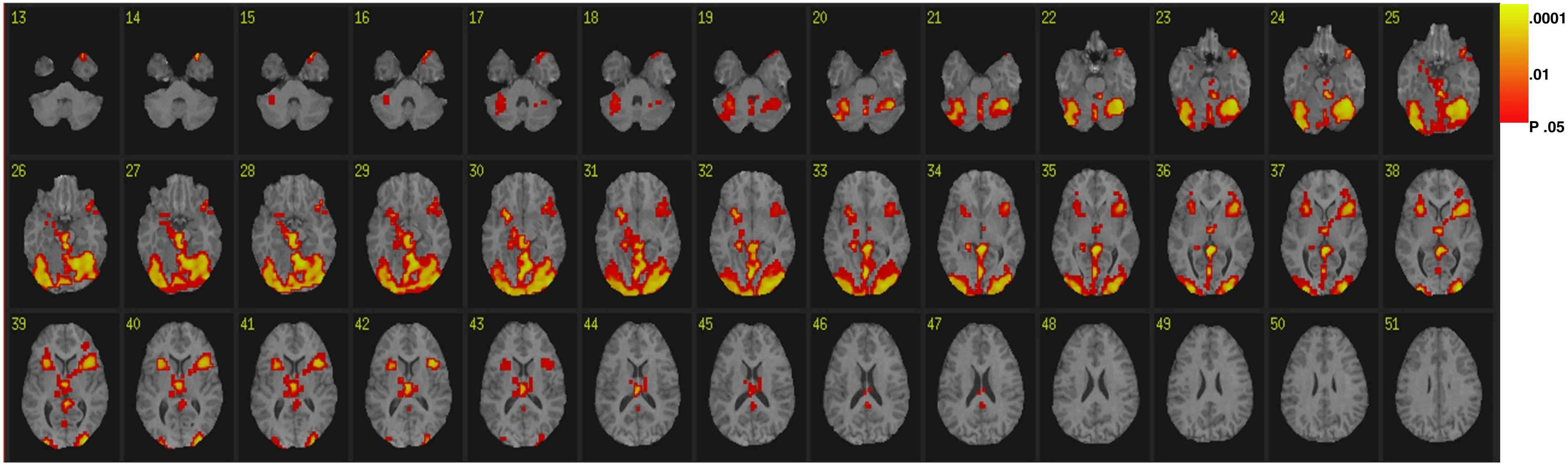
Sex Differences in age effects on CBF



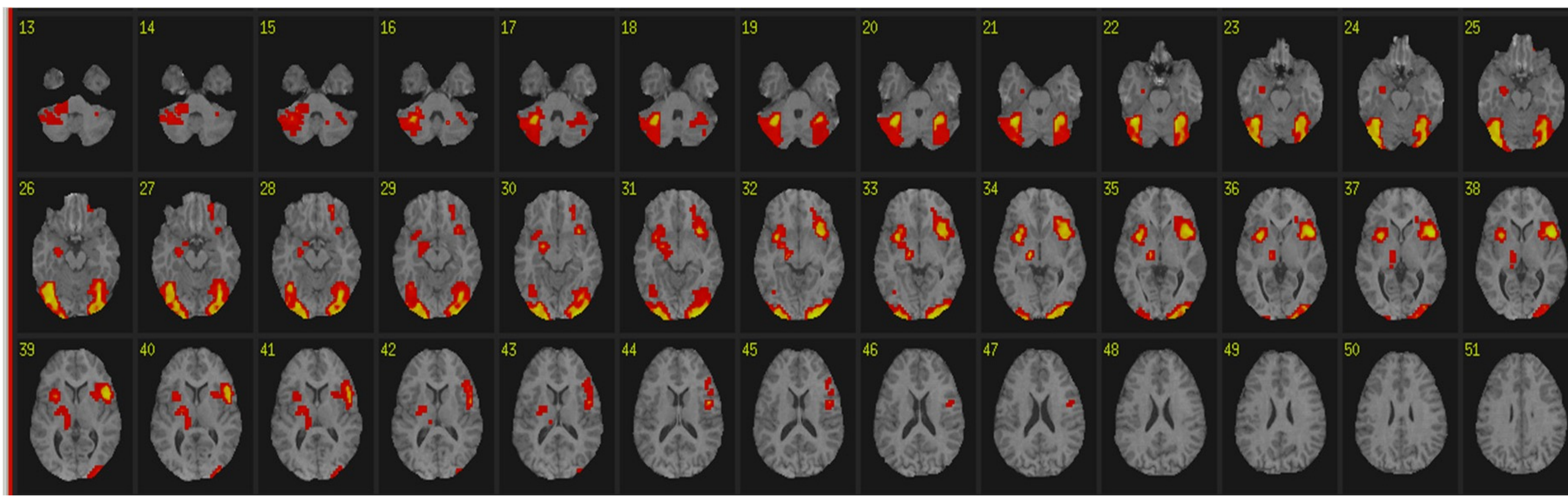
Satterthwaite et al., Proc Natl Acad Sci U S A. 2014

Functional MRI (fMRI)

MEN



WOMEN

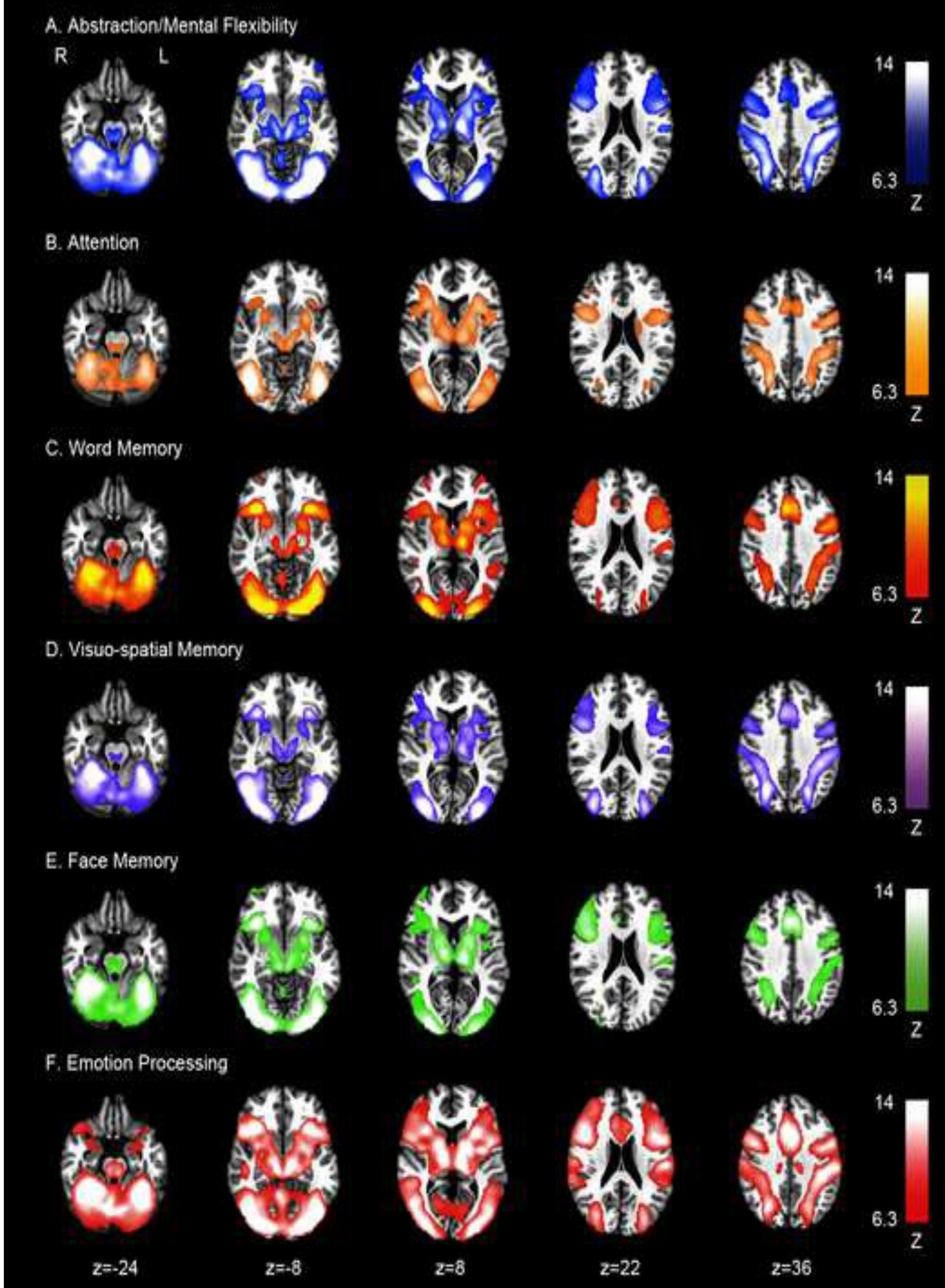


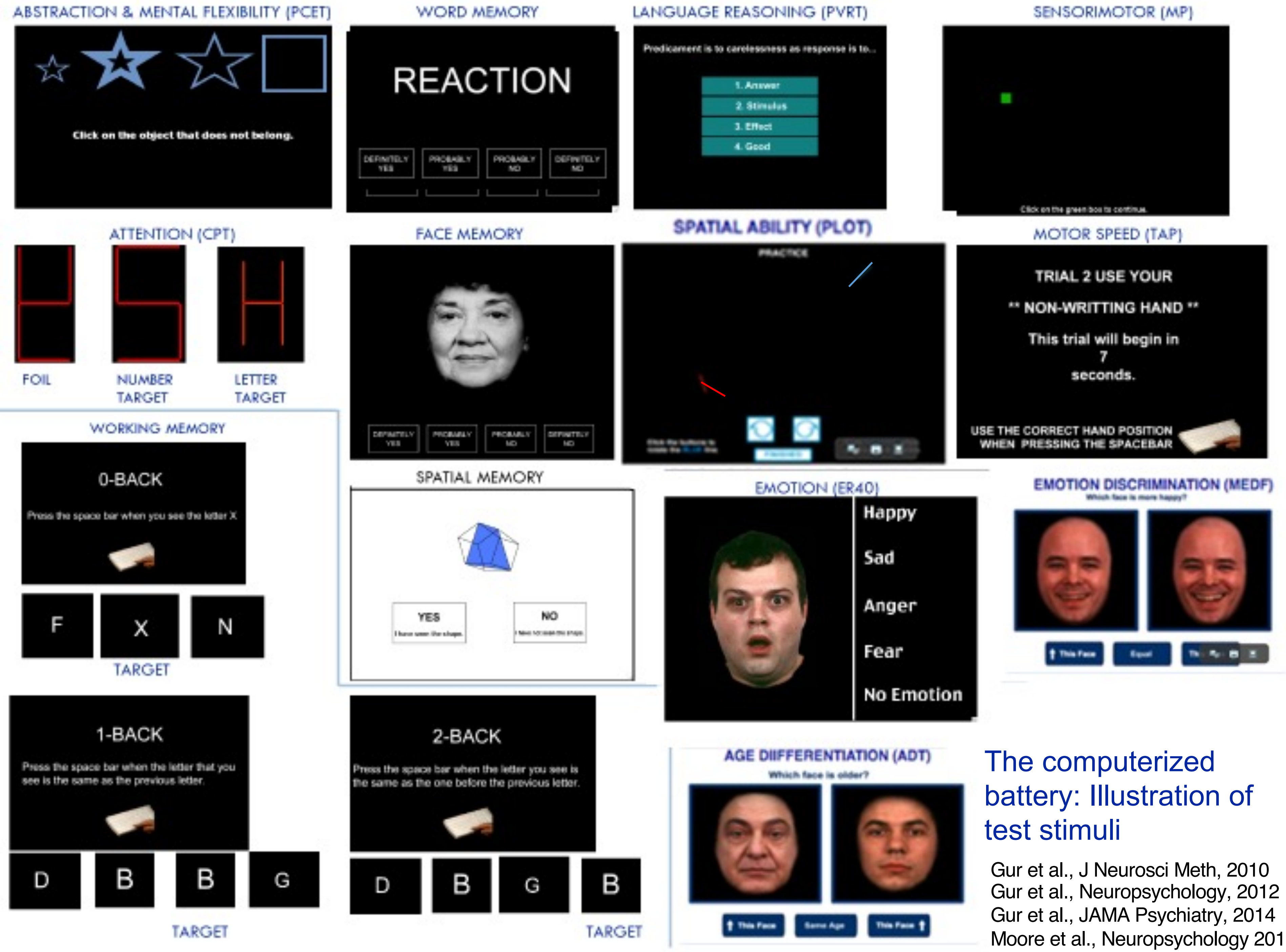
BRAIN MAPPING WITH fMRI

Penn-Pitt collaborative study

IN-SCANNER validation of the Computerized Neurocognitive Battery

Roalf et al., Neuropsychology, 2014





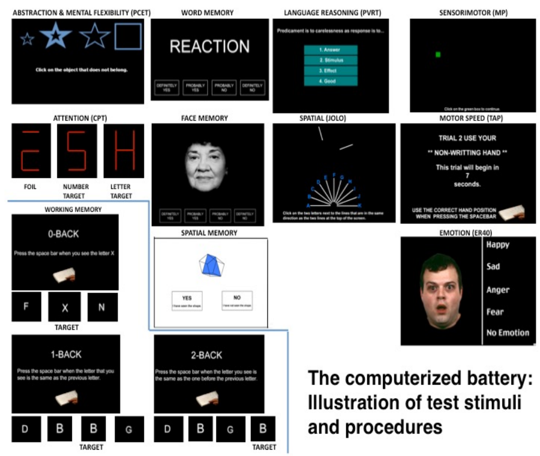
The computerized battery: Illustration of test stimuli

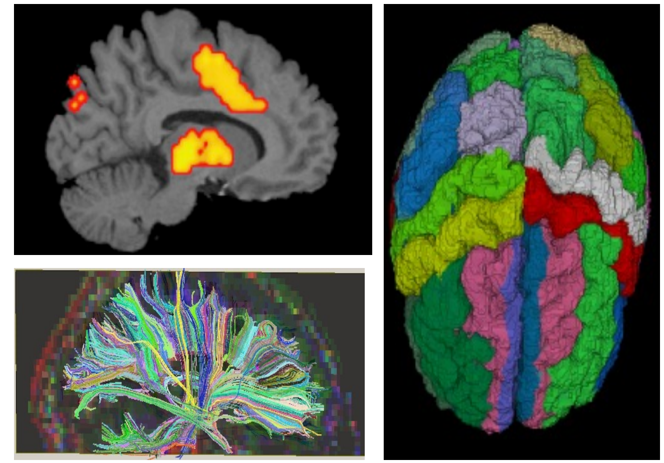
Gur et al., J Neurosci Meth, 2010
Gur et al., Neuropsychology, 2012
Gur et al., JAMA Psychiatry, 2014
Moore et al., Neuropsychology 2014

Clinical Assessment: GOASSESS

Computerized Neurocognitive Battery (CNB)

Neuroimaging: sMRI, DTI, fMRI,ASL





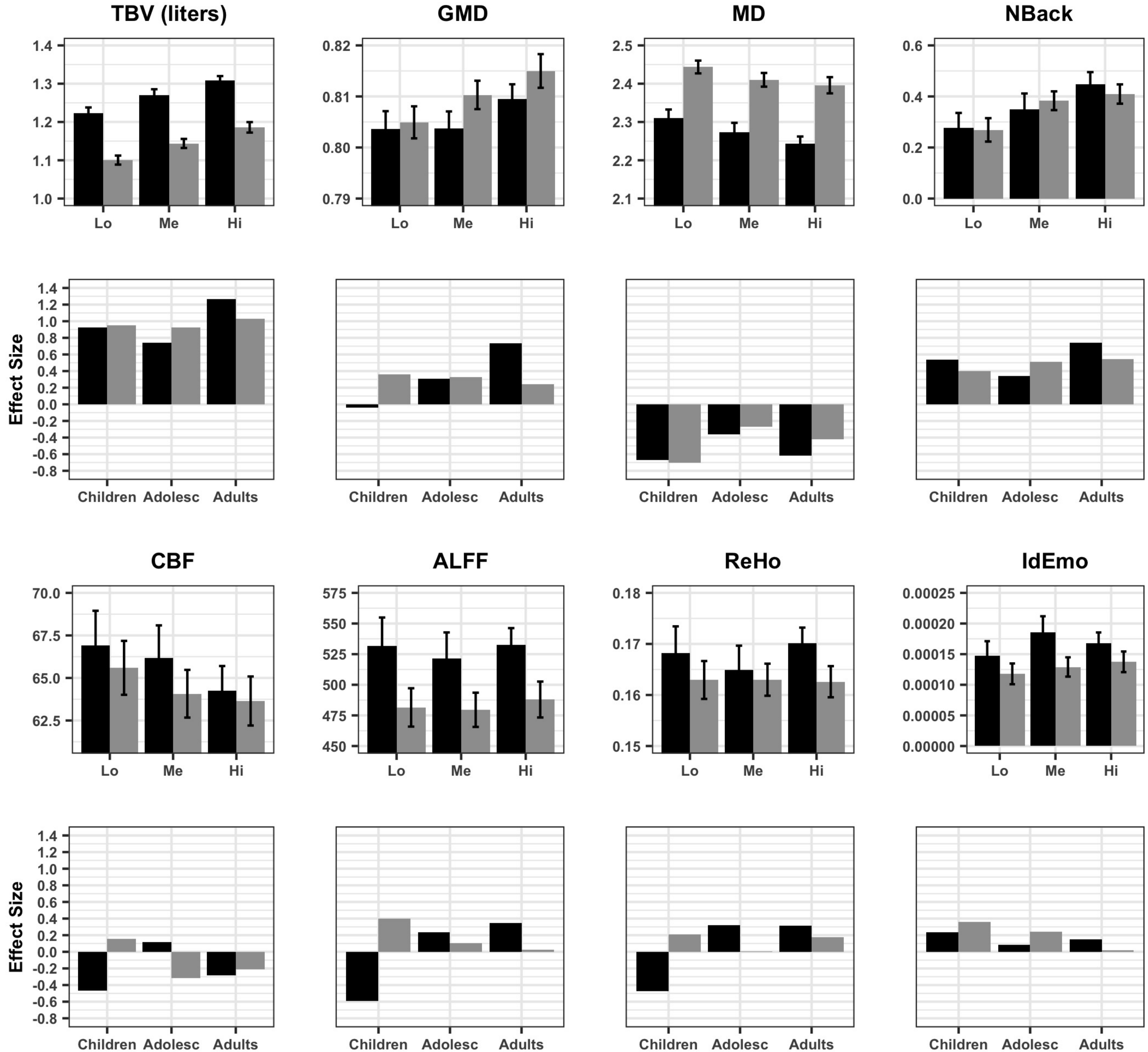
PHENOTYPING

CAG

EMR

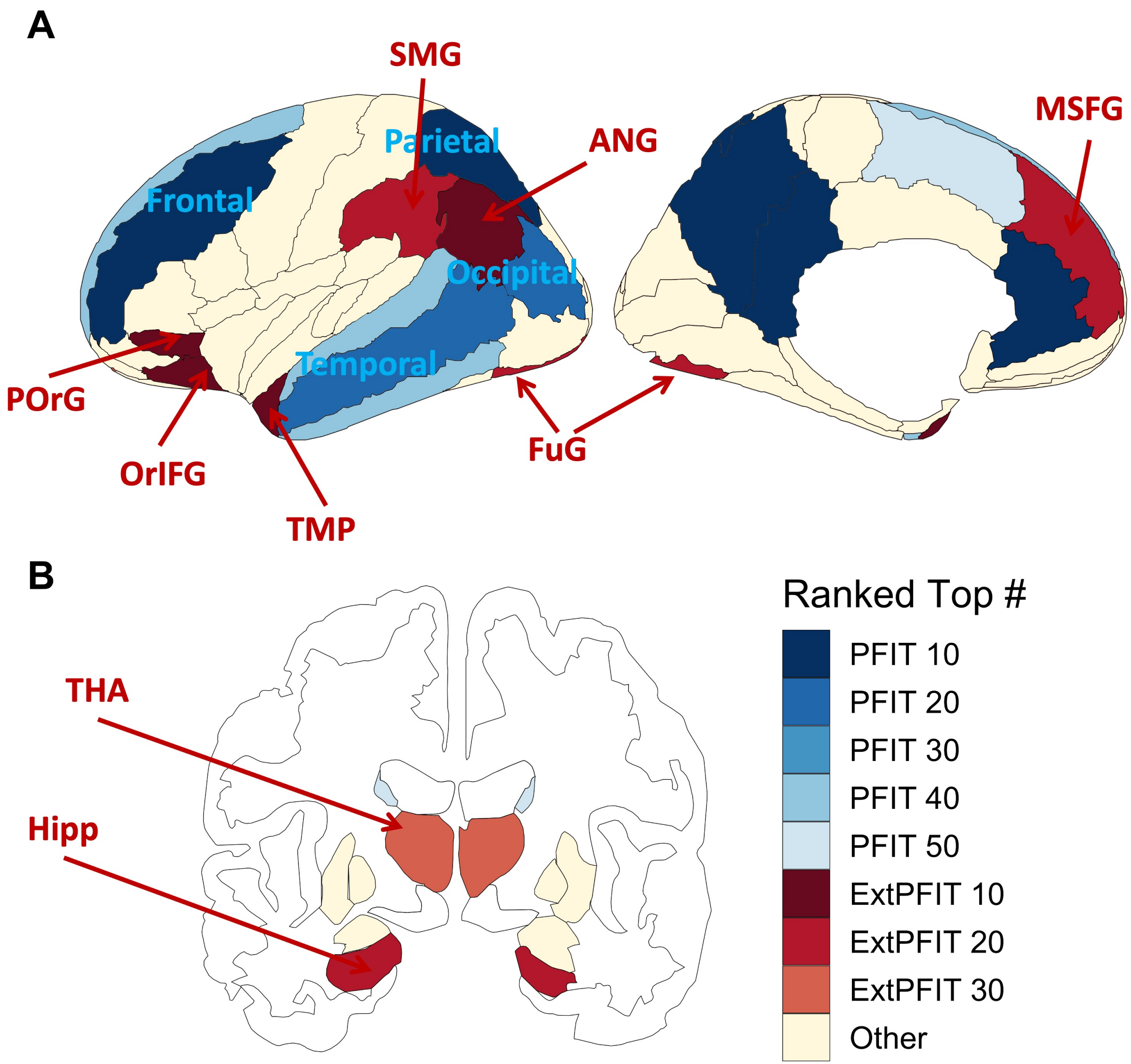
Center for Applied Genomics

Multimodal brain parameters related to performance



Gur et al. Cer Cor 2020

Network of parieto-frontal and limbic regions related to complex cognition performance across structural and functional parameters



Example of structural and functional neuroimaging application to study effects of low dose exposure

Multiple studies in rodents identify a network of limbic and frontal regions affected by low dose radiation and related to corresponding behavioral deficits

International Journal of
Radiation Oncology
biology • physics
www.redjournal.org

Biology Contribution

Fractionated Low-Dose Radiation Induces Long-Lasting Inflammatory Responses in the Hippocampal Stem Cell Niche

Zoé Schmal, PhD,* Ben Hammer, MD,* Andreas Müller, PhD,[†] and Claudia E. Rübe, PhD, MD*

frontiers in Behavioral Neuroscience
ORIGINAL RESEARCH
published: 11 October 2021
doi: 10.3389/fnbeh.2021.722780

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[†]These authors have contributed equally to this work and share first

Multi-Domain Touchscreen-Based Cognitive Assessment of C57BL/6J Female Mice Shows Whole-Body Exposure to ^{56}Fe Particle Space Radiation in Maturity Improves Discrimination Learning Yet Impairs Stimulus-Response Rule-Based Habit Learning

Ivan Soler[1†‡], Sanghee Yun[1,2,3†], Ryan P. Reynolds[2,3‡§], Cody W. Whoolery[2§], Fionya H. Tran[3], Priya L. Kumar[4], Yuying Rong[1], Matthew J. DeSalle[3], Adam D. Gibson[3], Ann M. Stowe[5‡], Frederico C. Kiffer[3] and Amelia J. Eisch[1,2,3,6*]*

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CELL CYCLE
2017, VOL. 16, NO. 13, 1266–1270
https://doi.org/10.1080/15384101.2017.1320003

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PERSPECTIVE

Check for updates

Low dose radiation effects on the brain – from mechanisms and behavioral outcomes to mitigation strategies

Anna Kovalchuk[a,b,c] and Bryan Kolb[a,b,c]

[a]Department of Neuroscience, University of Lethbridge, Lethbridge, AB, Canada; [b]Canadian Institute for Advanced Research, Toronto, ON, Canada; [c]Alberta Epigenetics Network, AB, Canada

frontiers in Behavioral Neuroscience
ORIGINAL RESEARCH
published: 04 May 2016
doi: 10.3389/fnbeh.2016.00083

CrossMark

Persistent Impact of *In utero* Irradiation on Mouse Brain Structure and Function Characterized by MR Imaging and Behavioral Analysis

Tine Verreet[1,2], Janaki Raman Rangarajan[3,4], Roel Quintens[1], Mieke Verslegers[1], Adrian C. Lo[5], Kristof Govaerts[6], Mieke Neefs[1], Liselotte Leysen[1], Sarah Baatout[1], Frederik Maes[4], Uwe Himmelreich[3,6], Rudi D'Hooge[5], Lieve Moons[2] and Mohammed A. Benotmane[1]*

[CANCER RESEARCH 63, 4021–4027, July 15, 2003]

Extreme Sensitivity of Adult Neurogenesis to Low Doses of X-Irradiation[1]

Shinichiro Mizumatsu, Michelle L. Monje, Duncan R. Morhardt, Radoslaw Rola, Theo D. Palmer, and John R. Fike[2]

Brain Tumor Research Center, Department of Neurological Surgery, University of California at San Francisco, San Francisco, California 94143 [S. M., D. R. M., R. R., J. R. F.], and Department of Neurosurgery, Stanford University, Stanford, California 94305 [M. L. M., T. D. P.]

Example of structural and functional neuroimaging application to study effects of low dose exposure

Few examples in humans

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Radiation Dose—Dependent Hippocampal Atrophy Detected With Longitudinal Volumetric Magnetic Resonance Imaging

Tyler M. Seibert, MD, PhD,* Roshan Karunamuni, PhD,*
Hauke Bartsch, PhD,† Samar Kaifi, MD,* Anitha Priya Krishnan, PhD,†
Yoseph Dalia, BS,* Jeffrey Burkeen, MD,* Vyacheslav Murzin, PhD,*
Vitali Moiseenko, PhD,* Joshua Kuperman, PhD,†
Nathan S. White, PhD,† James B. Brewer, MD, PhD,†,‡
Nikdokht Farid, MD,† Carrie R. McDonald, PhD,§
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*Departments of *Radiation Medicine and Applied Sciences, †Radiology, ‡Neurosciences, and §Psychiatry, University of California, San Diego, La Jolla, California*

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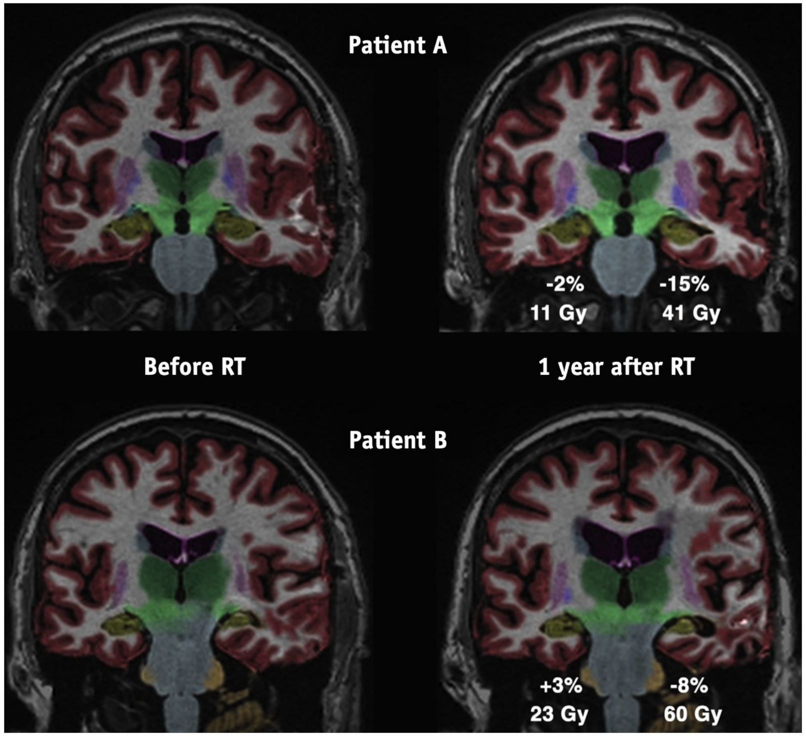


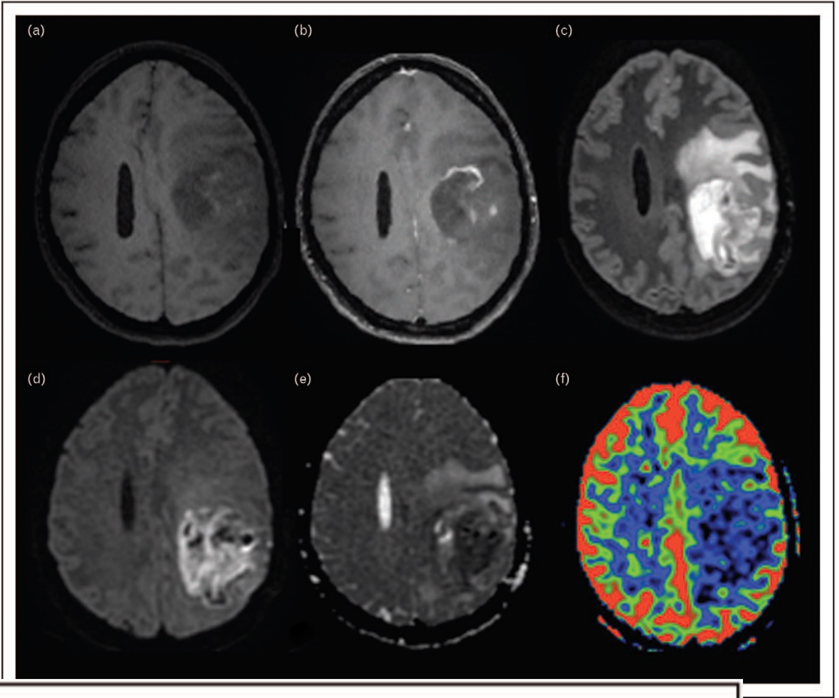
Fig. 1. Magnetic resonance images (MRI) from 2 illustrative cases. For each patient, preradiotherapy (Before RT) MRI (left), with color overlay showing automated segmentation of hippocampus in yellow. The text under each hippocampus on the segmented MRI 1 year after RT (right) gives the corresponding percentage change in hippocampal volume compared with pre-RT baseline and the mean hippocampus RT dose. (A color version of this figure is available at www.redjournal.org.)

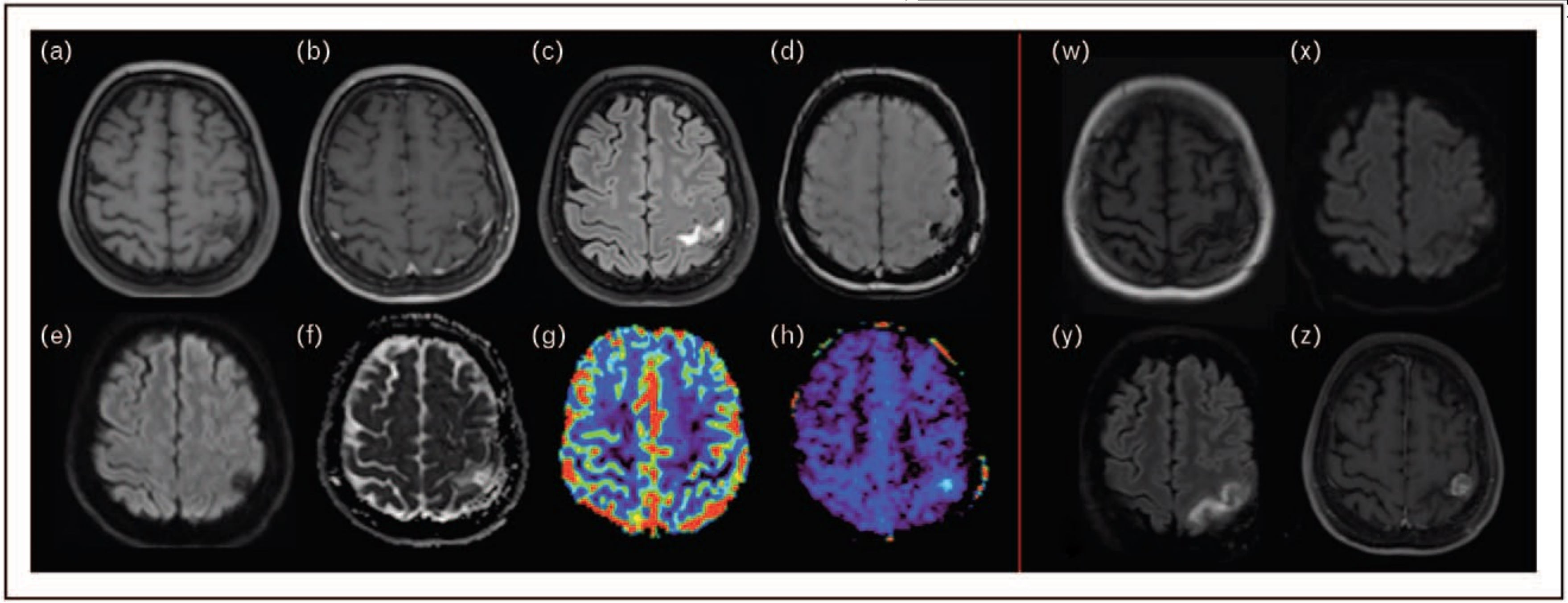
REVIEW

OPEN

Current emerging MRI tools for radionecrosis and pseudoprogression diagnosis

Lucia Nichelli[a,b] and Stefano Casagranda[c]





Nichelli & Casagranda, Curr Op Oncol, 2021

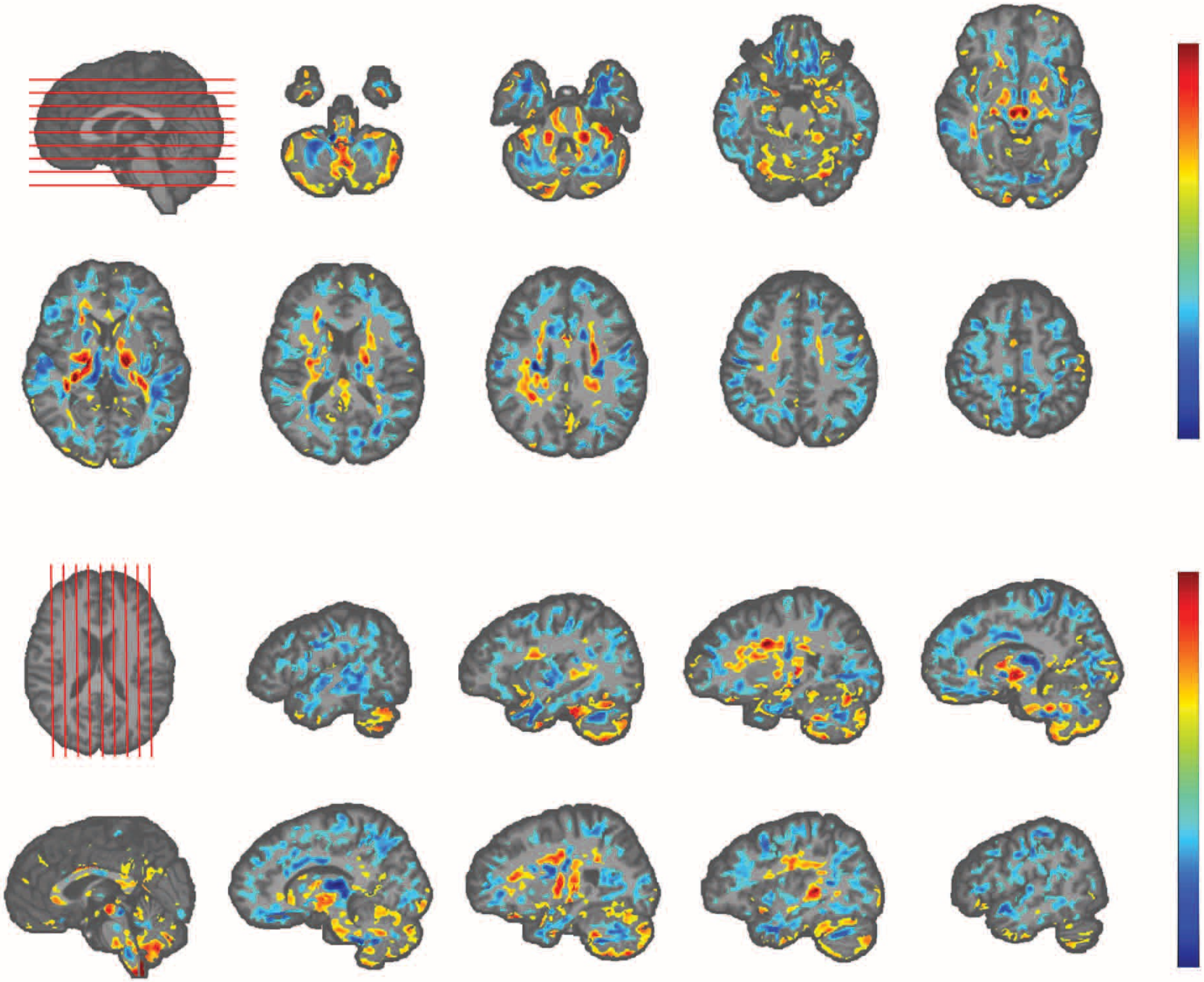
JAMA | Original Investigation

Neuroimaging Findings in US Government Personnel With Possible Exposure to Directional Phenomena in Havana, Cuba

Ragini Verma, PhD; Randel L. Swanson, DO, PhD; Drew Parker, BS; Abdol Aziz Ould Ismail, MD; Russell T. Shinohara, PhD; Jacob A. Alappatt, BTech; Jimit Doshi, MS; Christos Davatzikos, PhD; Michael Gallaway, OD; Diana Duda, PT, DPT; H. Isaac Chen, MD; Junghoon J. Kim, PhD; Ruben C. Gur, PhD; Ronald L. Wolf, MD, PhD; M. Sean Grady, MD; Stephen Hampton, MD; Ramon Diaz-Arrastia, MD, PhD; Douglas H. Smith, MD

Example of structural and functional neuroimaging application to study effects of low dose exposure

Volumetric Differences Between Patients and Controls



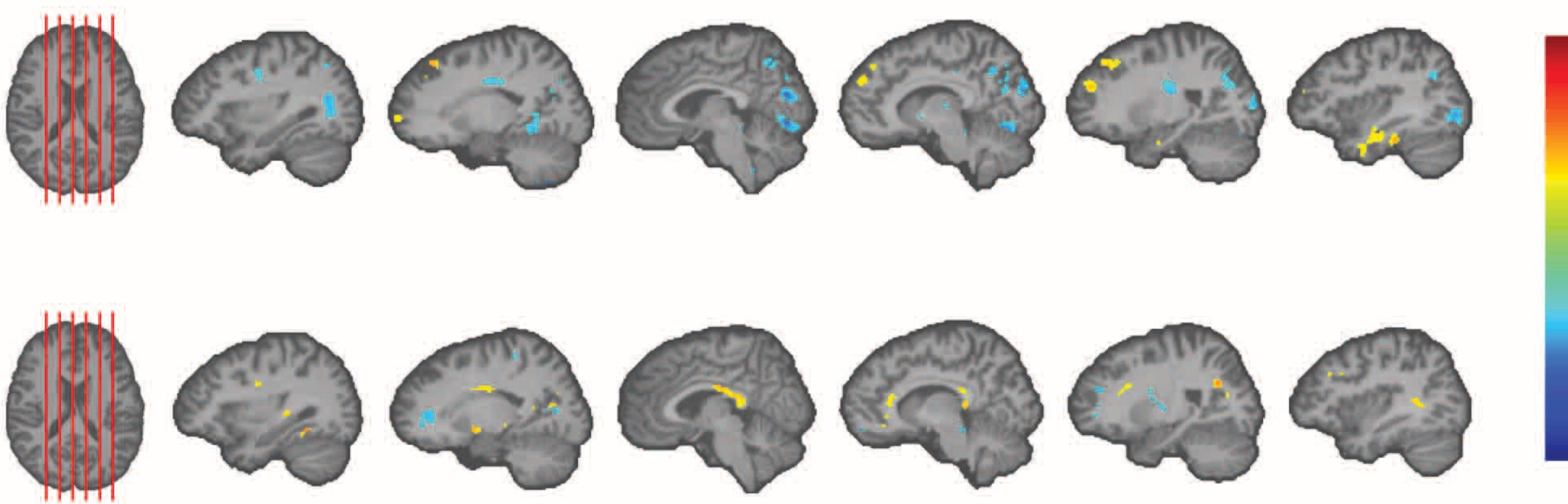
Verma et al. JAMA, 2019

JAMA | Original Investigation

Neuroimaging Findings in US Government Personnel With Possible Exposure to Directional Phenomena in Havana, Cuba

Ragini Verma, PhD; Randel L. Swanson, DO, PhD; Drew Parker, BS; Abdol Aziz Ould Ismail, MD; Russell T. Shinohara, PhD; Jacob A. Alappatt, BTech; Jimit Doshi, MS; Christos Davatzikos, PhD; Michael Gallaway, OD; Diana Duda, PT, DPT; H. Isaac Chen, MD; Junghoon J. Kim, PhD; Ruben C. Gur, PhD; Ronald L. Wolf, MD, PhD; M. Sean Grady, MD; Stephen Hampton, MD; Ramon Diaz-Arrastia, MD, PhD; Douglas H. Smith, MD

Differences in Tissue Microstructural Integrity in the Cerebrum



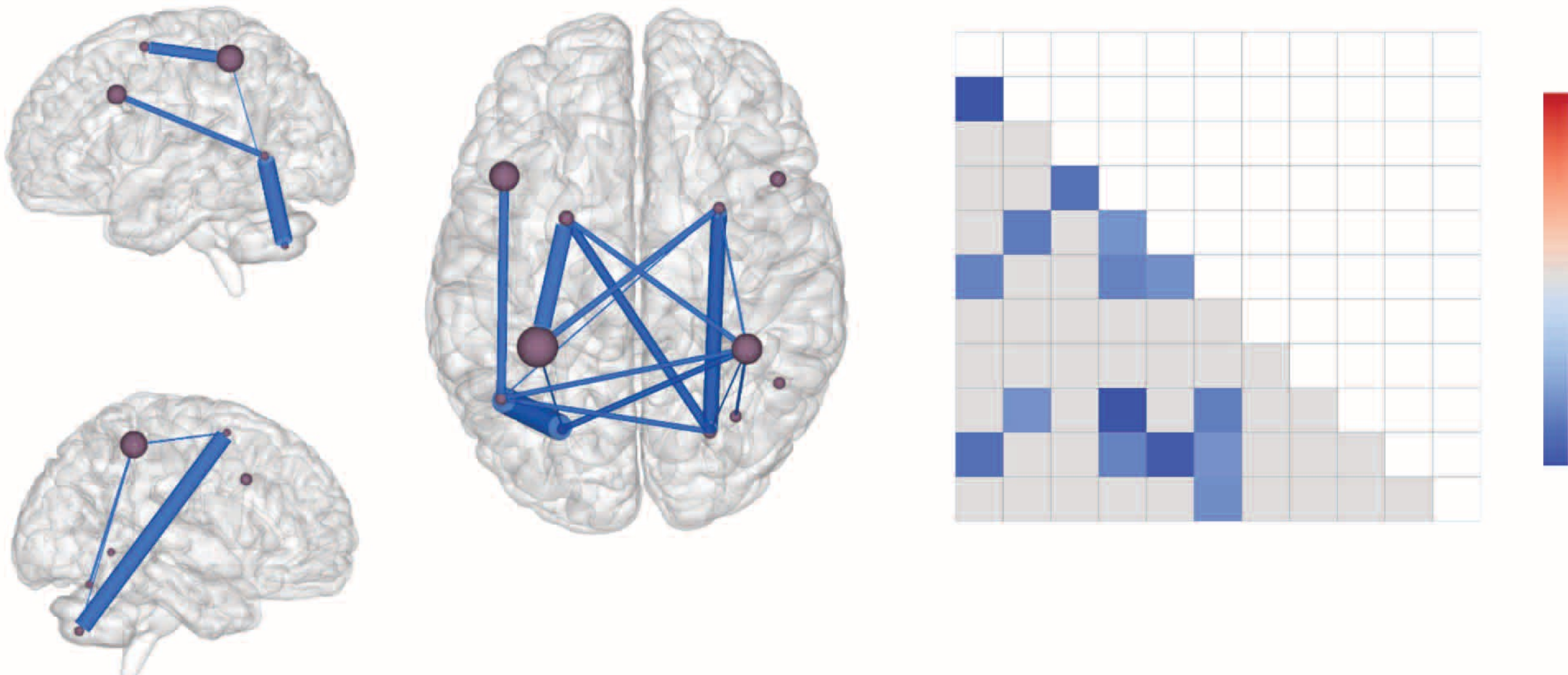
Verma et al. JAMA, 2019

JAMA | Original Investigation

Neuroimaging Findings in US Government Personnel With Possible Exposure to Directional Phenomena in Havana, Cuba

Ragini Verma, PhD; Randel L. Swanson, DO, PhD; Drew Parker, BS; Abdol Aziz Ould Ismail, MD; Russell T. Shinohara, PhD; Jacob A. Alappatt, BTech; Jimit Doshi, MS; Christos Davatzikos, PhD; Michael Gallaway, OD; Diana Duda, PT, DPT; H. Isaac Chen, MD; Junghoon J. Kim, PhD; Ruben C. Gur, PhD; Ronald L. Wolf, MD, PhD; M. Sean Grady, MD; Stephen Hampton, MD; Ramon Diaz-Arrastia, MD, PhD; Douglas H. Smith, MD

Comparisons of Visuospatial Subnetwork Functional Connectivity Between Patients and Controls



Verma et al. JAMA, 2019

□ Opportunities and challenges to use these techniques in low dose radiation exposures

OPPORTUNITIES

- Large international databases already exist with multimodal neuroimaging and neurocognitive data that can be related to probability of exposure to low dose radiation
- Tools are available to design and implement prospective and longitudinal large-scale studies in targeted populations such as pilots and air crews, radiation technologists, astronauts and astronaut analogues (in progress by NASA)

CHALLENGES

- Overcoming the clinical/research divide and facilitating incorporation of multimodal clinical data
- Finding the resources to implement data mining and collection of new data

□ Views on research priorities

- Invest in data mining of available relevant datasets
- Design and implement large-scale prospective and longitudinal neuroimaging studies in targeted populations
- Given the wealth of data on rodent models, design and validate analogous behavioral measures to enhance translational value

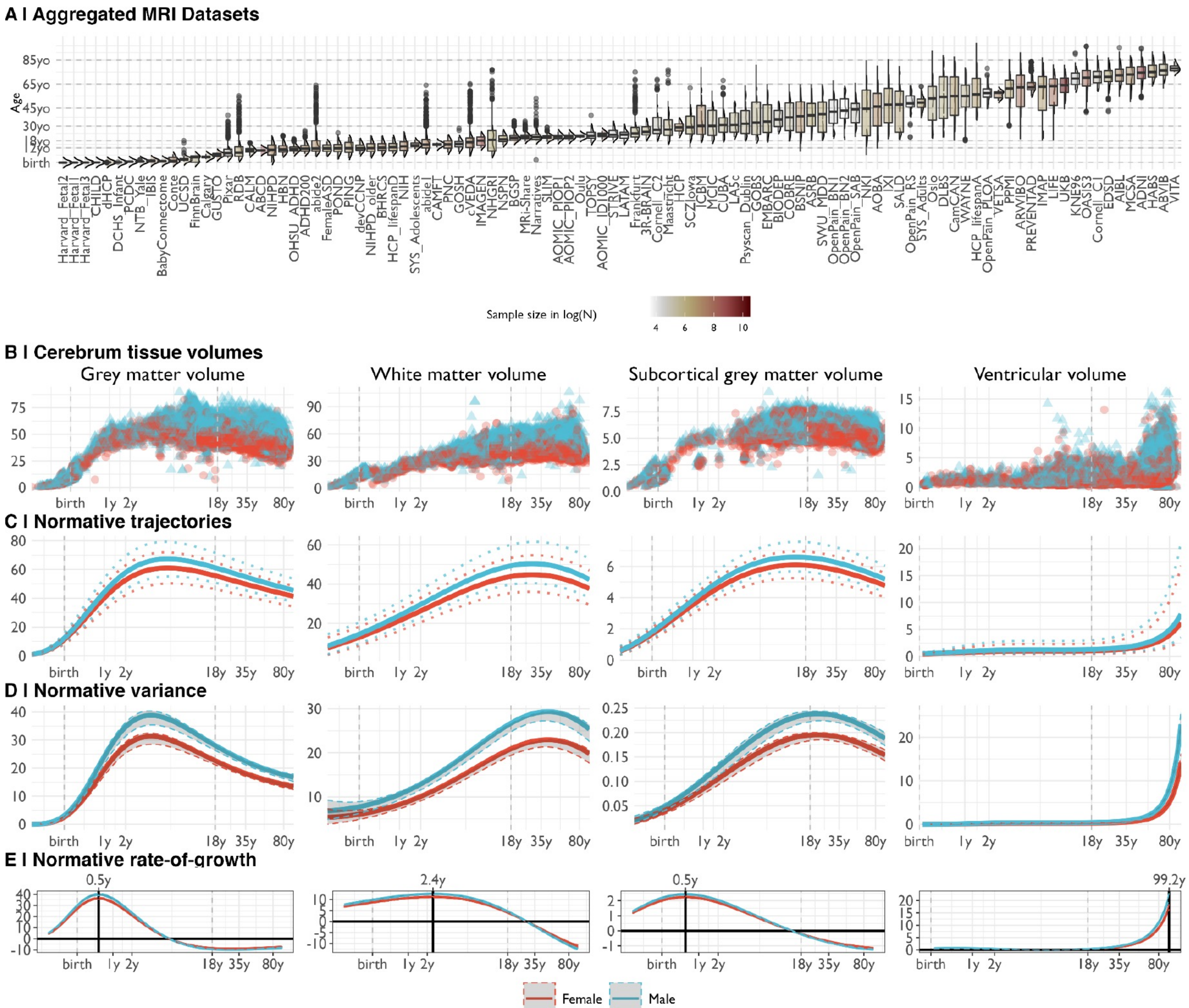


Fig. 1. Human brain charts. *A | MRI data were aggregated from 100 primary studies comprising 123,984 scans that collectively spanned the age range from late pregnancy to 100 postnatal years. Box-violin plots*

Bethlehem et al. 2021, Under consideration

Re: NASEM Low-Dose Radiation Study: Final preparations for the November 16-17 Public Meeting

Re: NASEM Low-Dose Radiation Study: Final preparations for the November 16-17 Public Meeting

AA Alavi, Abass <Abass.Alavi@pennmedicine.upenn.edu> Yesterday at 8:51 PM

To: Gur, Ruben

From: Alavi, Abass <Abass.Alavi@pennmedicine.upenn.edu>
Date: Friday, November 12, 2021 at 1:34 PM
To: Gur, Ruben <gur@pennmedicine.upenn.edu>
Subject: RE: NASEM Low-Dose Radiation Study: Final preparations for the November 16-17 Public Meeting

Dear Ruben, I know of no research study that has looked at the effects of radiation on brain function or structure, however, right now, we are analyzing our FDG-PET data on a relatively large number of patients with Head and Neck cancer who have undergone curative radiation therapy with either X-Ray or Proton therapy, we will have our data available in the coming month or two to share with you, but, our hypothesis is that brain is the most resistant organ to such effects while most organs are damaged by radiation, you can quote me about this fact, I entered the field worrying about radiation exposure from patients and animal research causing harmful effects on my body organs, thanks to almighty, after 50 years of radiation exposure, my body organs are functioning well so far, this includes my brain, I only published 60 papers last year!!, so, there is no detectable effects on my cerebral function my friend!!

All the best, Ruben

Re: NASEM Low-Dose Radiation Study: Final preparations for the November 16-17 Public Meeting

AA

Alavi, Abass <Abass.Alavi@pennmedicine.upenn.edu>

Yesterday at 8:51 PM

To: Gur, Ruben

Absolutely Ruben, there is evidence that limited radiation exposure enhances human body function in various organs including the brain, during the past decade I have doubled the number of my publications and tripled/quadrupled my citations, this is due radiation exposure during the past 5 decades my friend,

Very best to you and Raquel, Abass

From: "Gur, Ruben" <gur@pennmedicine.upenn.edu>
Date: Sunday, November 14, 2021 at 8:12 PM
To: "Alavi, Abass" <Abass.Alavi@pennmedicine.upenn.edu>
Subject: Re: NASEM Low-Dose Radiation Study: Final preparations for the November 16-17 Public Meeting

Thank you Abass, 60 papers! Perhaps radiation helps the brain?

Might quote you in my talk.

All the best, Ruben