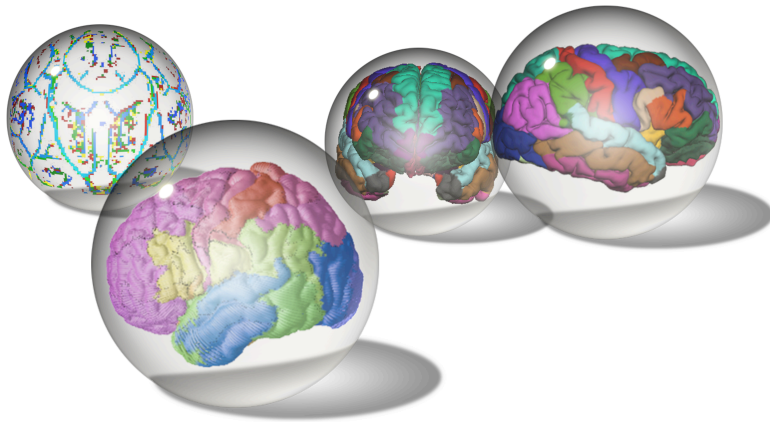
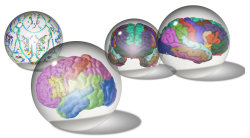
Harmonizing DTI data: Mind Research Network, Oxford, and Rotterdam, a view from the trenches



Tonya White, MD, PhD
Associate Professor of Child and Adolescent Psychiatry
Erasmus MC, Rotterdam, Netherlands

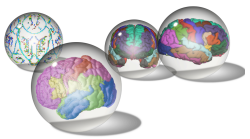


Generation R

Erasmus MC

Sources of Noise

- Physiological noise
- B_0 inhomogeneity
  - Imperfect shimming
  - Imperfections in B0 field
  - Localized susceptibility differences
- Eddy currents
- Hardware instability
  - Time variant (drift)

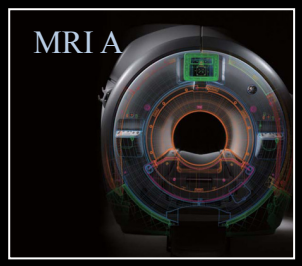


Generation R

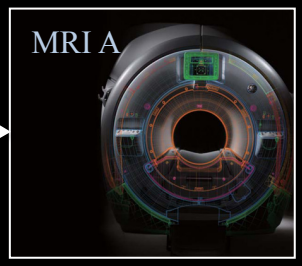
Erasmus MC

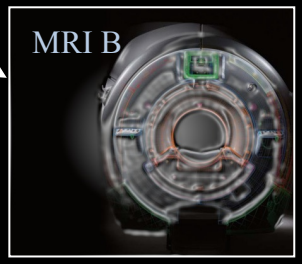
Within- versus across-site differences

DTI Time 1



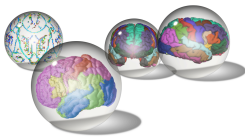
DTI Time 2





Study (FA)	Within-scanner	Between-scanners
Pfefferbaum et al. (2003)	1.9-2.6%	4.5-7.5%
Cercignani et al. (2003)	5.45	7.71%
White et al. (2009)		5.0-7.2%
Vollmar et al. (2010)	0.8-3.0%	1.0-4.1%
Teipel et al. (2011)		14%

ENIGMA DTI – Johanshad et al. (2012) & Kochunov et al. (2014)



Generation R

Erasmus MC

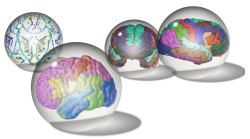
Neuroinform (2013) 11:367–388
DOI 10.1007/s12021-013-9184-3

ORIGINAL DATA ARTICLE

The MCIC Collection: A Shared Repository of Multi-Modal, Multi-Site Brain Image Data from a Clinical Investigation of Schizophrenia

Randy L. Gollub · Jody M. Shoemaker · Margaret D. King · Tonya White · Stefan Ehrlich · Scott R. Sponheim · Vincent P. Clark · Jessica A. Turner · Bryon A. Mueller · Vince Magnotta · Daniel O'Leary · Beng C. Ho · Stefan Brauns · Dara S. Manoach · Larry Seidman · Juan R. Bustillo · John Lauriello · Jeremy Bockholt · Kelvin O. Lim · Bruce R. Rosen · S. Charles Schulz · Vince D. Calhoun · Nancy C. Andreasen

The MCIC imaging and clinical data are available through the COINS (COllaborative Informatics Neuroimaging Suite) database (Scott et al. 2011) and may be freely used with no restrictions.



Generation R

Erasmus MC

University of Minnesota

Patients n = 27

Controls n = 22

Siemens Trio 3 T

12 directions

Massachusetts General Hospital

Patients n = 28

Controls n = 21

Siemens Sonata 1.5 T

60 directions

University of New Mexico

Patients n = 41

Controls n = 43

Siemens Sonata 1.5 T

12 directions

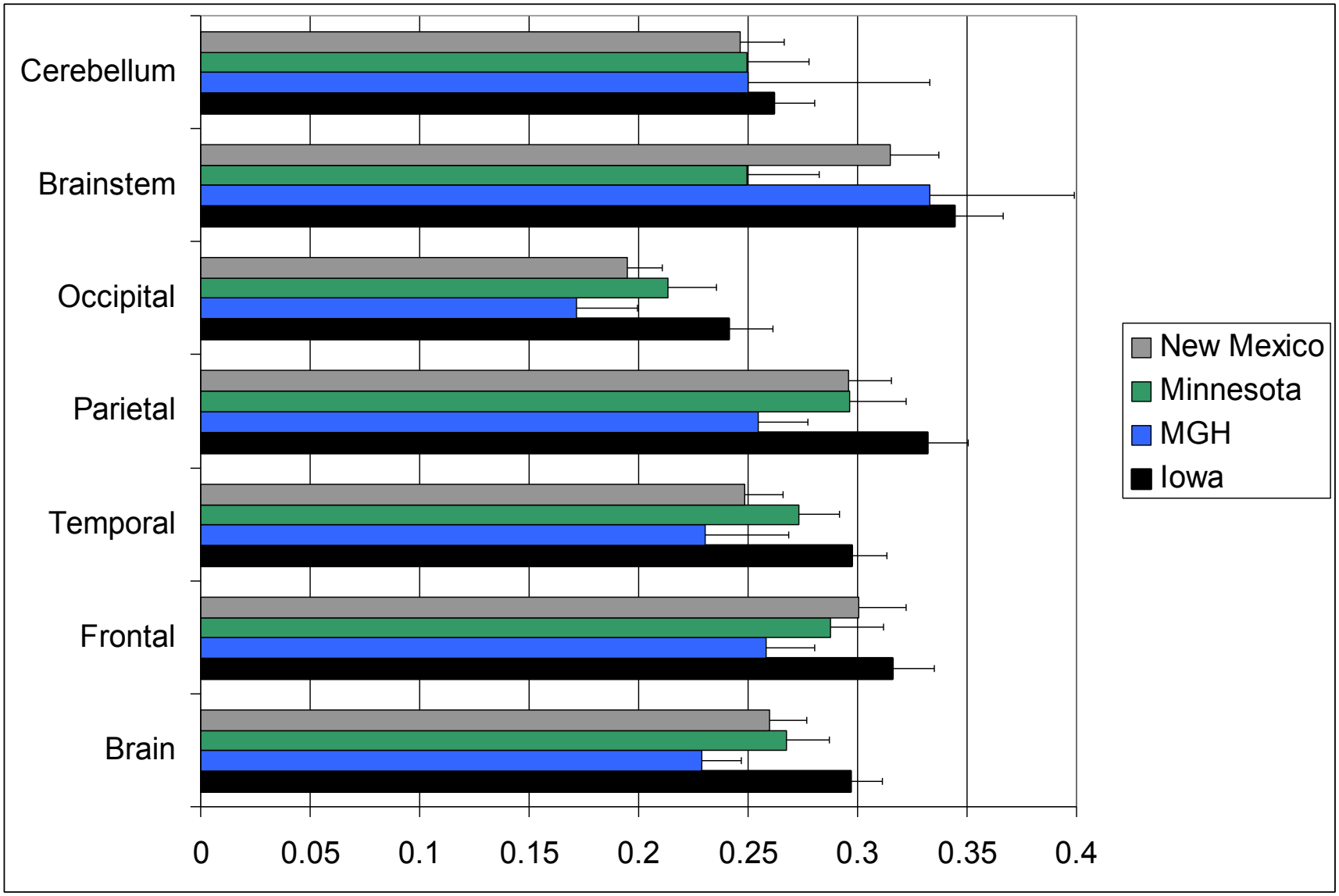
University of Iowa

Patients n = 19

Controls n = 52

Siemens Trio 3 T

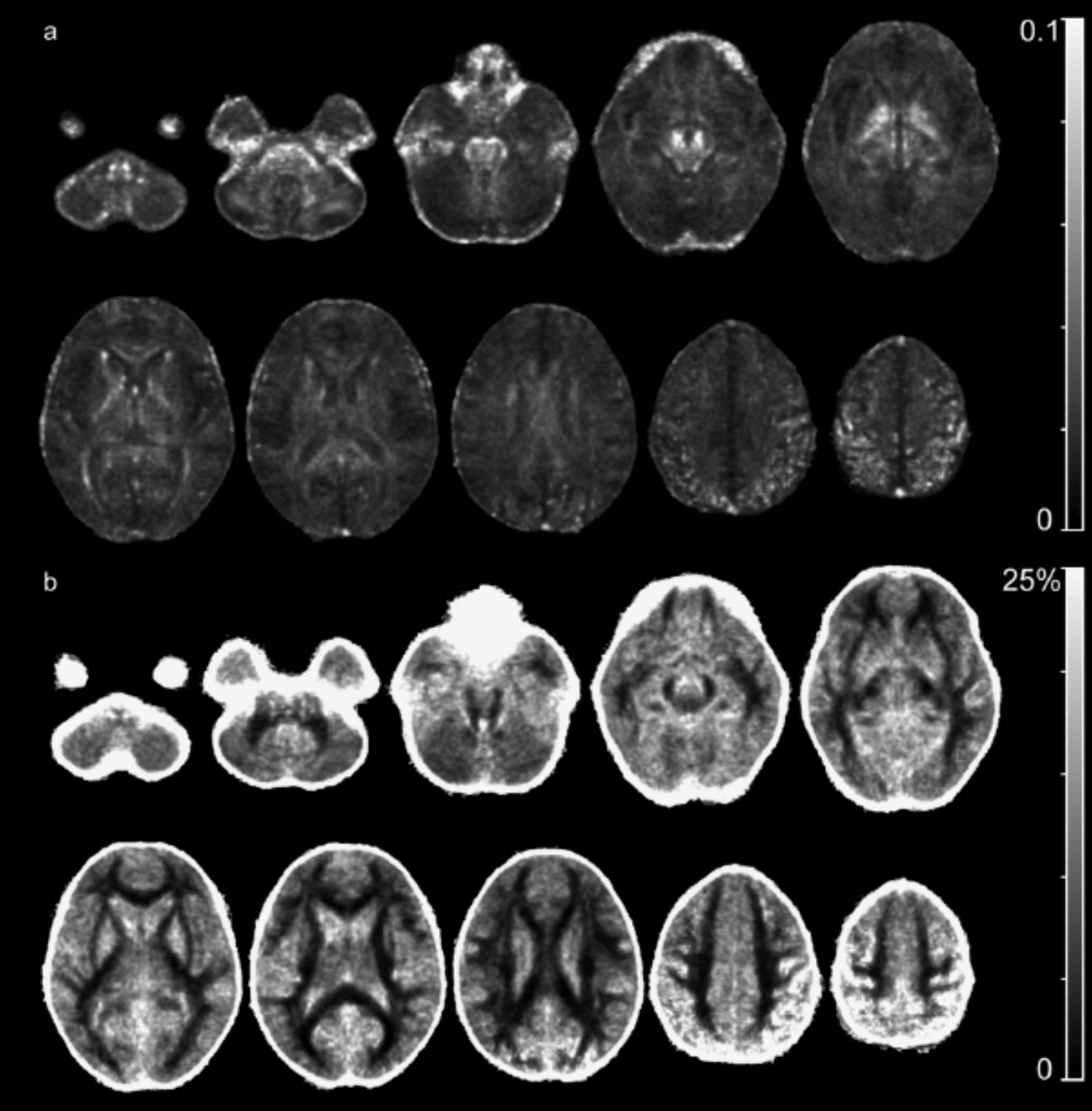
6 directions



Generation R

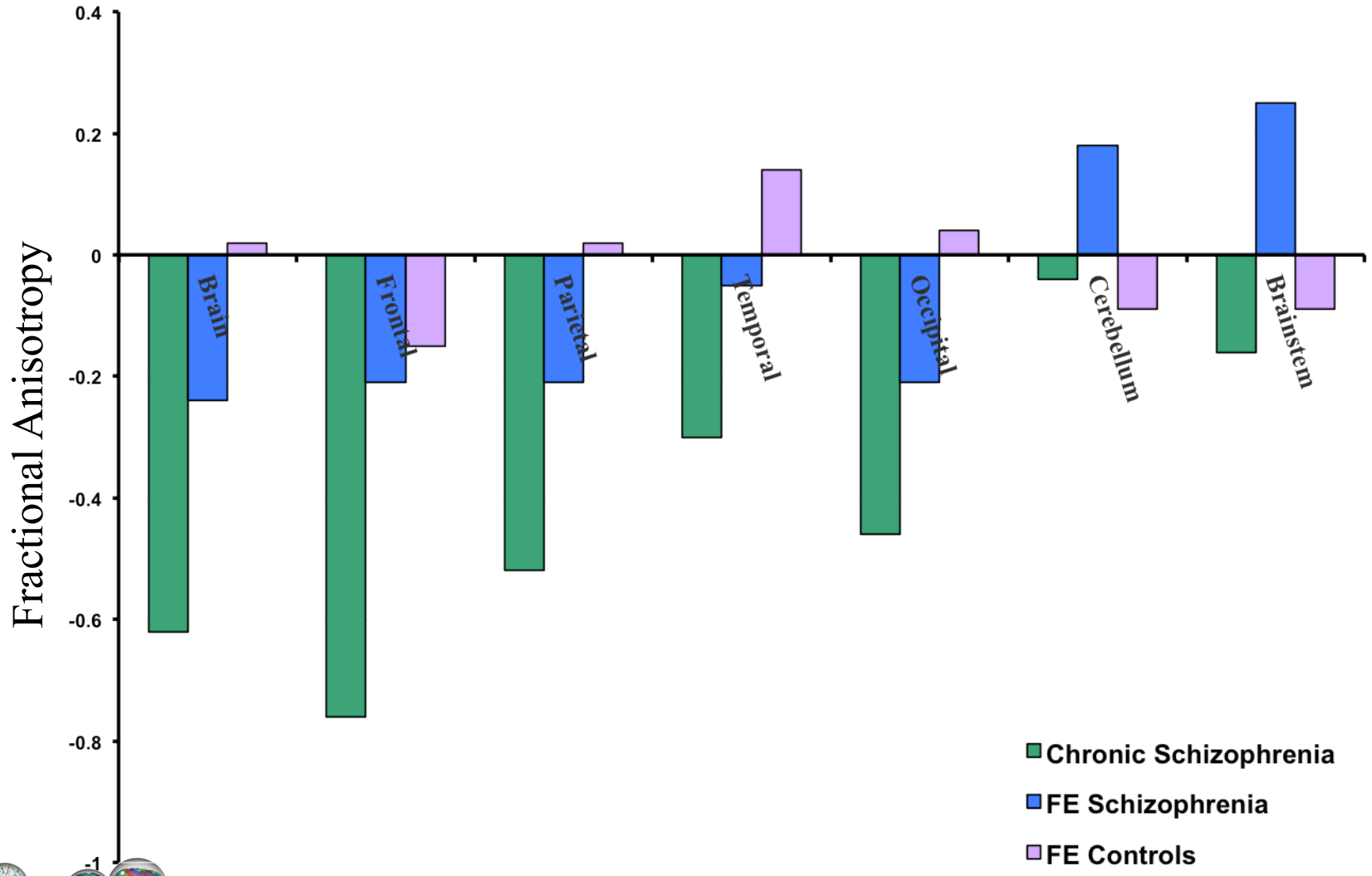
White et al. (2009) Schiz Bull

Erasmus MC



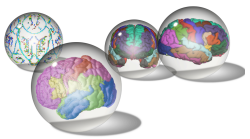
Vollmar et al. (2010)

Z-Transformed Measures of Fractional Anisotropy



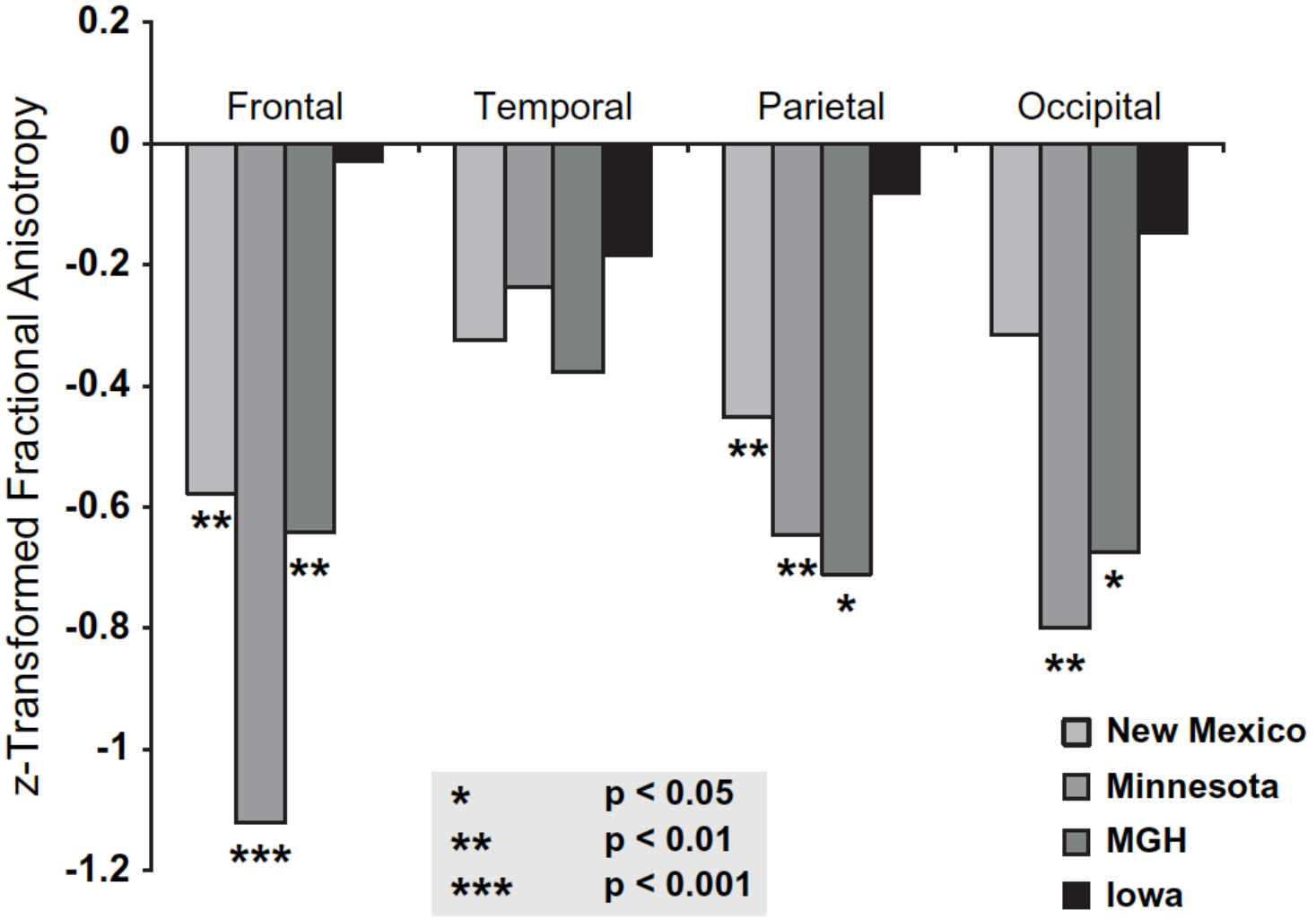
White et al. 2009

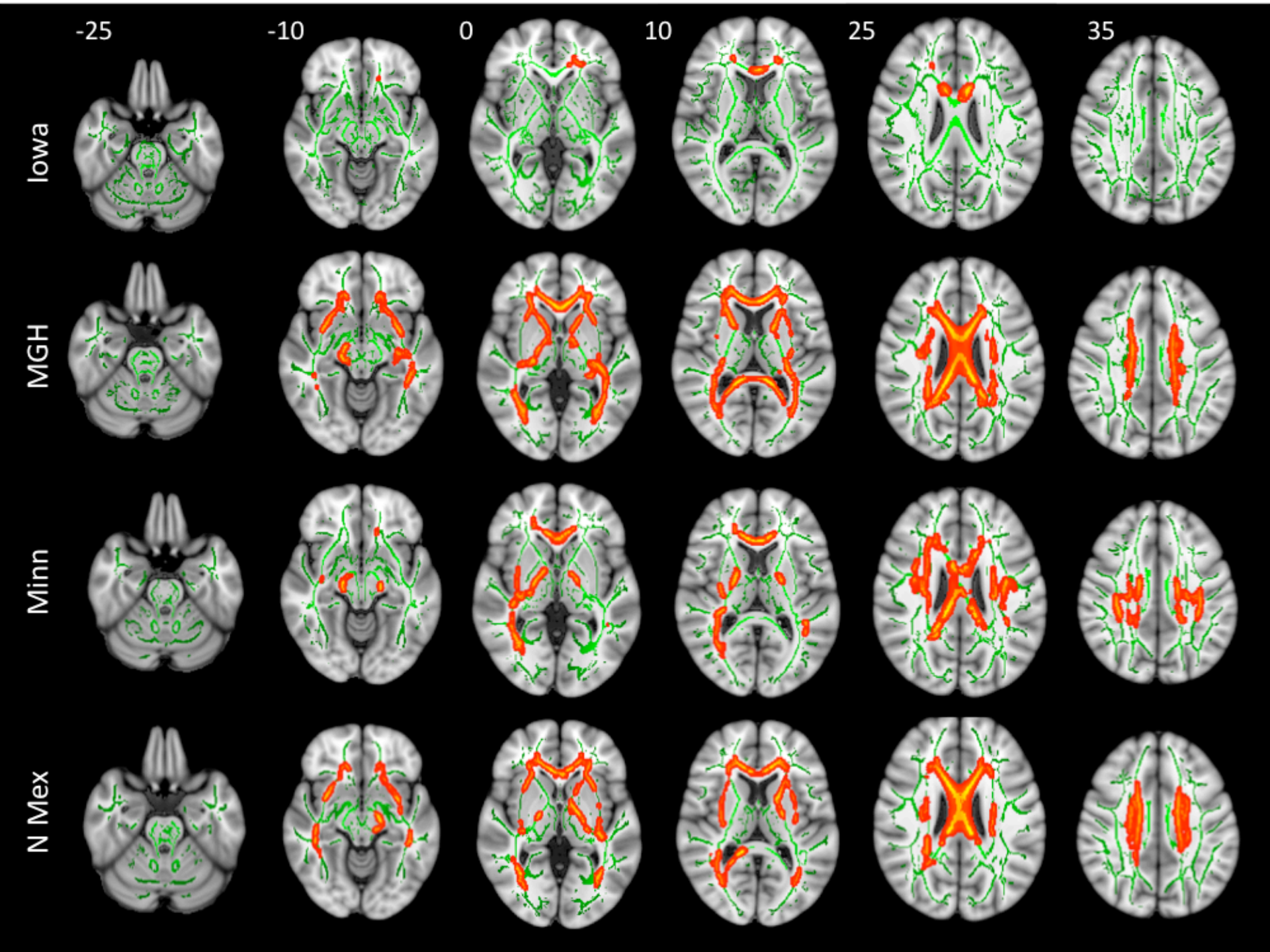
"The limitations of the study are that the original data were assembled from 4 different regions of the U.S., that both 3 T and 1.5 T scanners were used, that protocols were not standardized/designed a priori, and that subject samples from each of the regions were not very large. Therefore, any conclusions must necessarily address these possible confounds and this is also well addressed in the discussion section. No measure is provided on how well results from the different sites measure up, that is no subject seemed to have been examined at more that one site."



Generation R

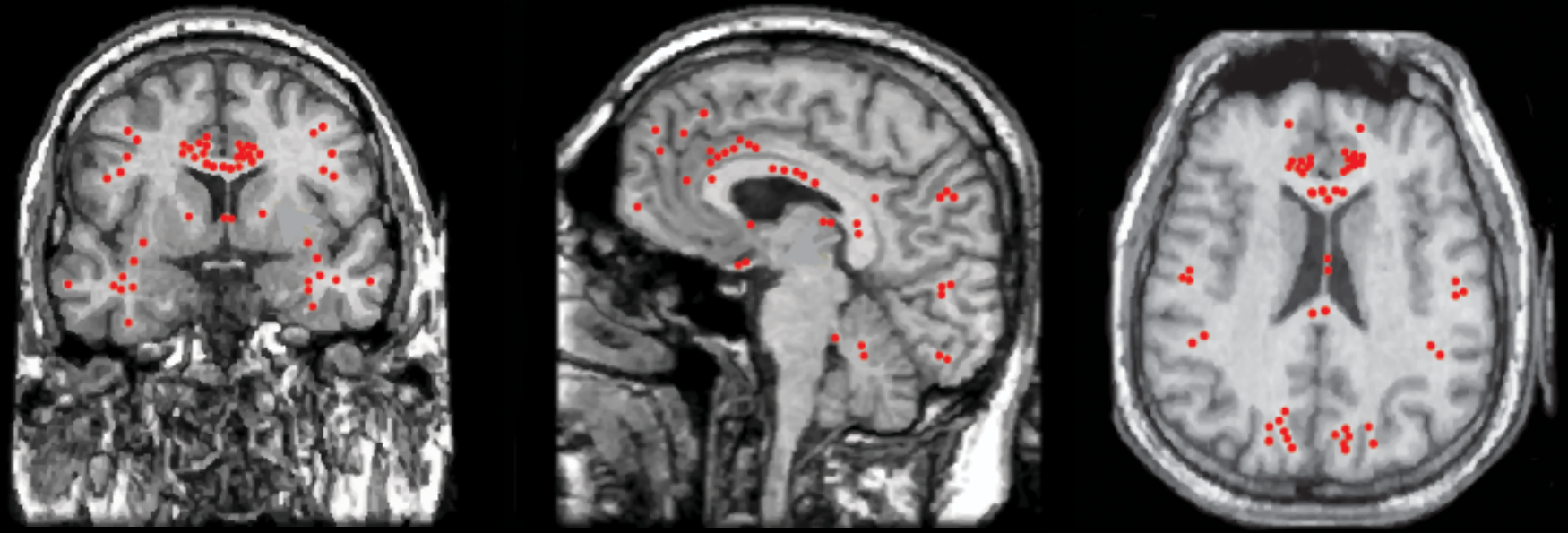
Erasmus MC


z-Transformed Fractional Anisotropy
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
Frontal
Temporal
Parietal
Occipital
**
***
**
**
**
*
**
*
* p < 0.05
** p < 0.01
*** p < 0.001
New Mexico
Minnesota
MGH
Iowa


-25
-10
0
10
25
35
Iowa
MGH
Minn
N Mex

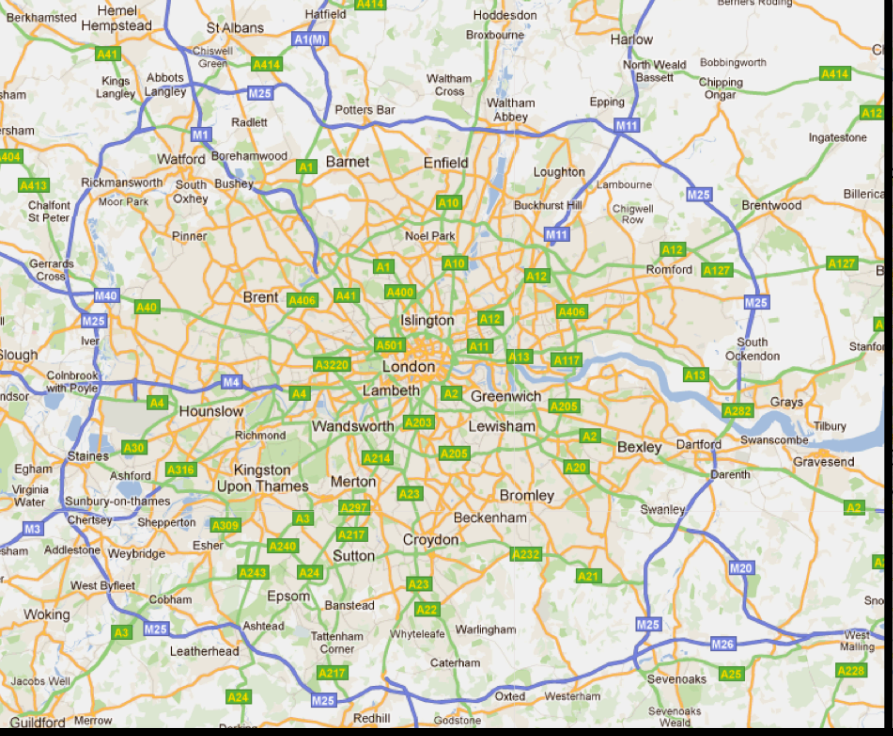
White Matter Abnormalities in Schizophrenia

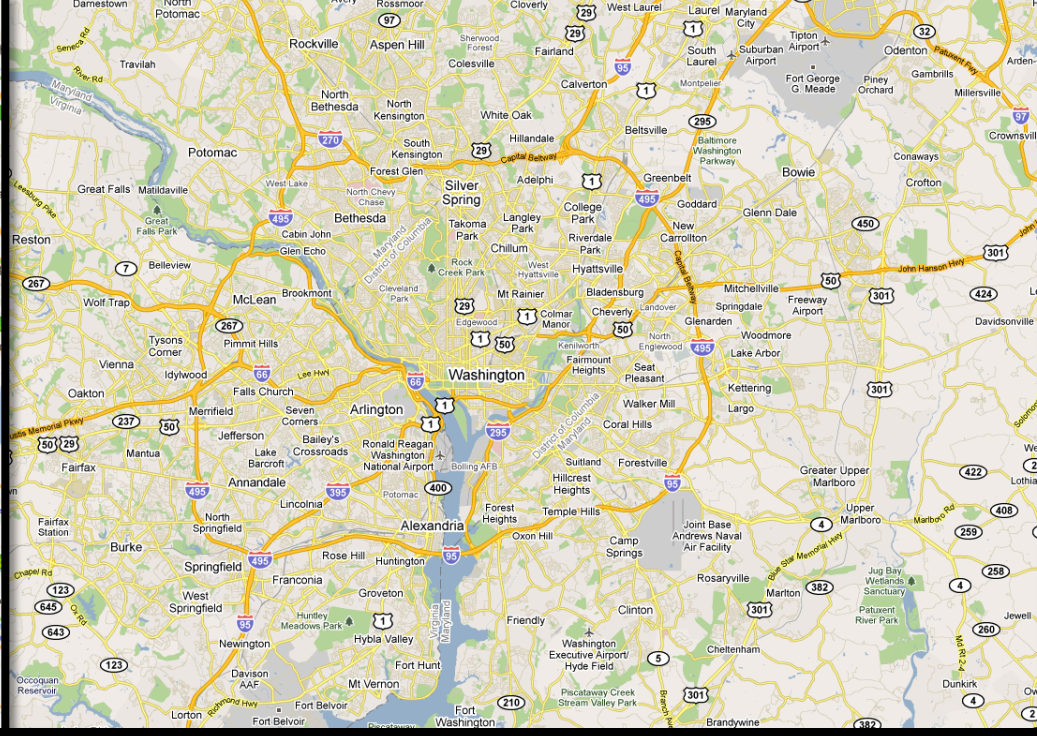
Summary of 50+ Studies

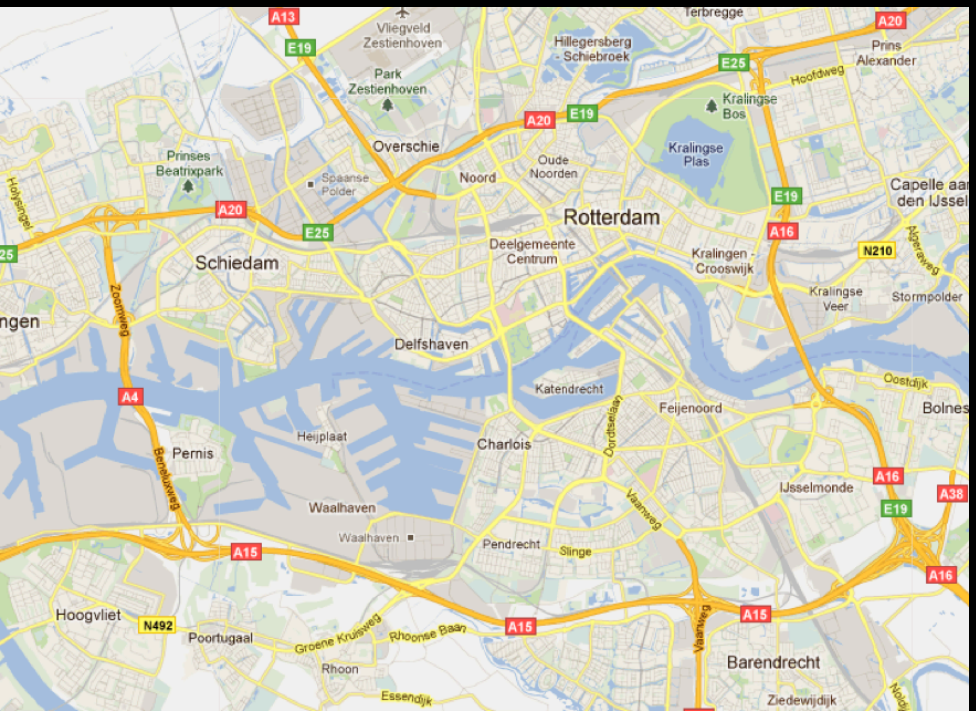


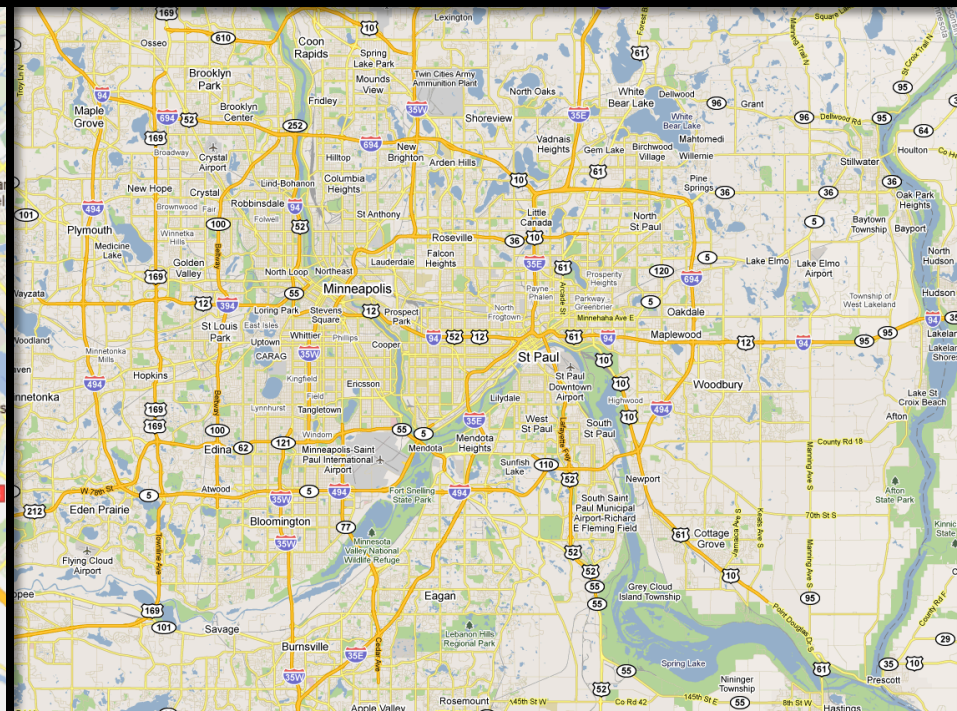
White, Nelson, Lim (2009)

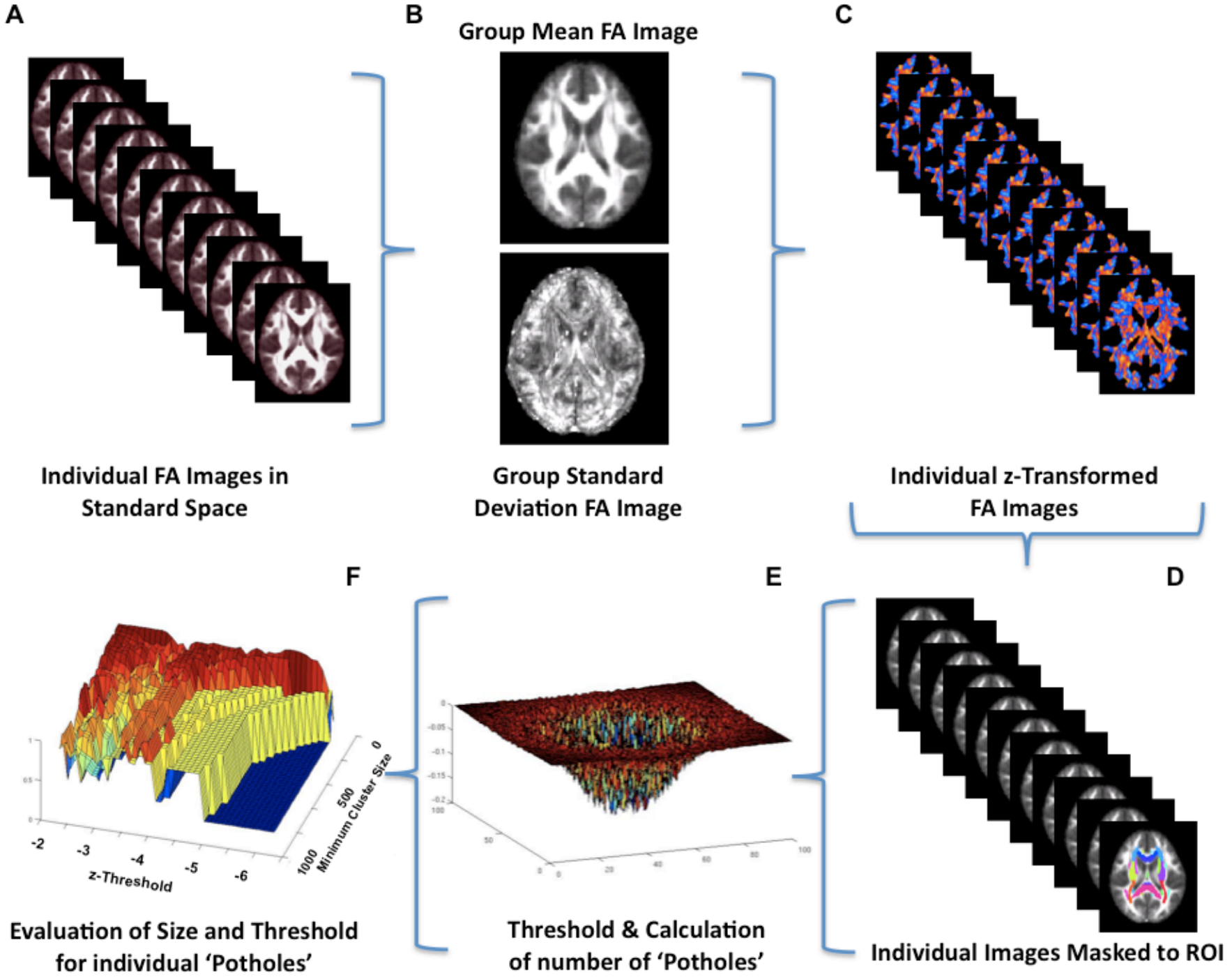

Den Haag
Leidschendam
Voorschoten
Zoeterwoude
Zoetermeer
Rijswijk
Nootdorp
Delft
Westland
Lansingerland
Gouda
Waddinxveen
Boskoop
Bodegraven
Woerden
Oudewater
Alphen aan Den Rijn
Rijnwoude
Moerkapelle
Moordrecht
Nieuwerkerk aan den IJssel
Ouderkerk
Capelle aan den IJssel
Rotterdam
Knijpen aan den IJssel
Vlaardingen
Schiedam
Maassluis
Rozenburg
Midden-Delfland
Schoonhoven
Bergambacht
Liesveld
Nieuw-Lekkerland
Graafstroom
Ridderkerk
Barendrecht
Albrandswaard
Spijkenisse
Hendrik-Ido-Ambacht
Papendrecht
Zwijndrecht
Dordrecht
Sliedrecht
Werkendam
Hardinxveld-Giessendam
Oud-Beijerland
Binnenmaas
Bernisse
Nederlek


Hemel Hempstead
St Albans
Hatfield
Hoddesdon
Broxbourne
Harlow
Chiswell Green
Kings Langley
Abbots Langley
Waltham Cross
Waltham Abbey
Epping
Chipping Ongar
Ingatestone
Radlett
Watford
Borehamwood
Barnet
Enfield
Loughton
Rickmansworth
South Oxhey
Bushey
Moor Park
Chalfont St Peter
Buckhurst Hill
Chigwell Row
Brentwood
Billerica
Pinner
Noel Park
Gerrards Cross
Romford
Brent
Islington
South Ockendon
Iver
Slough
Colnbrook with Poyle
London
Lambeth
Greenwich
Grays
Hounslow
Wandsworth
Lewisham
Tilbury
Richmond
Bexley
Dartford
Swanscombe
Staines
Egham
Ashford
Kingston Upon Thames
Merton
Gravesend
Darenth
Virginia Water
Sunbury-on-thames
Bromley
Chertsey
Shepperton
Beckenham
Swanley
Addlestone
Weybridge
Esher
Croydon
Sutton
West Byfleet
Cobham
Epsom
Banstead
Woking
Ashtead
Tattenham Corner
Whyteleafe
Warlingham
Leatherhead
Caterham
Jacobs Well
Guildford
Merrow
Redhill
Godstone
Oxted
Westerham
Sevenoaks
Sevenoaks Weald
West Malling

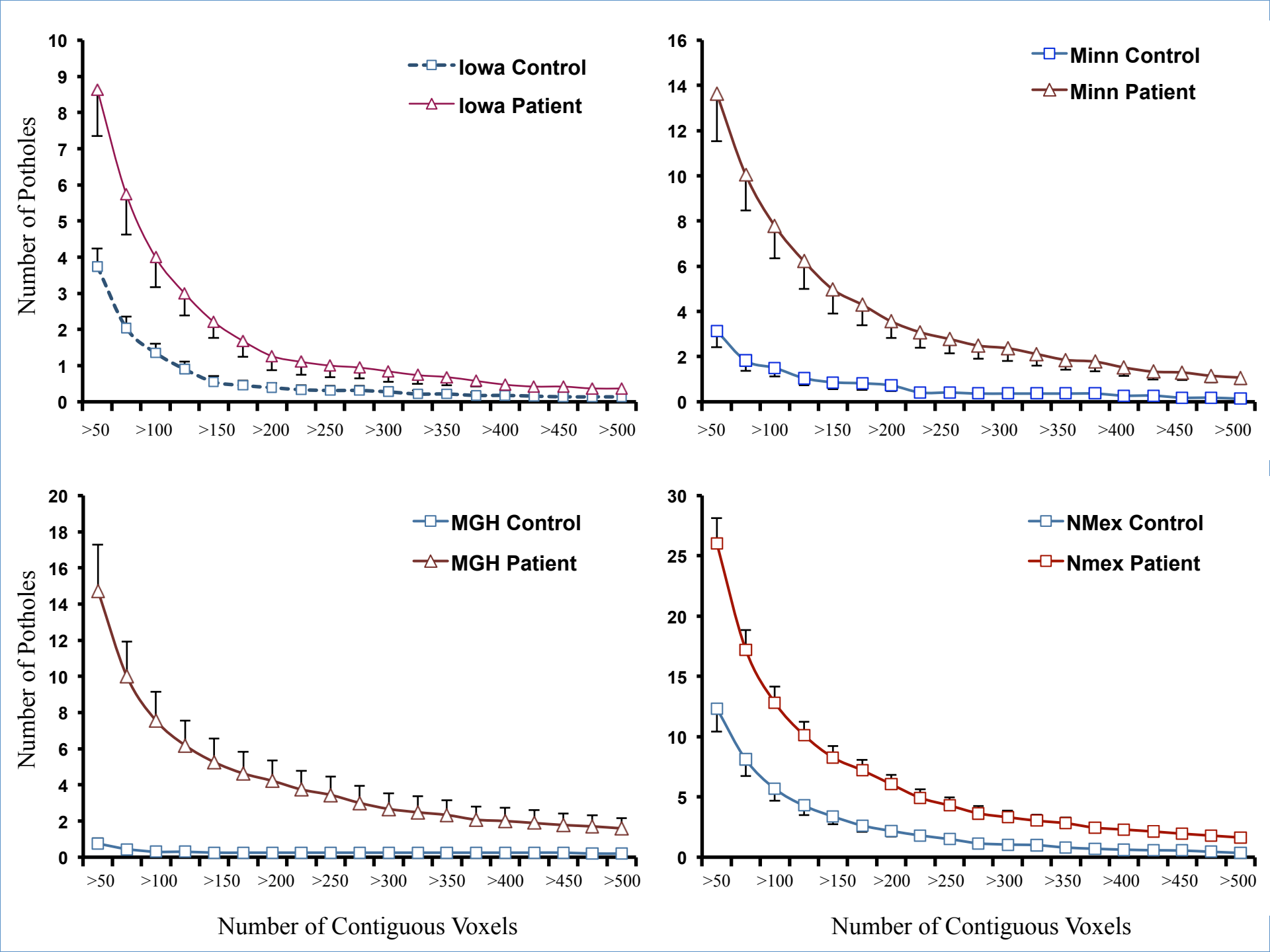

Darnestown
Potomac
Rockville
Aspen Hill
Fairland
Colesville
Travilah
Laurel
Maryland City
South Laurel
Suburban Airport
Tipton Airport
Odenton
Fort George G Meade
Piney Orchard
Gambrills
Millersville
Calverton
North Bethesda
North Kensington
White Oak
Beltsville
Hillandale
South Kensington
Forest Glen
Silver Spring
Adelphi
Greenbelt
Bowie
Conaways
Crofton
Great Falls
Matildaville
Bethesda
Takoma Park
Langley Park
College Park
Goddard
Glenn Dale
Reston
Cabin John
Glen Echo
Chillum
Riverdale Park
New Carrollton
Belleview
Rock Creek Park
Hyattsville
Wolf Trap
McLean
Brookmont
Mt Rainier
Bladensburg
Mitchellville
Springdale
Freeway Airport
Tysons Corner
Pimmit Hills
Cheverly
Colmar Manor
Glenarden
Woodmore
Vienna
Idylwood
Falls Church
Washington
Fairmount Heights
Lake Arbor
Oakton
Merrifield
Seven Corners
Arlington
Seat Pleasant
Kettering
Walker Mill
Largo
Jefferson
Bailey's Crossroads
Ronald Reagan Washington National Airport
Coral Hills
Mantua
Lake Barcroft
Fairfax
Annandale
Suitland
Forestville
Hillcrest Heights
Greater Upper Marlboro
Lincolnia
Temple Hills
Upper Marlboro
Fairfax Station
North Springfield
Alexandria
Forest Heights
Oxon Hill
Joint Base Andrews Naval Air Facility
Burke
Springfield
Rose Hill
Huntington
Camp Springs
Rosaryville
Franconia
Groveton
Marlton
West Springfield
Clinton
Hunting Meadows Park
Hybla Valley
Friendly
Newington
Washington Executive/Hyde Field
Cheltenham
Davison AAF
Fort Hunt
Mt Vernon
Occoquan Reservoir
Fort Belvoir
Piscataway Creek Stream Valley Park
Lorton
Fort Belvoir
Fort Washington
Brandywine

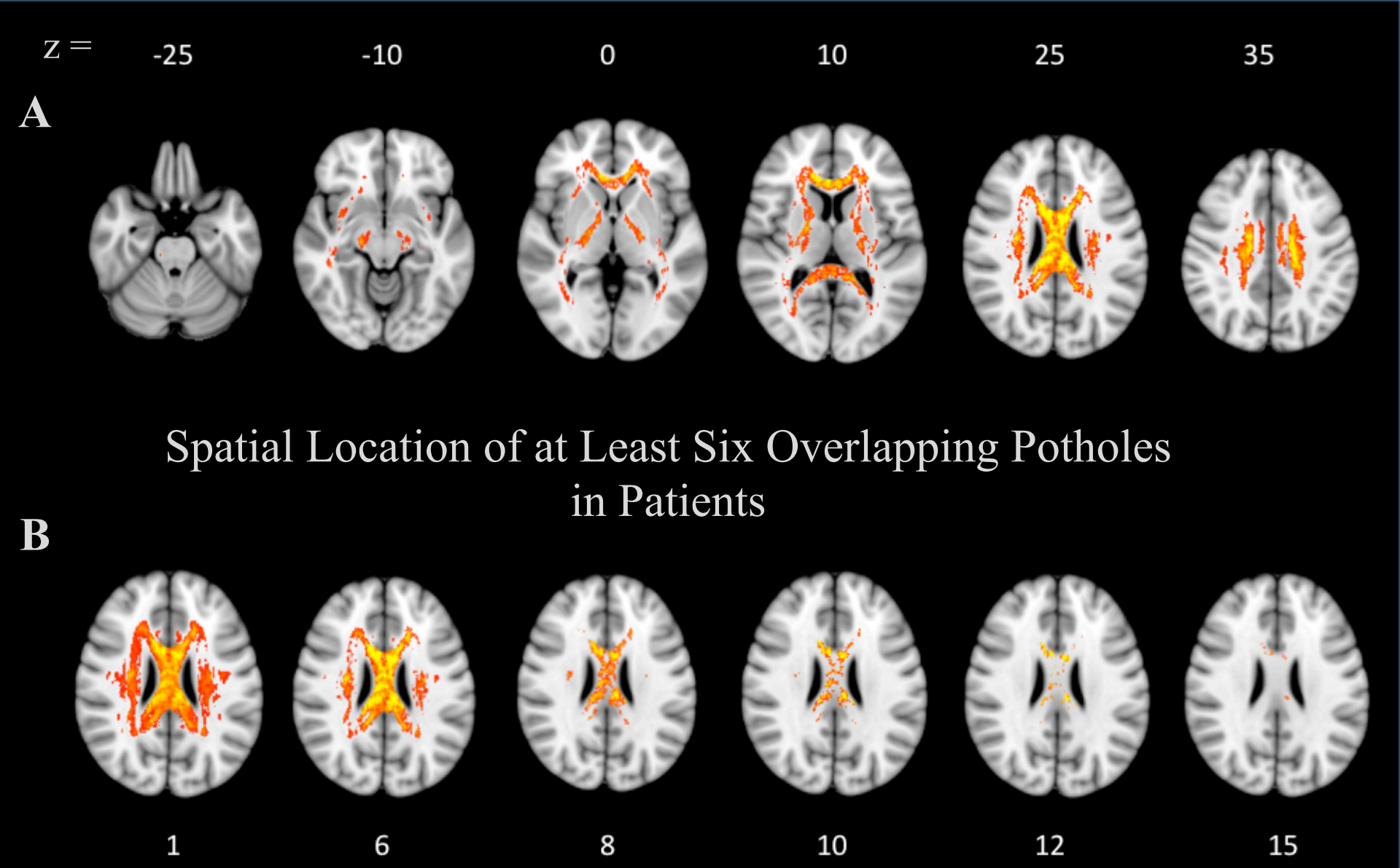

Terbregge
Vliegveld Zestienhoven
Hillegersberg - Schiebroek
Prins Alexander
Park Zestienhoven
Kralingse Bos
Hoofdweg
Overschie
Kralingse Plas
Prinses Beatrixpark
Spaanse Polder
Noord
Oude Noorden
Capelle aan den IJssel
Rotterdam
Deelgemeente Centrum
Kralingen - Crooswijk
Schiedam
Kralingse Veer
Stormpolder
Delfshaven
Katendrecht
Feijenoord
Oostdijk
Bolnes
Heijplaat
Charlois
Pernis
IJsselmonde
Waalhaven
Pendrecht
Slinge
Hoogvliet
Poortugaal
Groene Kruisweg
Rhoonse Baan
Rhoon
Barendrecht
Essendijk
Ziedewijdijk


Lexington
Osseo
Coon Rapids
Spring Lake Park
Brooklyn Park
Mounds View
Twin Cities Army Ammunition Plant
Maple Grove
Brooklyn Center
Fridley
North Oaks
Shoreview
White Bear Lake
Dellwood
Grant
Vadnais Heights
Gem Lake
Birchwood Village
Willernie
Mahtomedi
Stillwater
Houlton
Crystal Airport
Hilltop
New Brighton
Arden Hills
New Hope
Crystal
Lind-Bohanon
Columbia Heights
Pine Springs
Oak Park Heights
Robbinsdale
Little Canada
Plymouth
St Anthony
North St Paul
Baytown Township
Bayport
Medicine Lake
Roseville
Golden Valley
Falcon Heights
Lauderdale
Lake Elmo
Lake Elmo Airport
North Loop
Northeast
Minneapolis
Wayzata
Stevens Square
Prospect Park
Oakdale
Hudson
St Louis Park
Whittier
Phillips
Cooper
Maplewood
Minnetonka Mills
Hopkins
Kingfield
Ericsson
St Paul
St Paul Downtown Airport
Woodbury
Minnetonka
Tangletown
Lilydale
Highwood
Lake St Croix Beach
Edina
Windom
Minneapolis-Saint Paul International Airport
Mendota
Mendota Heights
West St Paul
South St Paul
Afton
Sunfish Lake
Atwood
Fort Snelling State Park
Eden Prairie
Bloomington
Minnesota Valley National Wildlife Refuge
Flying Cloud Airport
South Saint Paul Municipal Airport-Richard E Fleming Field
Cottage Grove
Eagan
Grey Cloud Island Township
Savage
Burnsville
Lebanon Hills Regional Park
Spring Lake
Ninninger Township
Rosemount
Apple Valley
Prescott


A
B
Group Mean FA Image
C
Individual FA Images in Standard Space
Group Standard Deviation FA Image
Individual z-Transformed FA Images
F
E
D
-2
-3
-4
-5
-6
z-Threshold
0
500
1000
Minimum Cluster Size
Evaluation of Size and Threshold for individual 'Potholes'
Threshold & Calculation of number of 'Potholes'
Individual Images Masked to ROI

Potholes in nature


Number of Potholes
Iowa Control
Iowa Patient
Minn Control
Minn Patient
MGH Control
MGH Patient
NMex Control
Nmex Patient
>50
>100
>150
>200
>250
>300
>350
>400
>450
>500
Number of Contiguous Voxels
Number of Contiguous Voxels


z =
-25
-10
0
10
25
35
A
Spatial Location of at Least Six Overlapping Potholes in Patients
B
1
6
8
10
12
15
Number of Overlapping Potholes at z = -25

Oxford Data

Subjects

- Schizophrenia spectrum
  - n = 42 (24 males / 19 females)
  - Mean age: 17.0 (SD 1.8) years
- Bipolar affective disorder
  - n = 13 (6 males / 7 females)
  - Mean age: 15.4 (SD 2.1) years
- Obsessive compulsive disorder
  - n = 17 (9 males / 8 females)
  - Mean age: 16.2 (SD 1.6) years
- Controls
  - n = 29 (15 males / 14 females)
  - Mean age: 16.5 (SD 2.0) years

Sequence Acquisition

1.5 Tesla

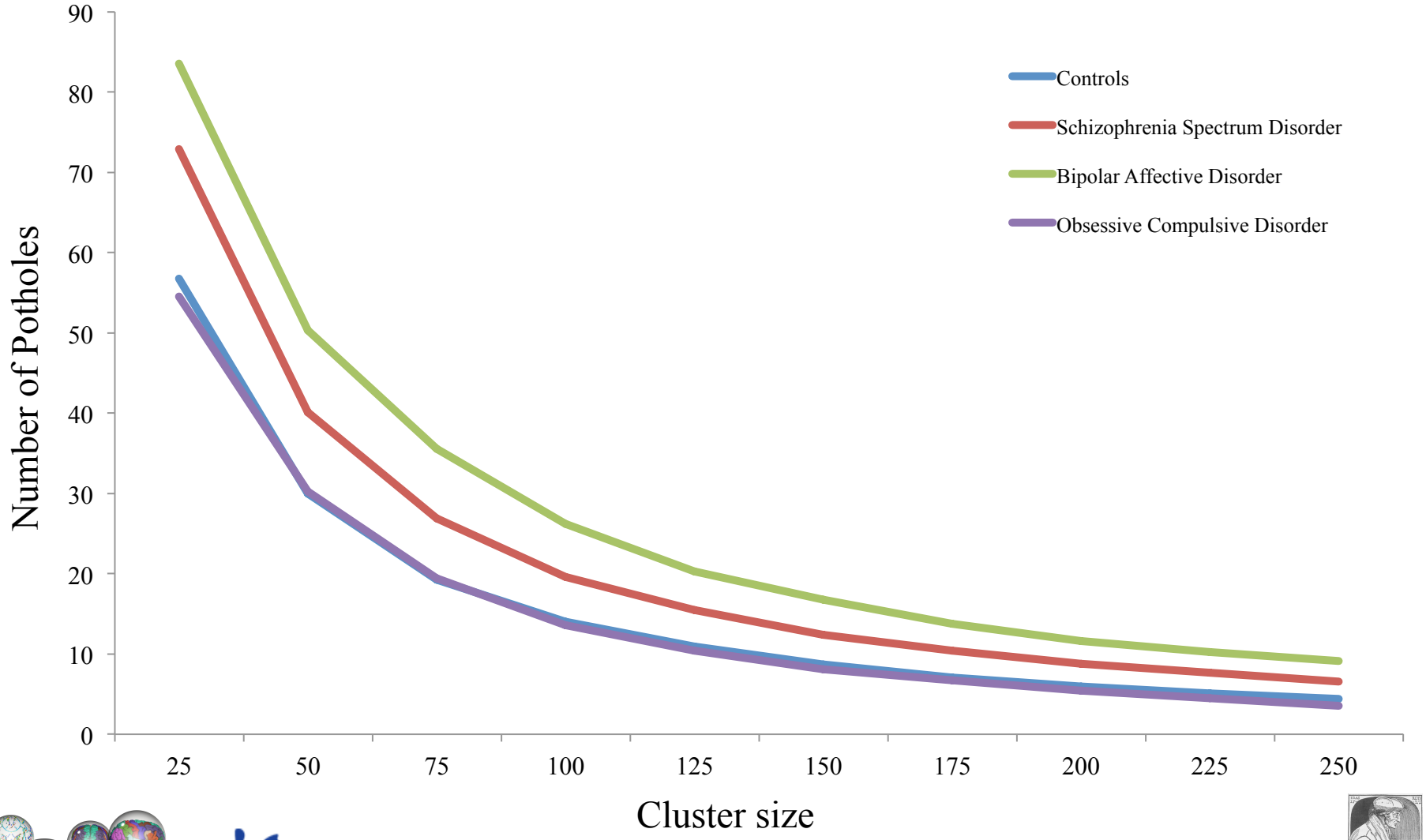
2.5 x 2.5 x 2.5 mm

60 directions

Generation R

Erasmus MC

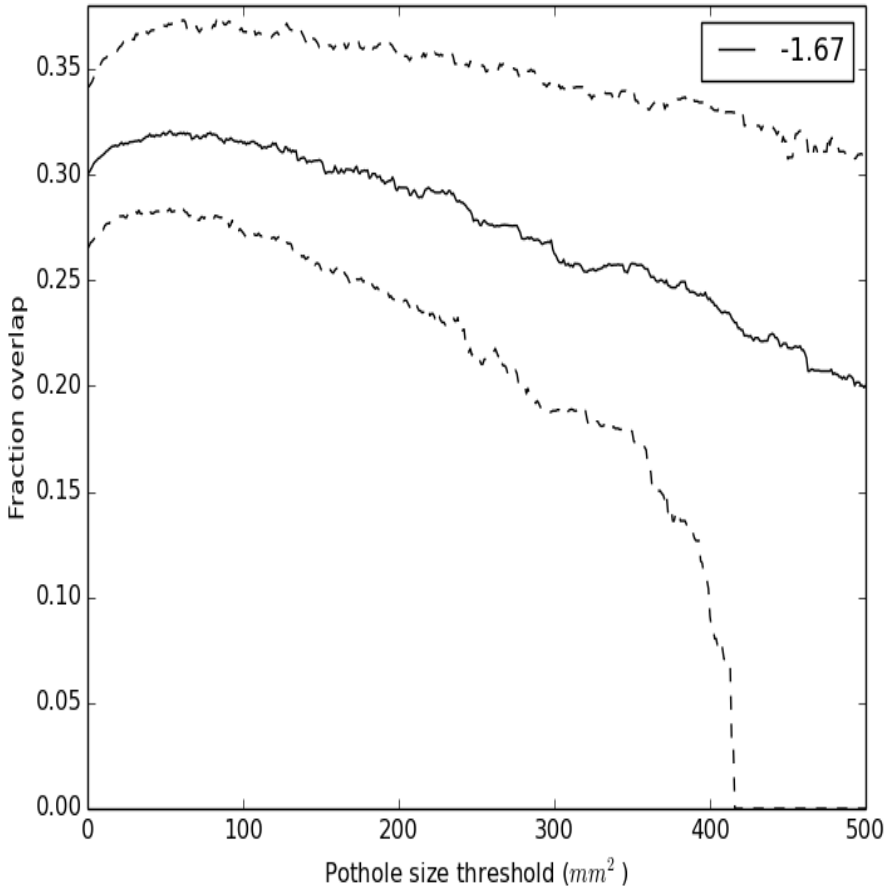
Potholes in Oxford Data



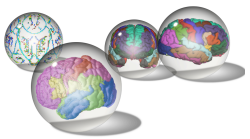
Intra-scanner correlation of number of potholes between runs

	Run 1	Run 2	Run 3
Run 1	1	0.95	0.96
Run 2	0.95	1	0.93
Run 3	0.96	0.93	1

Spatial overlap of potholes at time 1, 2 & 3 as a function of cluster size threshold



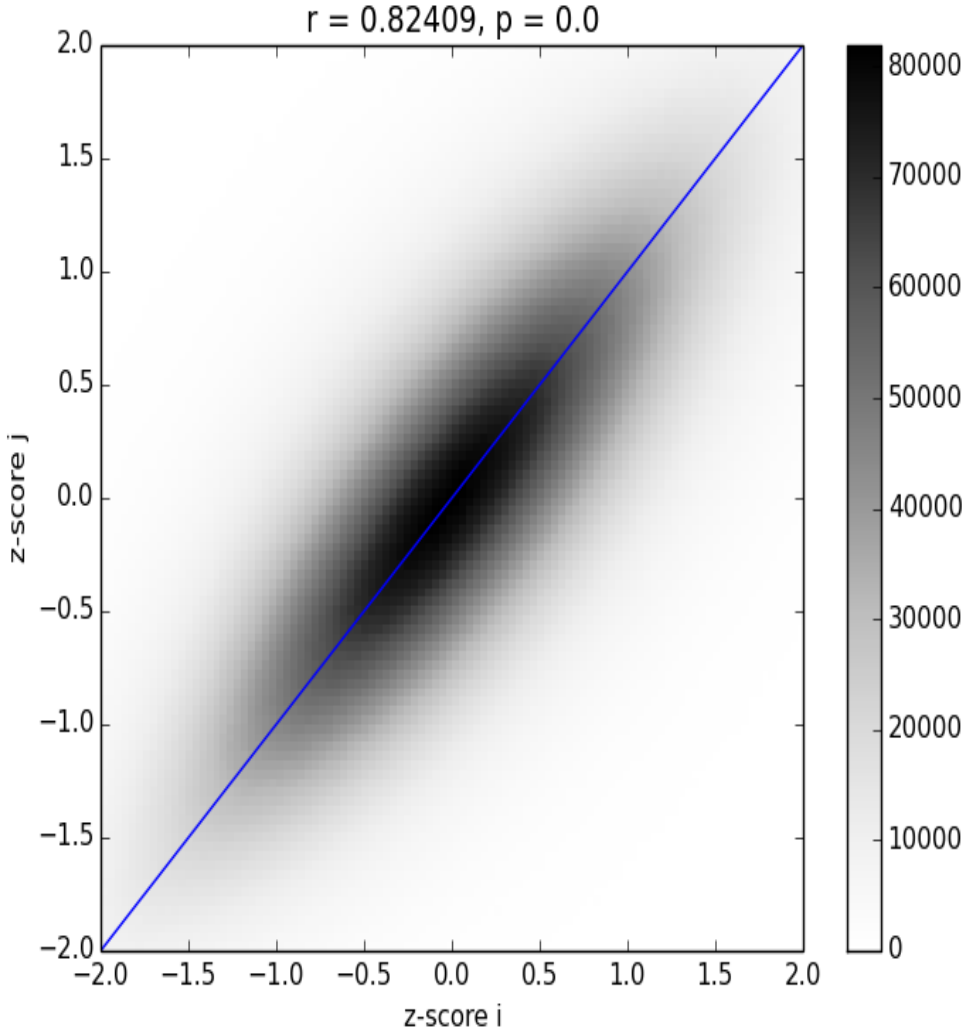
$$\varphi = \frac{A_j \cap A_k}{A_j \cup A_k}$$



Generation R

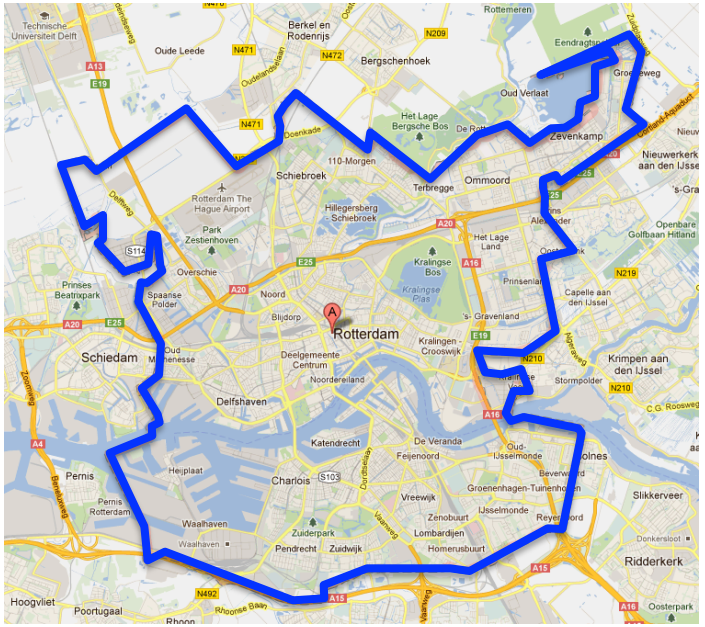
Erasmus MC

Scatter plot of z-scores



Generation R

Generation R Study Design



- Prospective cohort design
- 9,778 mothers and their children
- Born between 2002 and 2006
- Plan is to follow the children into young adulthood

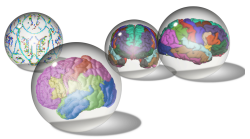
- Goal to describe normal and abnormal patterns of growth and development

Generation R

Erasmus MC

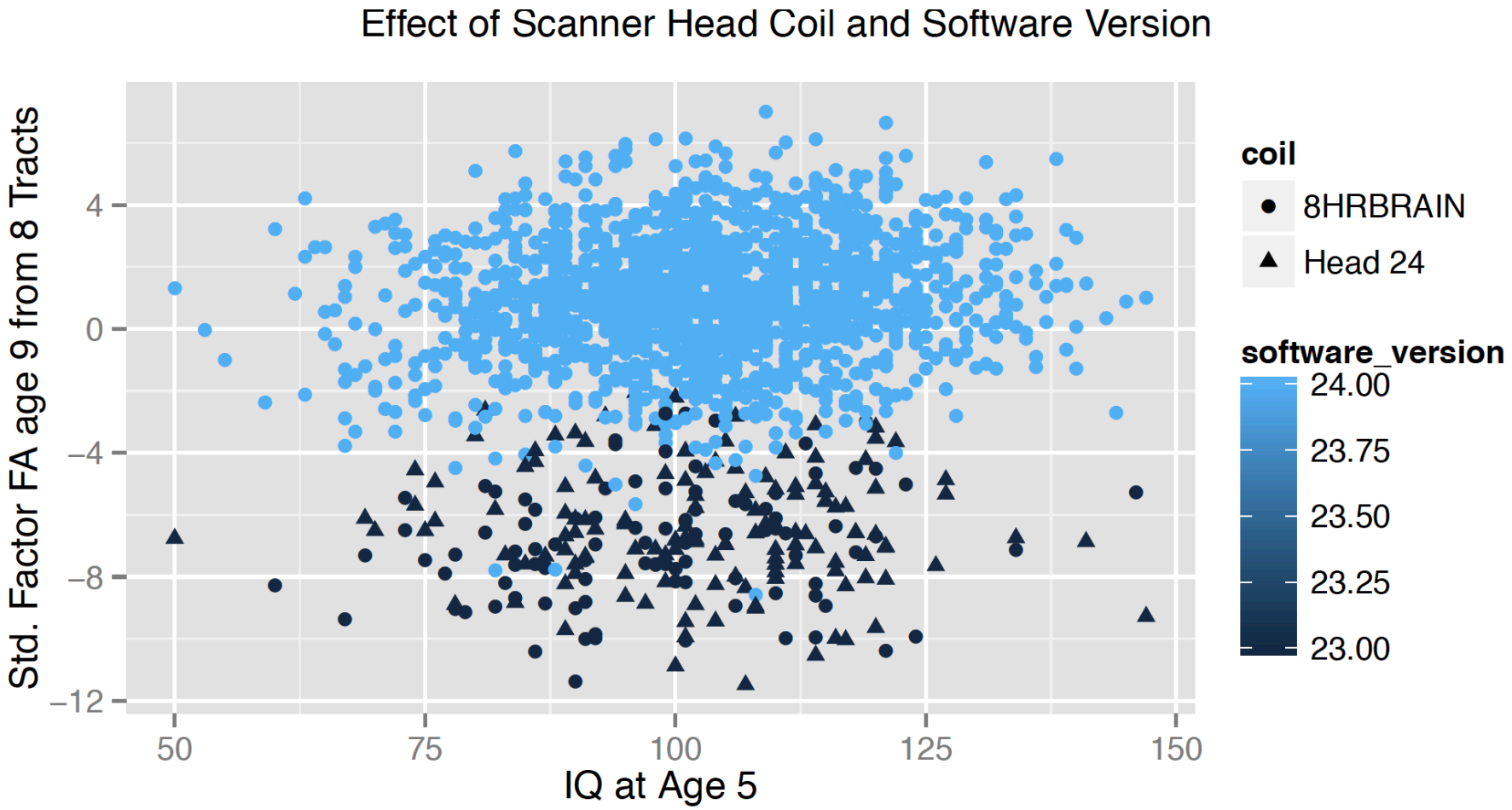
Generation R Neuroimaging

- Pilot/feasibility study: Began September 2009
  - Completed phase I in July 2013
    - 1,070 six to eight year old children scanned
  - 2013: Dedicated Scanner Installed
    - Began scanning Focus @ 9 cohort in April 2013
    - Scanned over 3,500 nine to ten year old children to date.
      - Averaging 140 – 160 children per month
      - Goal of 5,000 children scanned at time 2
      - Then begin scanning at time 3

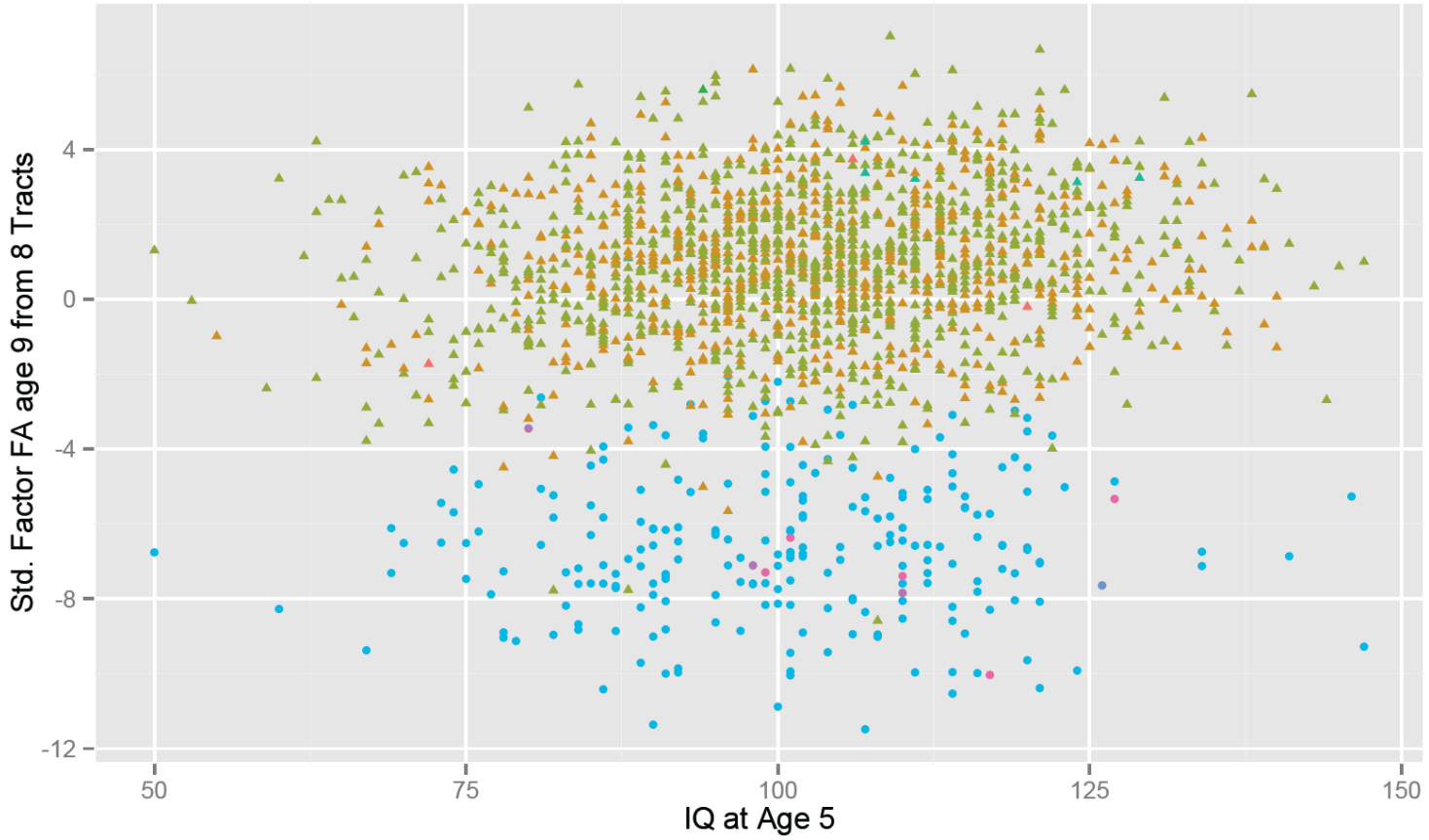


Generation R

Erasmus MC



Generation R



Generation R

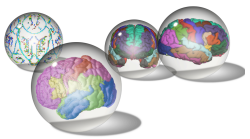
Conclusions

- Harmonization should also consider harmonization in demographics and an accurate classification of the clinical phenotype
- Specific image processing algorithms are associated with corresponding assumptions.
- Decreasing the inter-site image acquisition variability can be achieved by:
  - Selecting similar sequence parameters and scanners
  - Non-linear registration approaches
  - Focal ROI's (corpus callosum) or whole brain DWI measures
- Big data is good


HOLLAND AMERIKA LIJN

DTI data – different scanners and acquisition sequences were used at the different sites. No information is provided on reliability of measures between scanners as could be obtained by imaging the same individuals on scanners at each site.

This is an excellent point and prior to the current study, a reliability study was performed where subjects traveled between sites and were scanned. However, since then one site (Iowa) upgraded from a 1.5 Tesla GE to a 3 Tesla Siemens scanner and several sites altered their DTI sequences. After these changes in scanner updates and sequences were made, we lacked the resources to perform a second reliability study. To address site related differences, we have analyzed and presented the data for each site separately, as shown in Figure 2. We agree that had we been able to repeat the reliability study it would be a very valuable contribution to this paper and the literature at large.



Thank you for your attention

NWO
Netherlands Organisation for Scientific Research

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vrienden van het Sophia

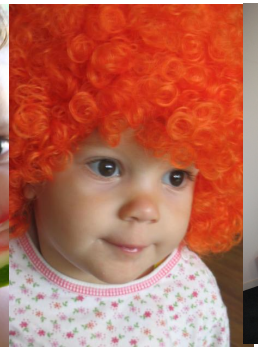
Nutri MENTHE

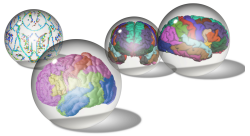
BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

SEVENTH FRAMEWORK PROGRAMME



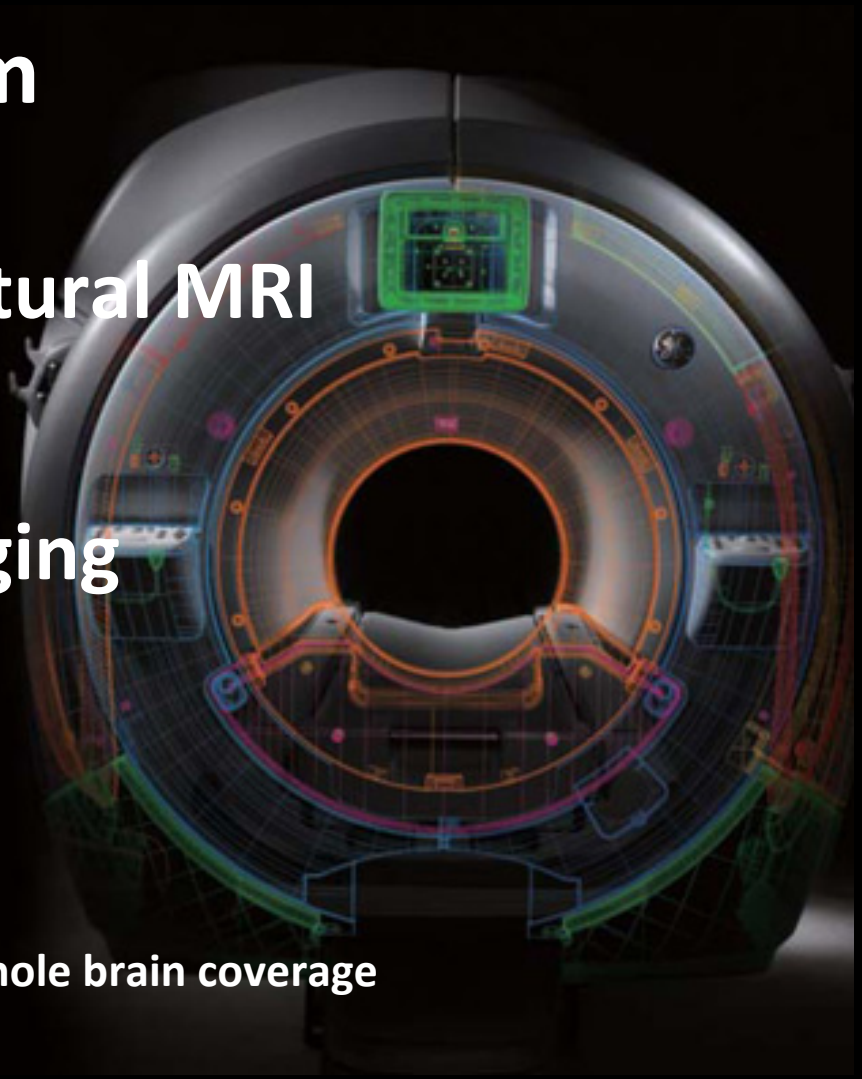



Generation R

Erasmus MC

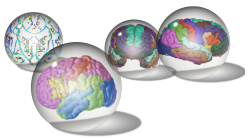
Neuroimaging

- GE 3 Tesla 750 System
  - 8 Channel head coil
- High-resolution structural MRI
  - T1 FLASH sequence
  - 0.9 mm isotropic resolution
- Diffusion Tensor Imaging
  - 2 mm isotropic resolution
  - 35 directions
- Functional MRI
  - Gradient Echo (BOLD) sequence
  - 4 mm isotropic resolution with whole brain coverage



Methods

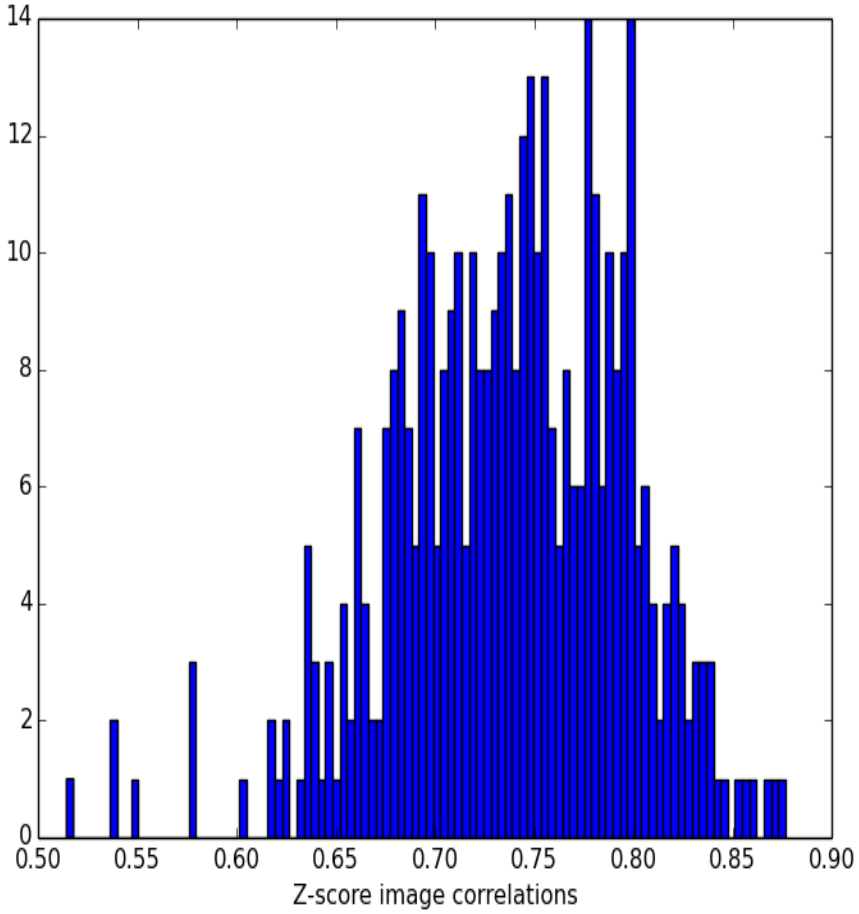
- Preprocessing:
  - Eddy-current corrected and upsampled to 1mm isotropic (Elastix)
  - Rotated gradient tables with eddy current according to transform parameters
  - Brain mask generated
  - Fit tensors, generate FA iamges (dtifit)
  - Registration to MNI 152 (Elastix):
    - Rigidly registered all 3 repetitions to their mean space
    - Registered mean FA image to MNI152 (affine + b-spline)
    - Applied rigid + affine + b-spline registrations to each repetition

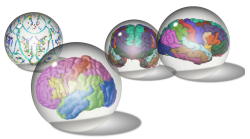


Generation R

Erasmus MC

Distribution of z-score correlations

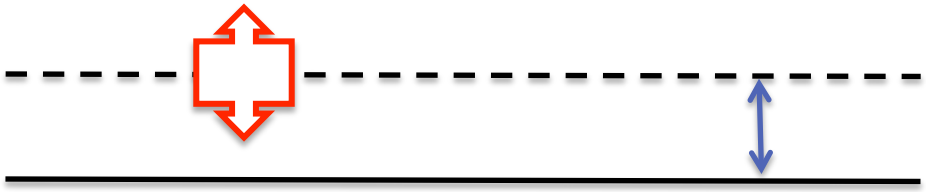


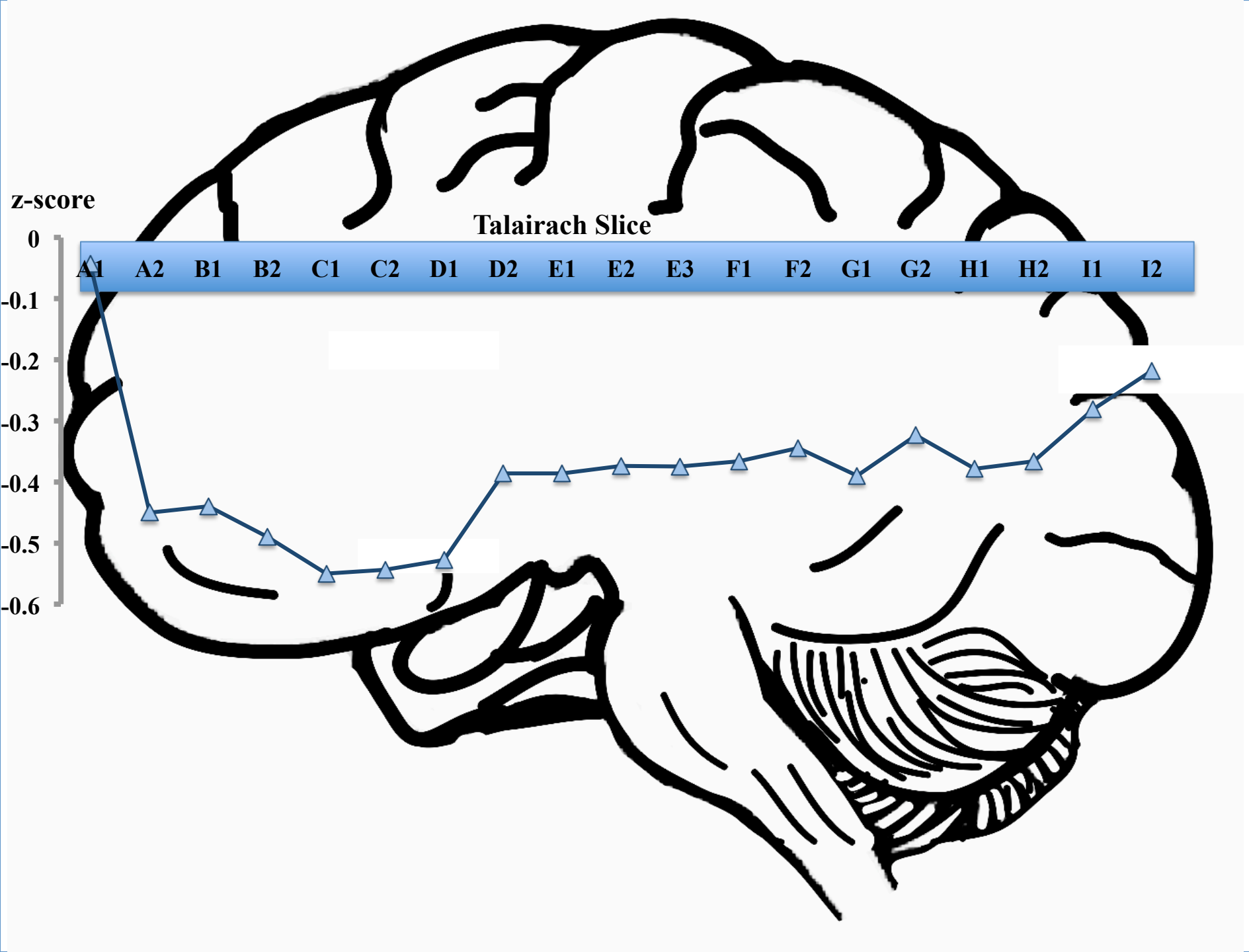


Generation R

Erasmus MC

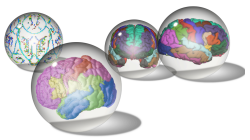
Accuracy versus Precision




z-score
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
Talairach Slice
A1
A2
B1
B2
C1
C2
D1
D2
E1
E2
E3
F1
F2
G1
G2
H1
H2
I1
I2

Group Difference in Number of Potholes

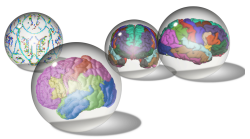
	Controls	Sz	BPAD	OCD
Controls		p = 0.012	p = 0.003	n.s.
Sz			n.s.	p = 0.03
BPAD				p = 0.03
OCD				



Threshhold: z < -2
Blobsize > 100 voxels

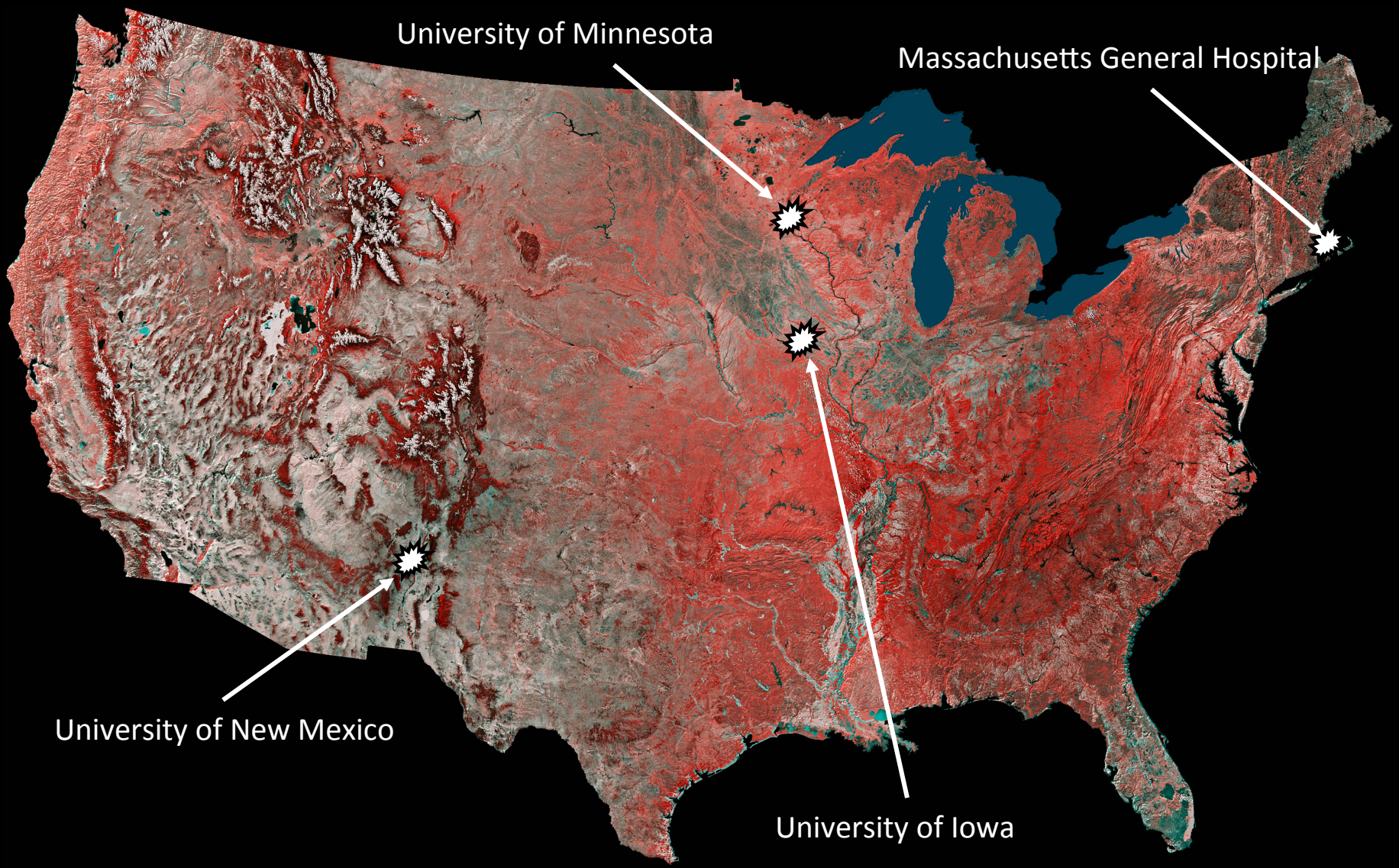
Overview

- Mind Research Network
  - Combining multisite data
- Oxford
  - Scan/rescan reliability
- Rotterdam
  - Combining time 1/time 2 data



Generation R

Erasmus MC



The Mind Research Network