Methods for Whole-Brain Comparisons of Resting State Functional Connectivity

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Functional Connectivity of Spontaneous Activity at Rest (i.e. "Resting State")

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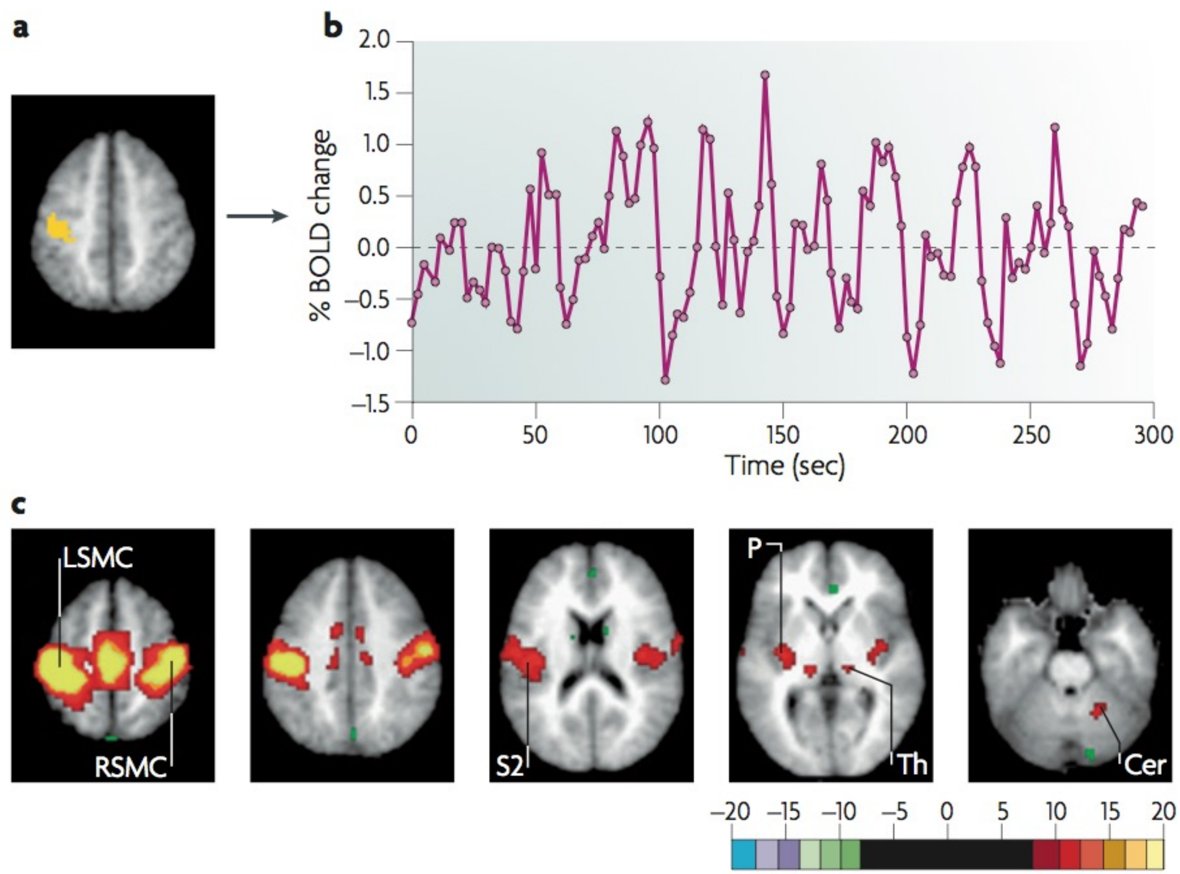
For review:

Fox & Raichle (2007). *Nat Rev Neurosci*

Power, Schlaggar, & Petersen (2014). *Neuron*



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But what to do for functional connectivity studies?

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Other options:

- Predefined Regions of Interest
  - but might not capture the full picture
- Methods that decompose the data into smaller numbers of elements, such as **ICA**
  - requires some assumptions about the nature of the data

Today's Talk

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Two different whole-brain approaches that are more purely statistical (based in cluster-size correction), with fewer *a priori* assumptions about network structure:

- Using average "connectedness" (centrality)
- Testing every voxel as a seed (without averaging)

Average Connectedness (Centrality)

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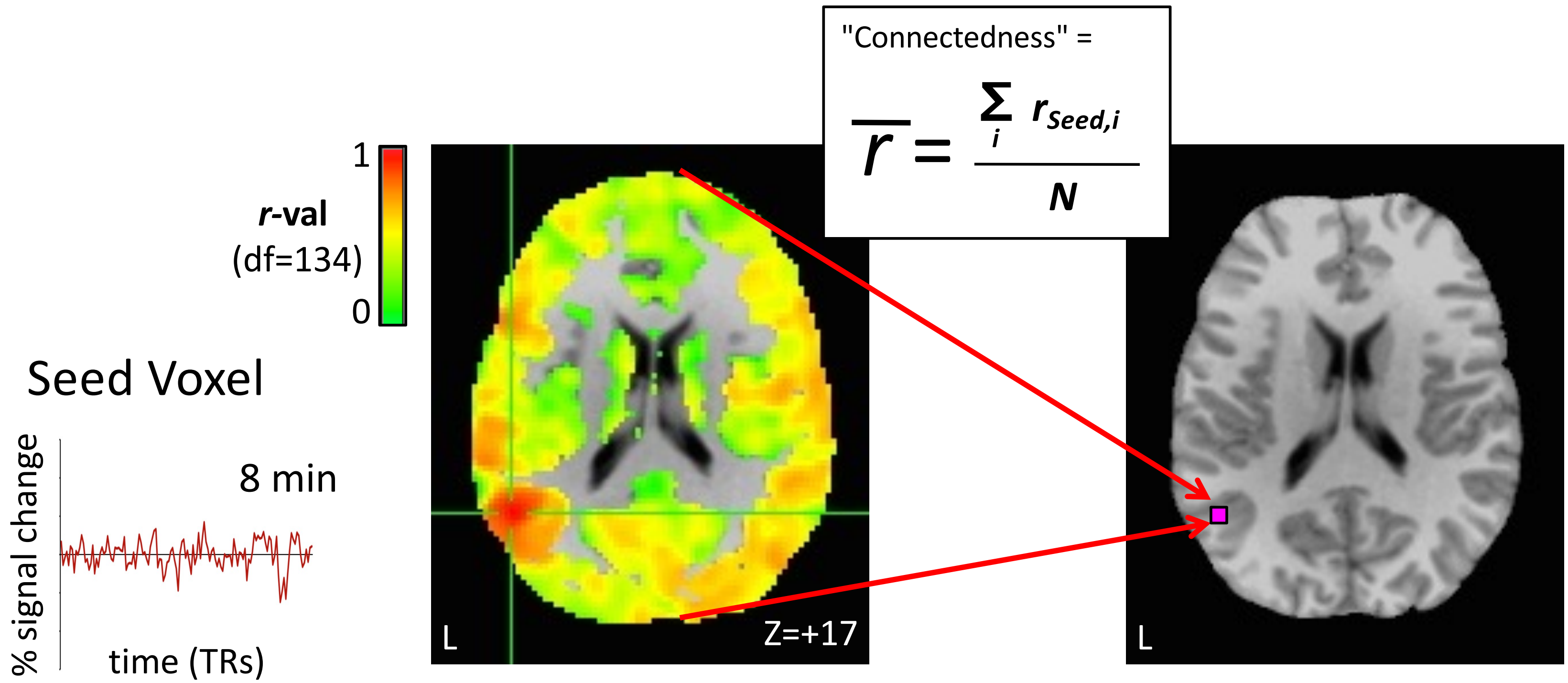
Compress the all-to-all voxels problem into a single map of "connectedness" for each subject (per condition)



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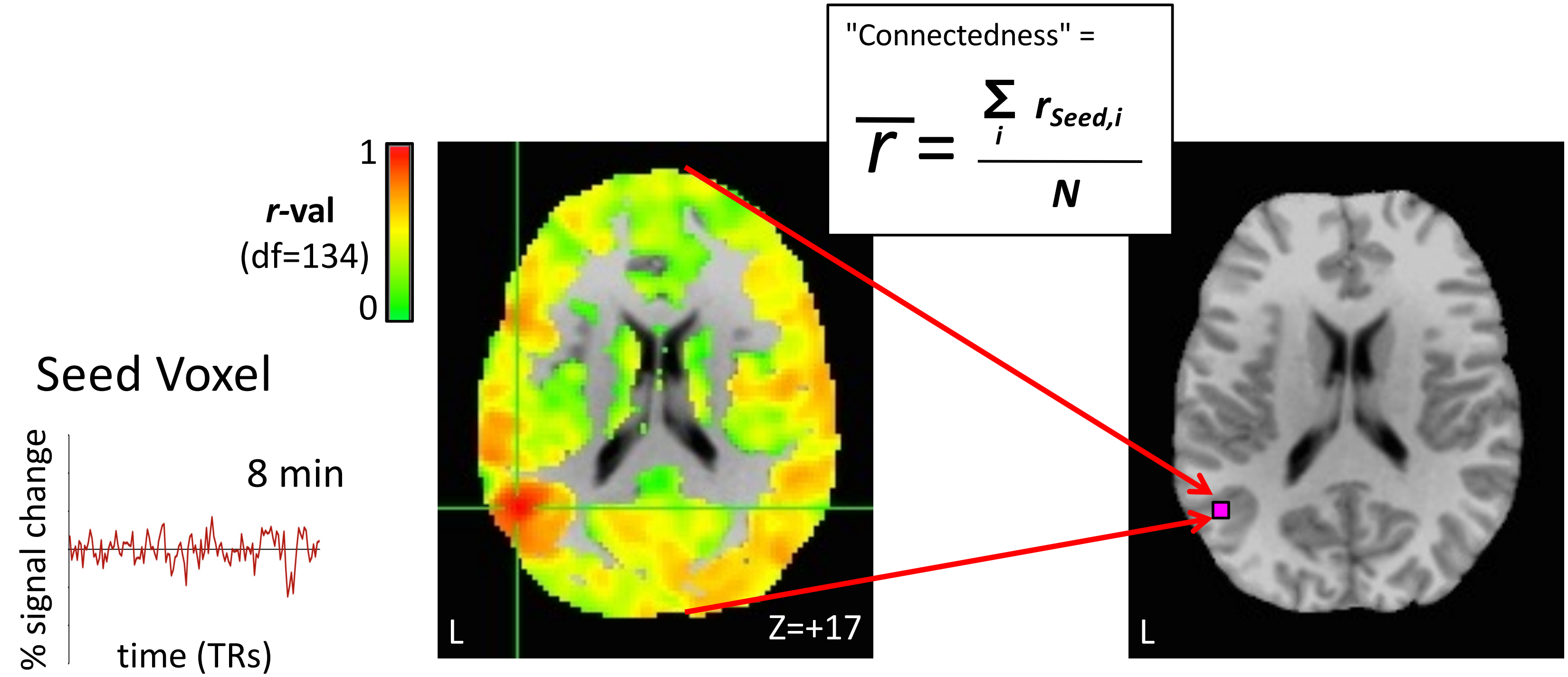

**** a la Bob Cox and his AFNI group***

Average Connectedness (Centrality)

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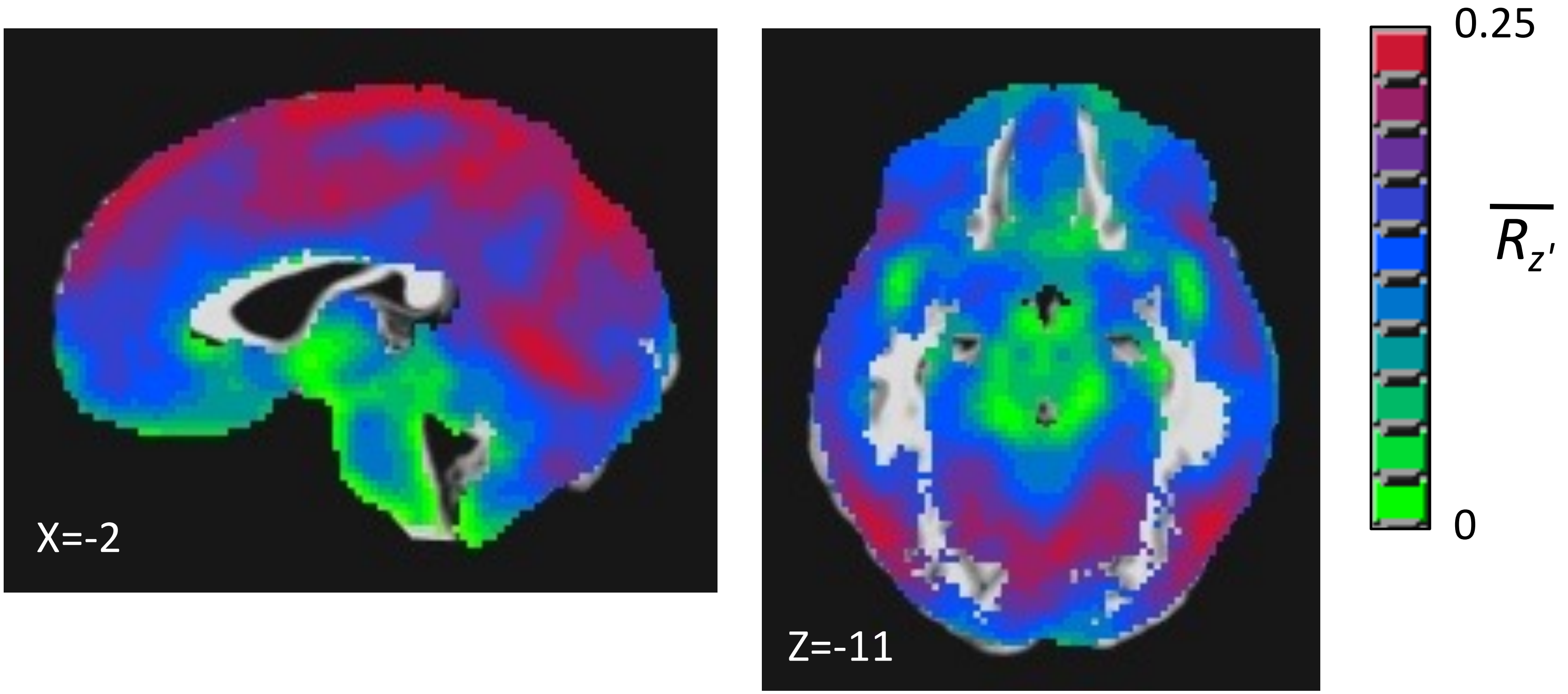
Group Average Connectedness (per condition):



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Pro: Preserves a lot of the spatial resolution in the data, Regardless of the group comparison, has a shot at finding "under" or "over-connected" voxels

Con: Might miss more spatially restricted effects and mixtures of under/over-connection

Example:
Autism (ASD) vs. Typically Developing (TD)

doi:10.1093/brain/aws160 Brain 2012: 135; 2711–2725 | 2711

BRAIN
A JOURNAL OF NEUROLOGY

Fractionation of social brain circuits in autism spectrum disorders

Stephen J. Gotts,[1] W. Kyle Simmons,[2] Lydia A. Milbury,[1] Gregory L. Wallace,[1]
Robert W. Cox[3] and Alex Martin[1]

Altered Functional Connectivity in Autism Spectrum Disorders (ASD)

31 High-Functioning ASD adolescents

- Using DSM-IV criteria + ADI, ADOS
- "Triad" of impairments:
  - Impaired social functioning
  - Restricted interests/repetitive behaviors
  - Language/communication impairments

29 Typically Developing (TD) controls

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Sex	95% male subjects

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Scanned at rest with 3.5 sec TR for 8 min 10 sec with 1.7 x 1.7 x 3 voxels

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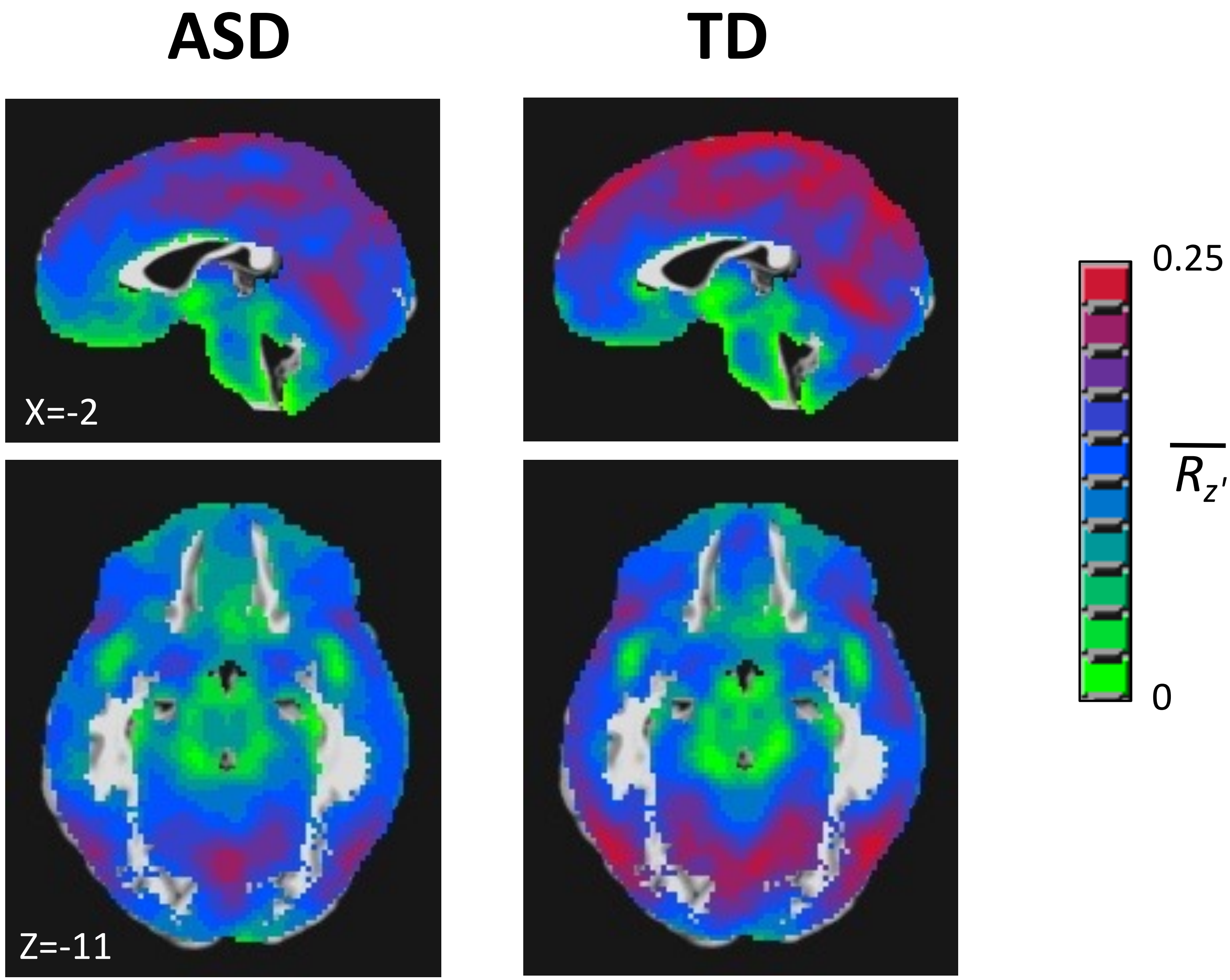
- Increase in Local Interactions ?   (**)

The "Social Brain"

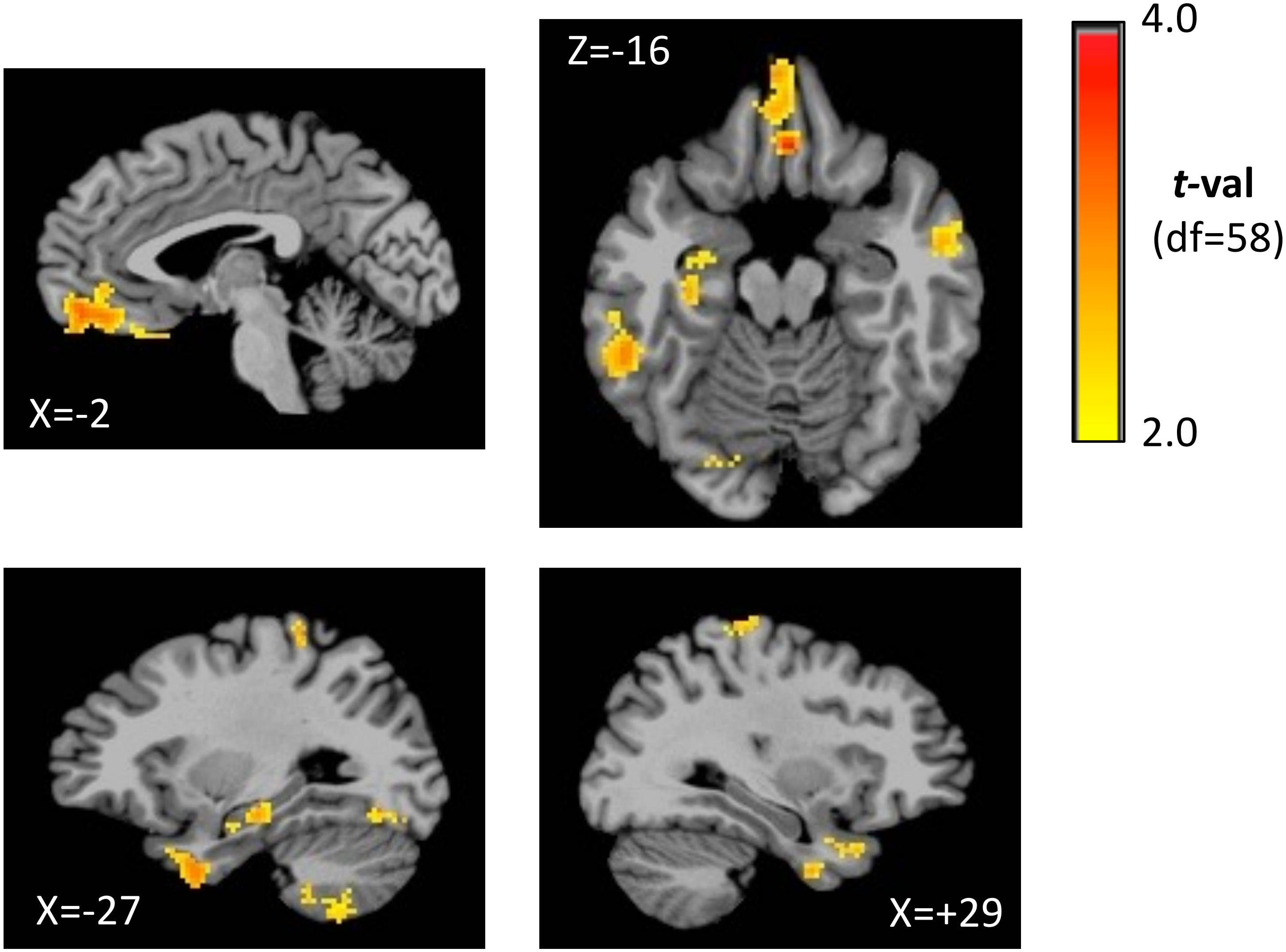
(a la Brothers, 1990; Frith & Frith, 2007; Adolphs, 2009)

Using Group Connectedness to Find Seeds



Using Group Connectedness to Find Seeds

TD - ASD



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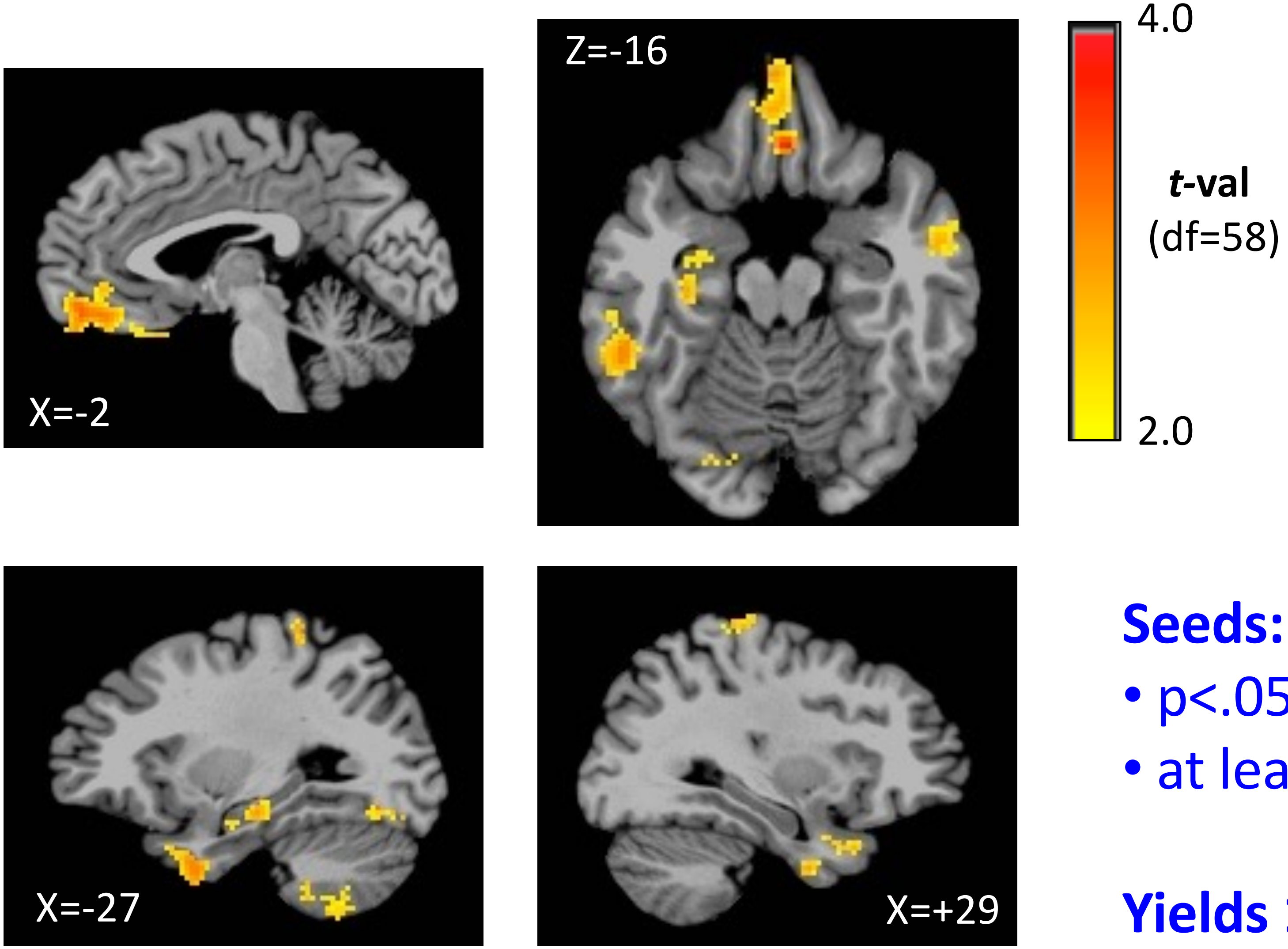
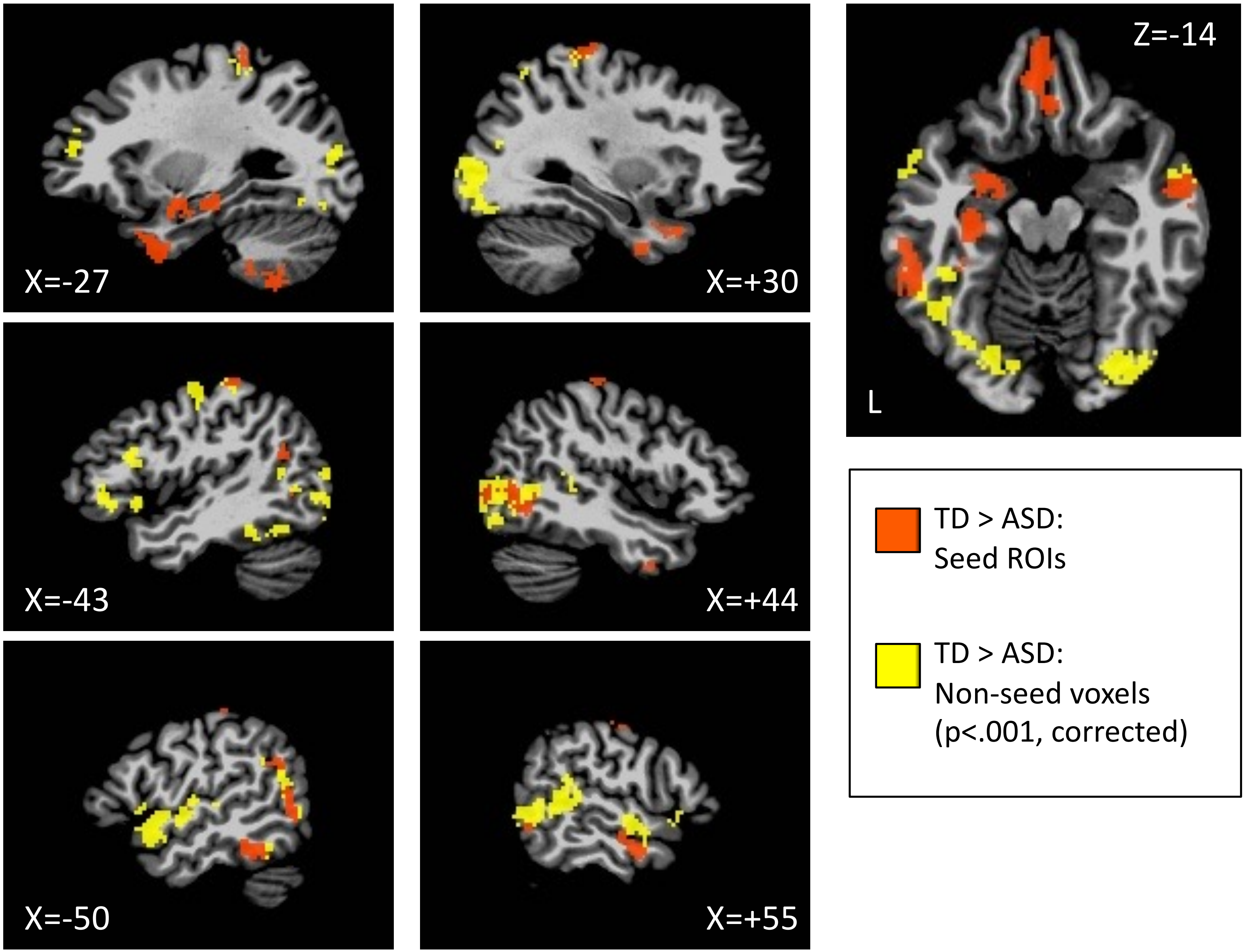


Seeds:
- $p<.05$
- at least 100 voxels

Yields 14 Seeds

Seeds + Seed Tests --> 27 Total Regions of Interest



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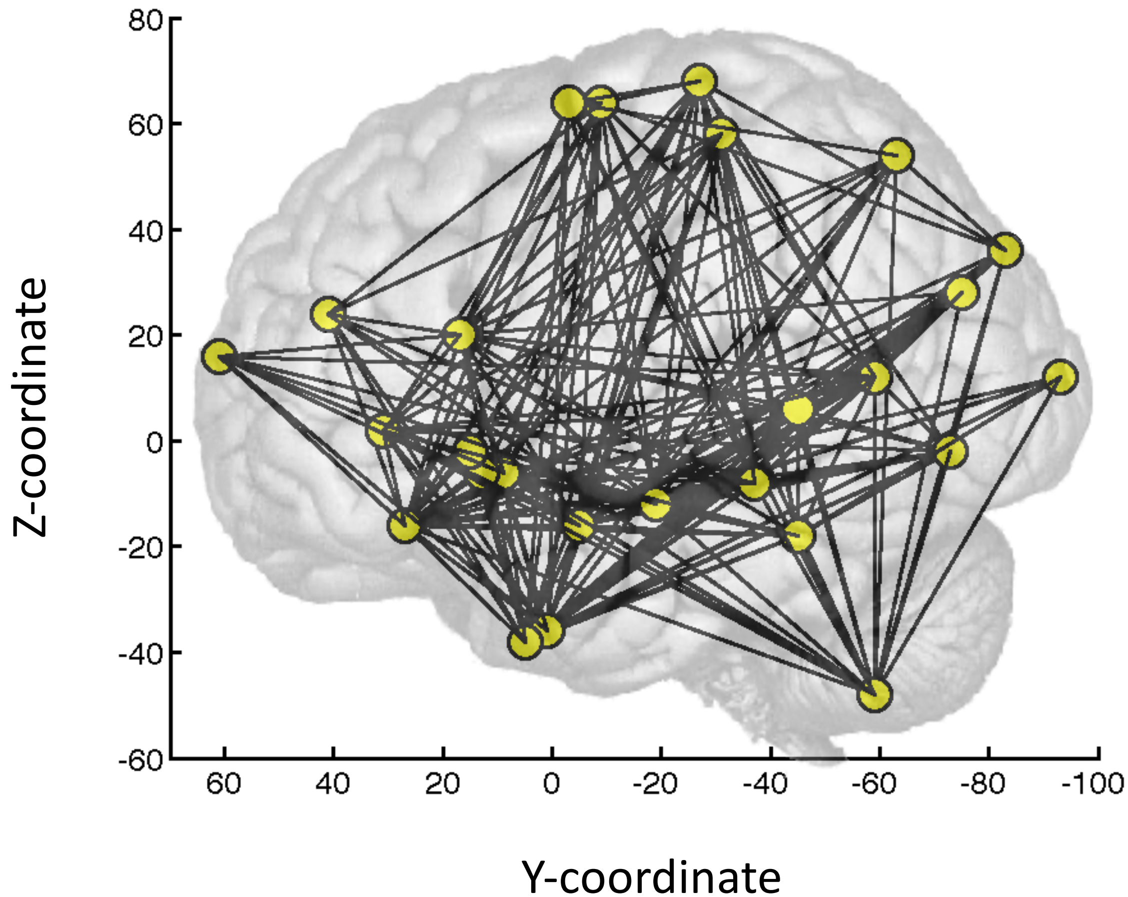

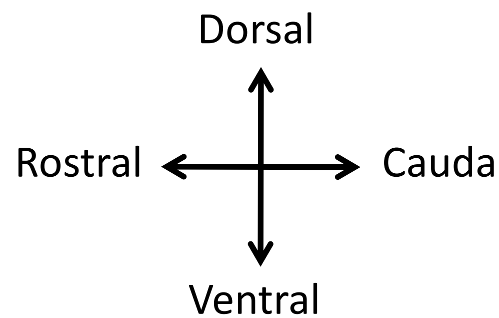

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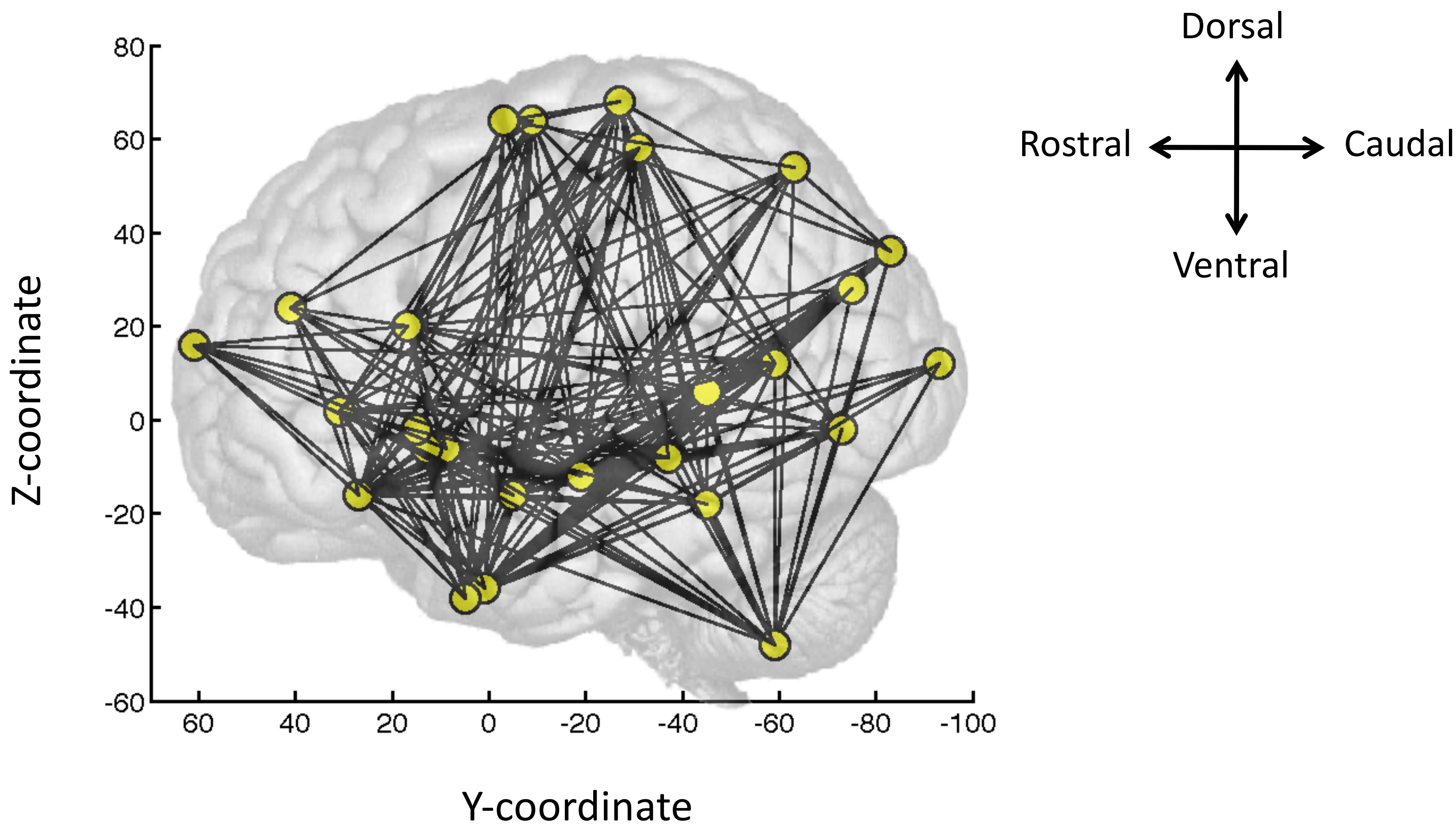
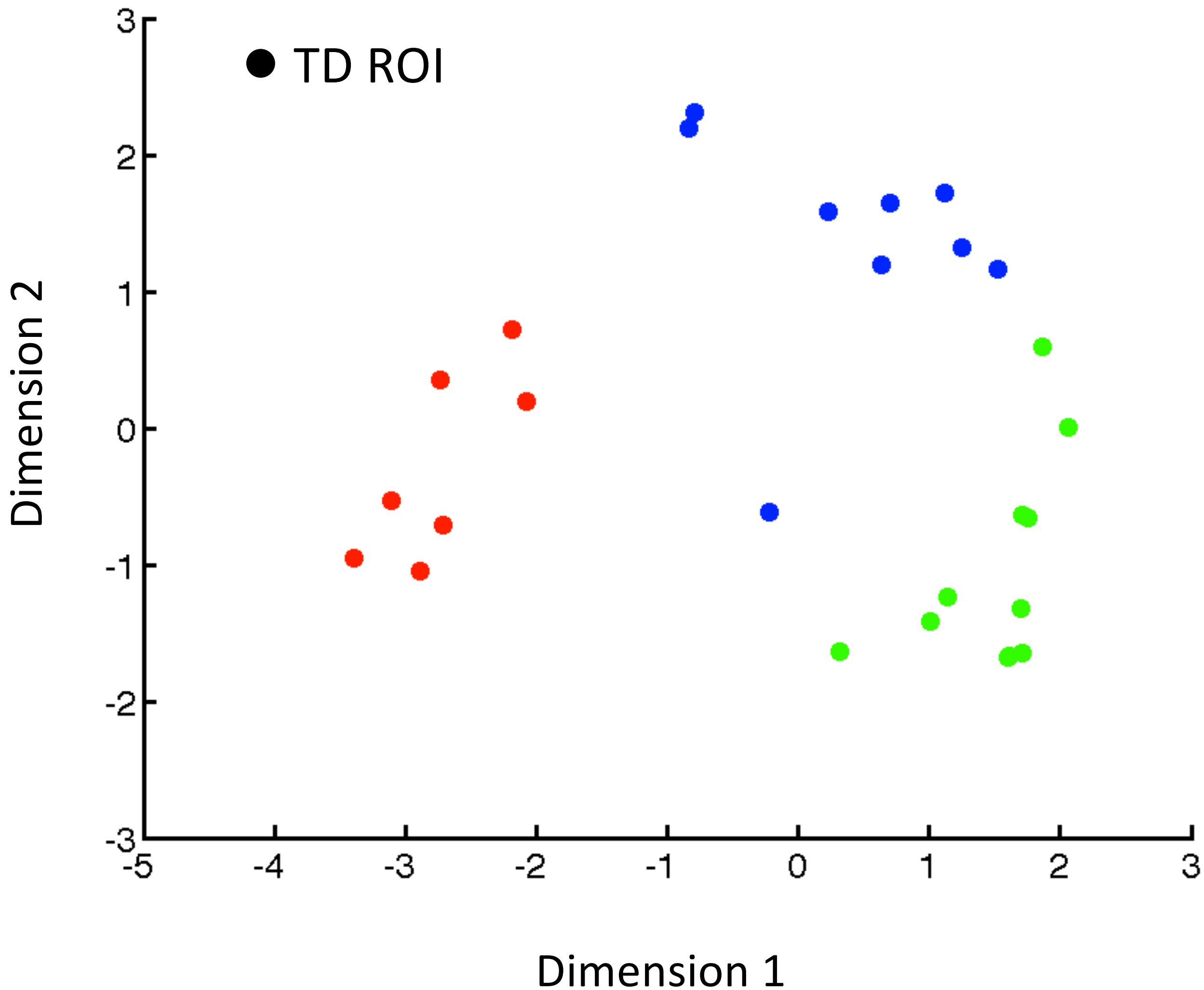


How do these areas relate to each other ?

Visualizing ROI-ROI correlations with Multi-Dimensional Scaling and K-Means Clustering (K=3)



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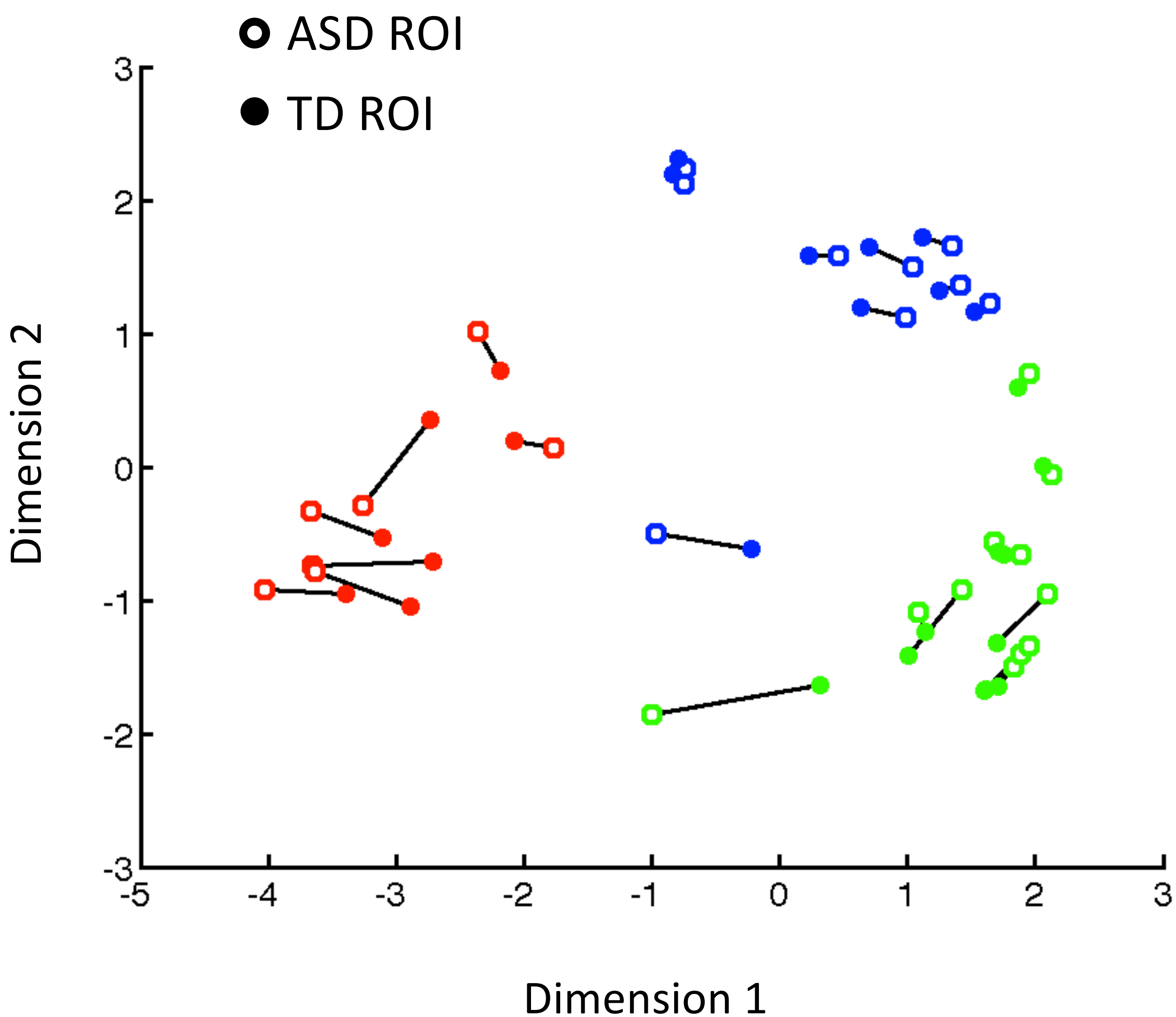

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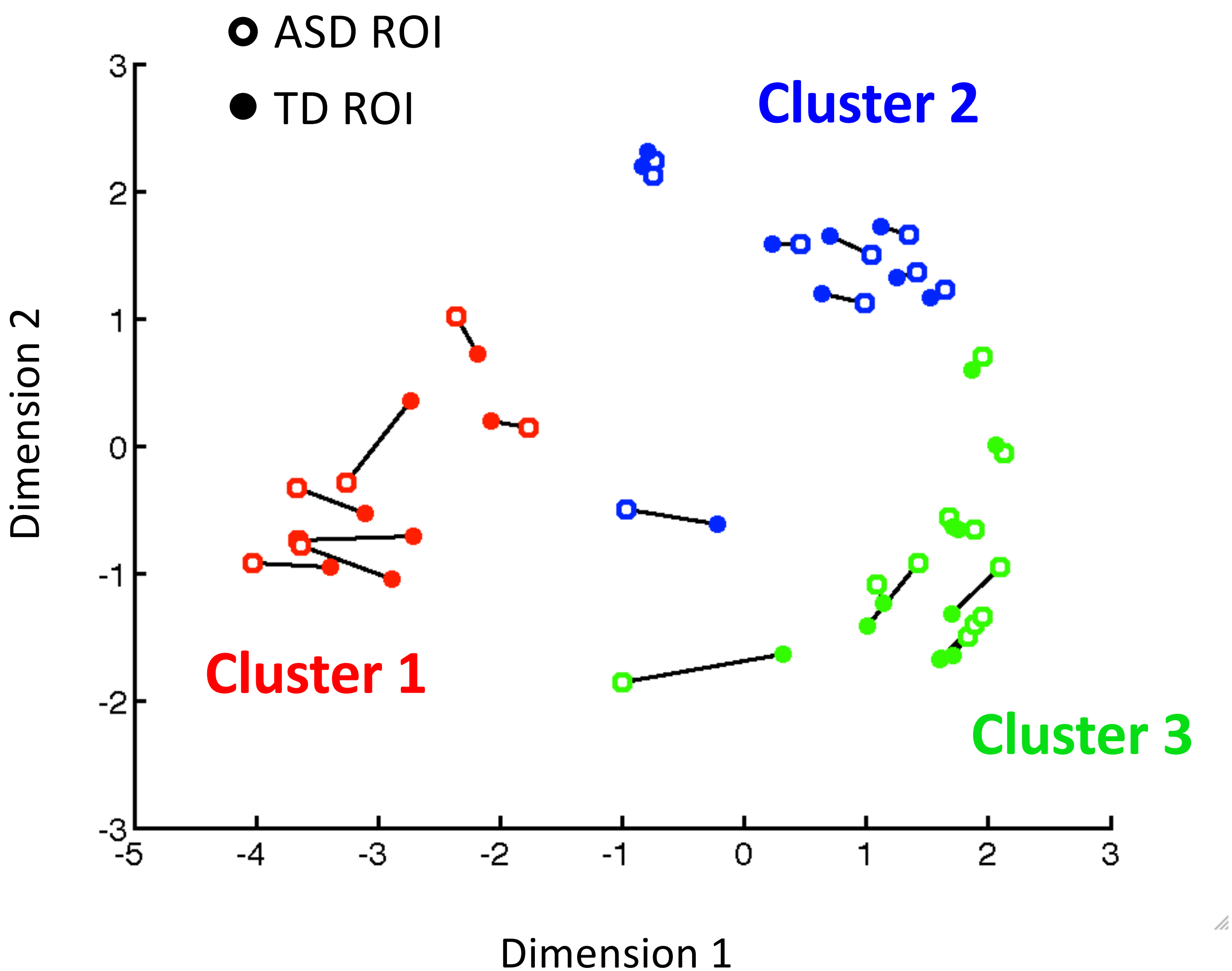

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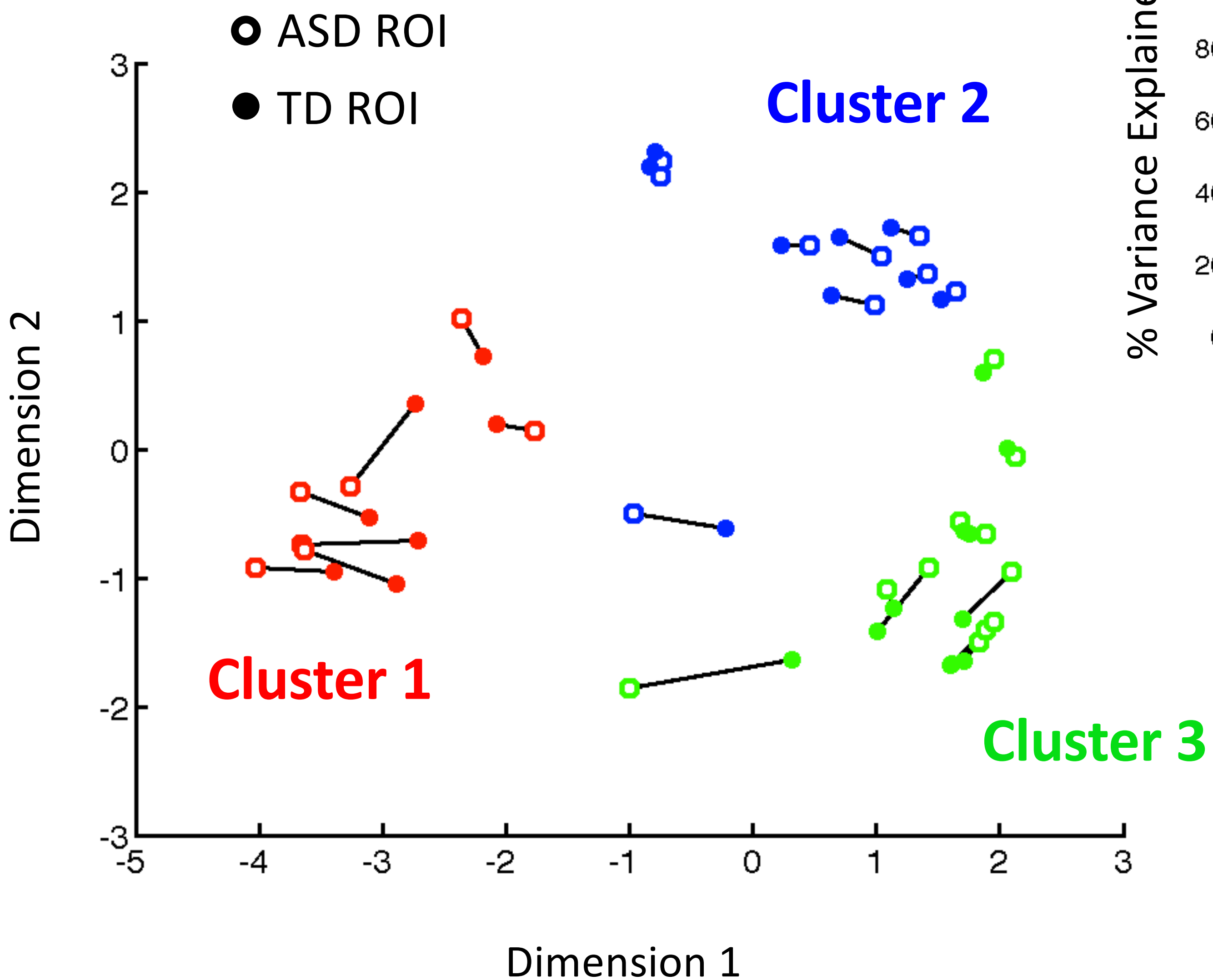
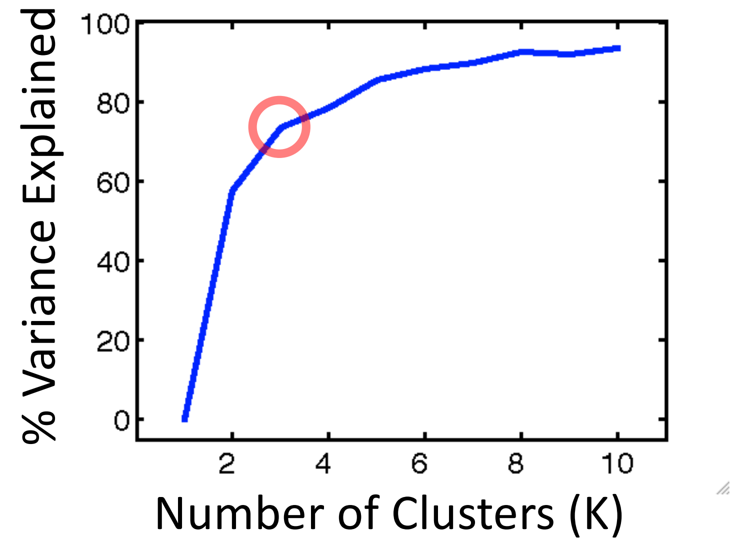
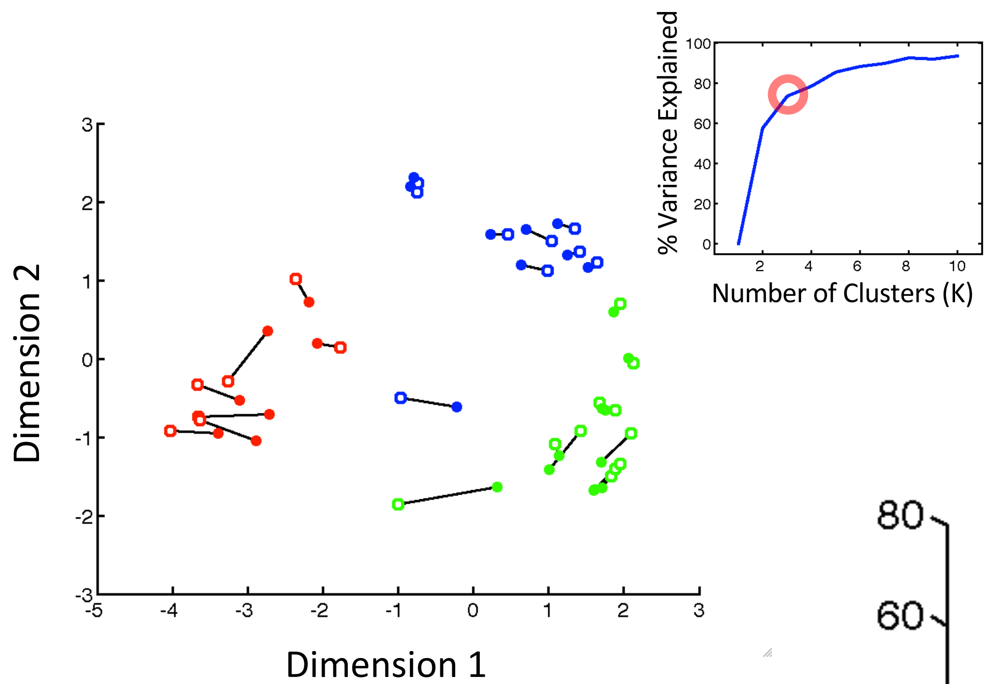


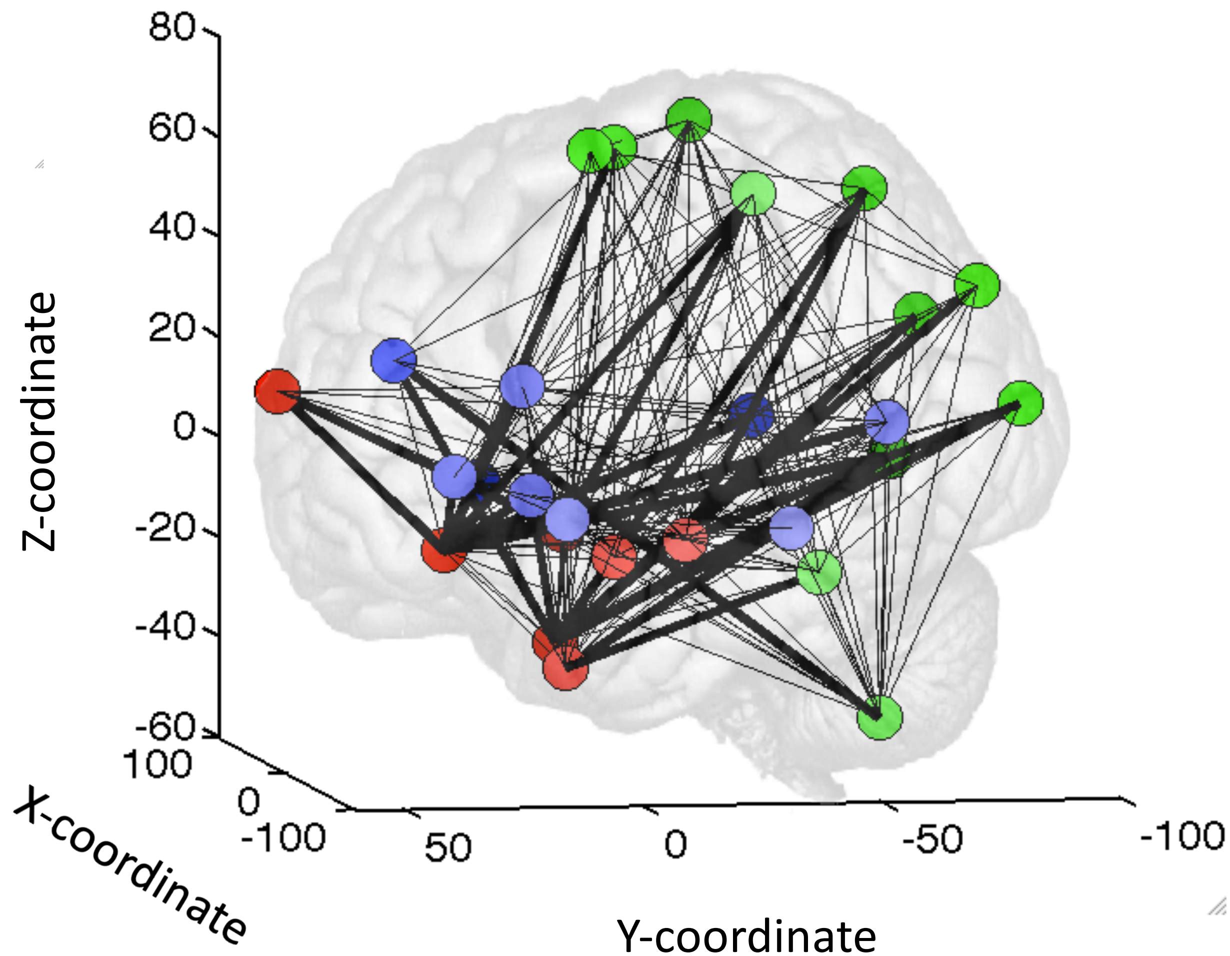


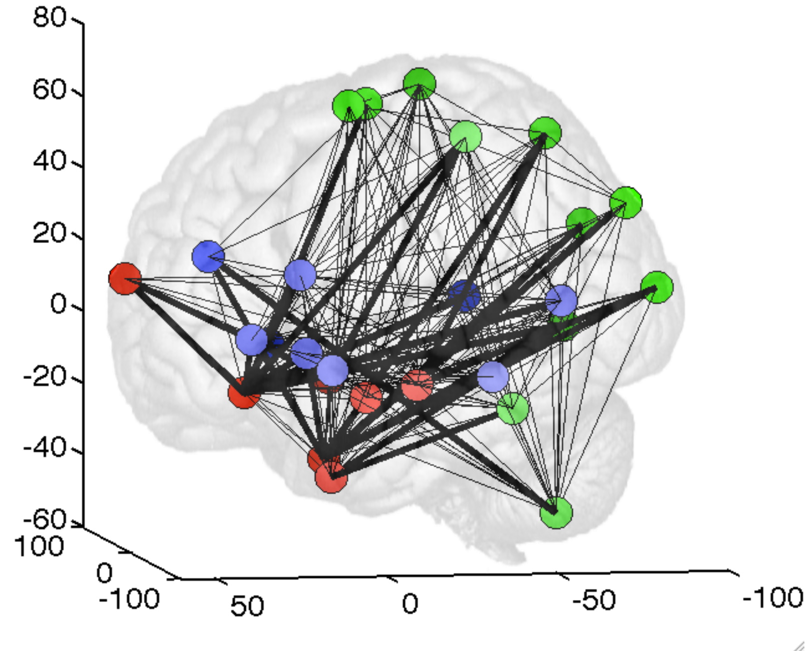


TD > ASD (t-val)

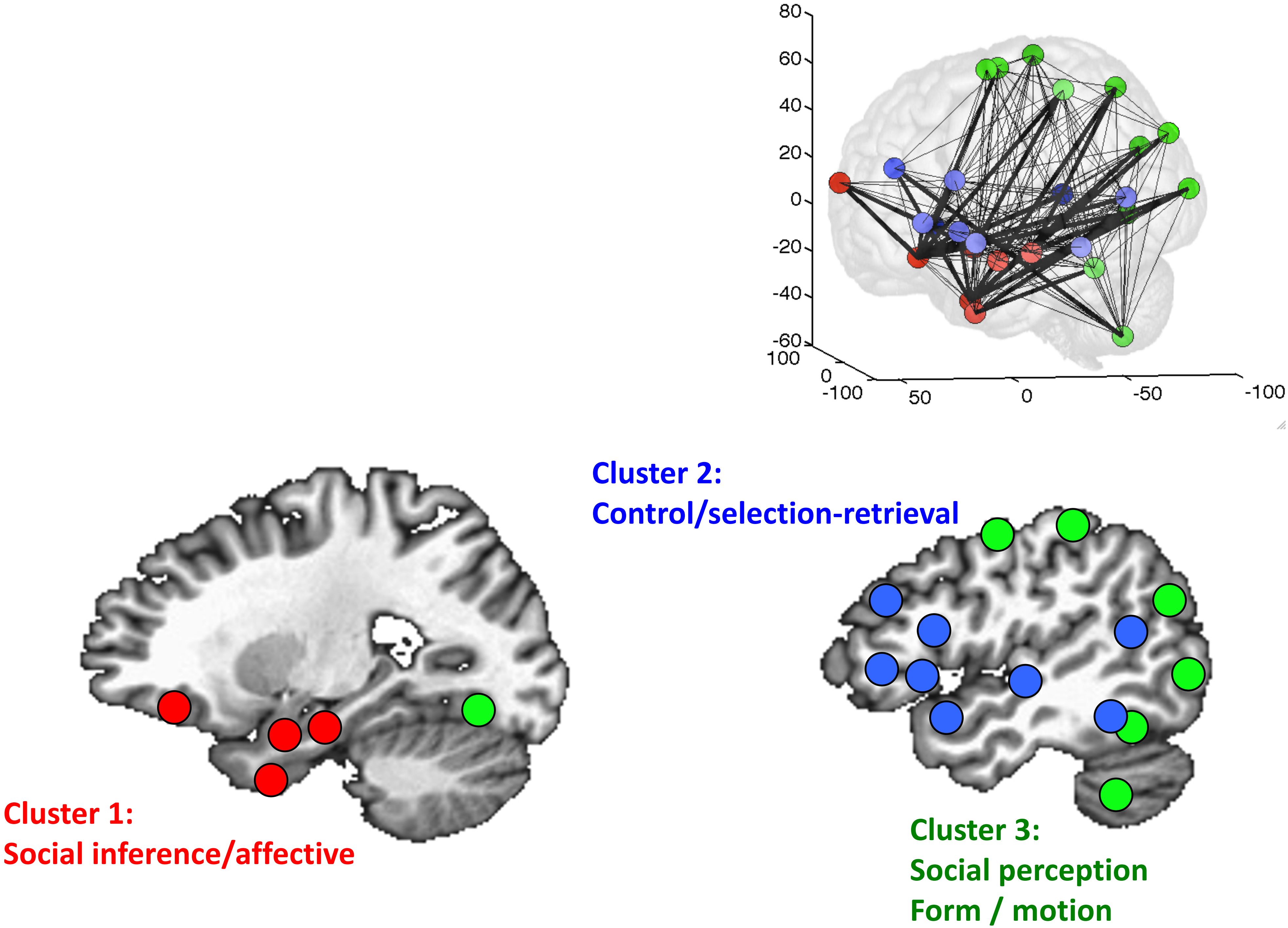
P<.05 (Bonferroni-corrected)

P<.05 (uncorrected)

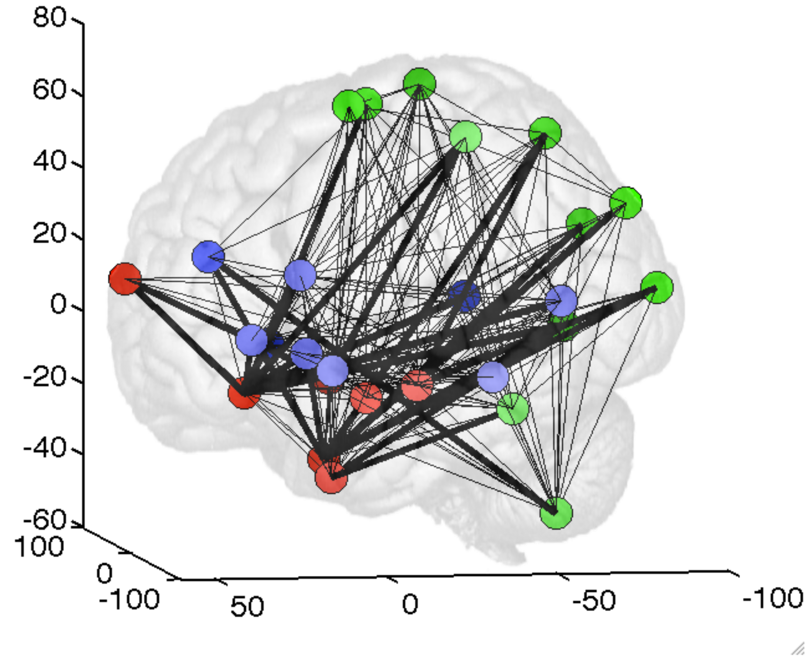




80
60
40
20
0
-20
-40
-60
100
0
-100
50
0
-50
-100


Cluster 2:
Control/selection-retrieval
Cluster 1:
Social inference/affective
Cluster 3:
Social perception
Form / motion

Back to ROI-ROI Correlation Matrices



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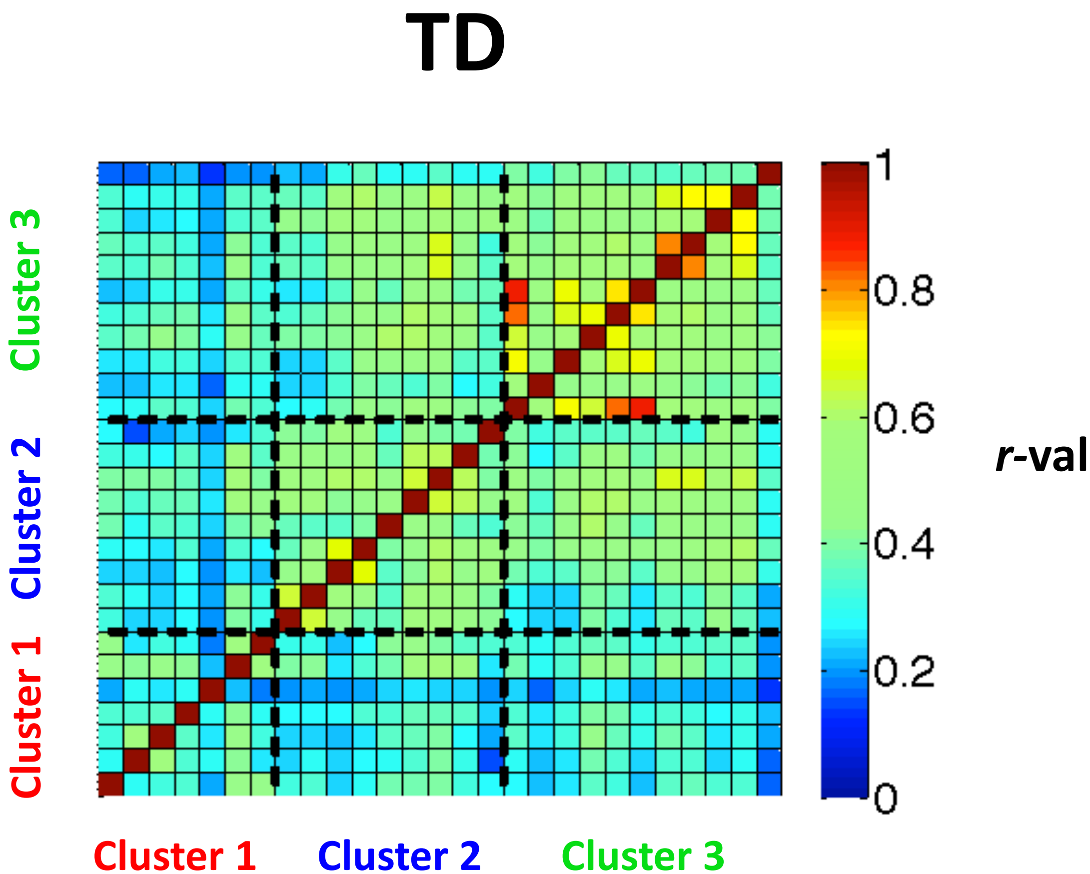
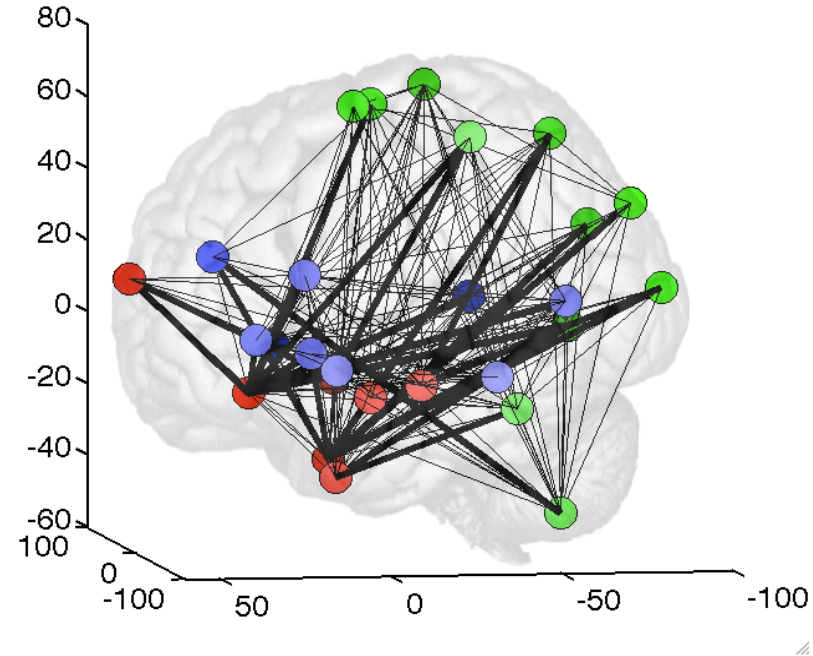
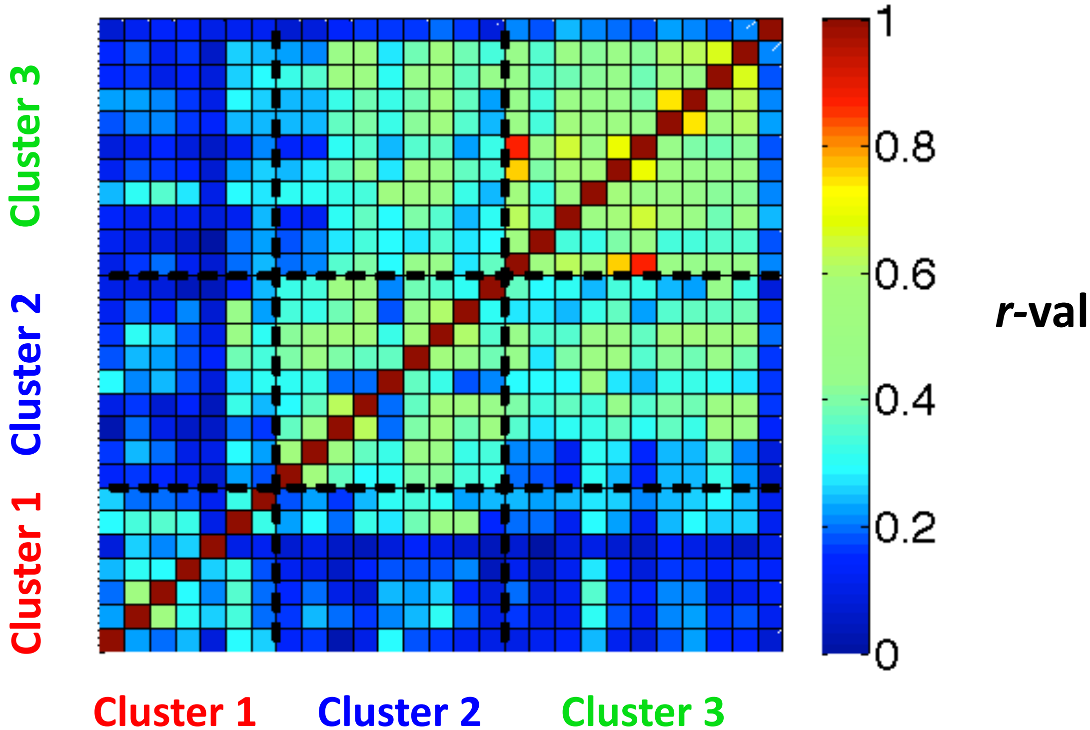
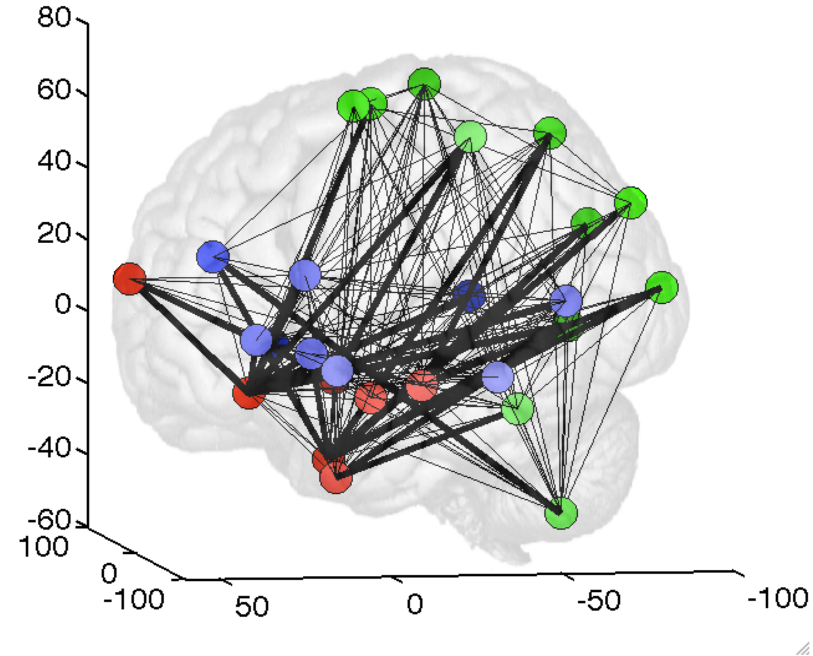




Back to ROI-ROI Correlation Matrices

ASD





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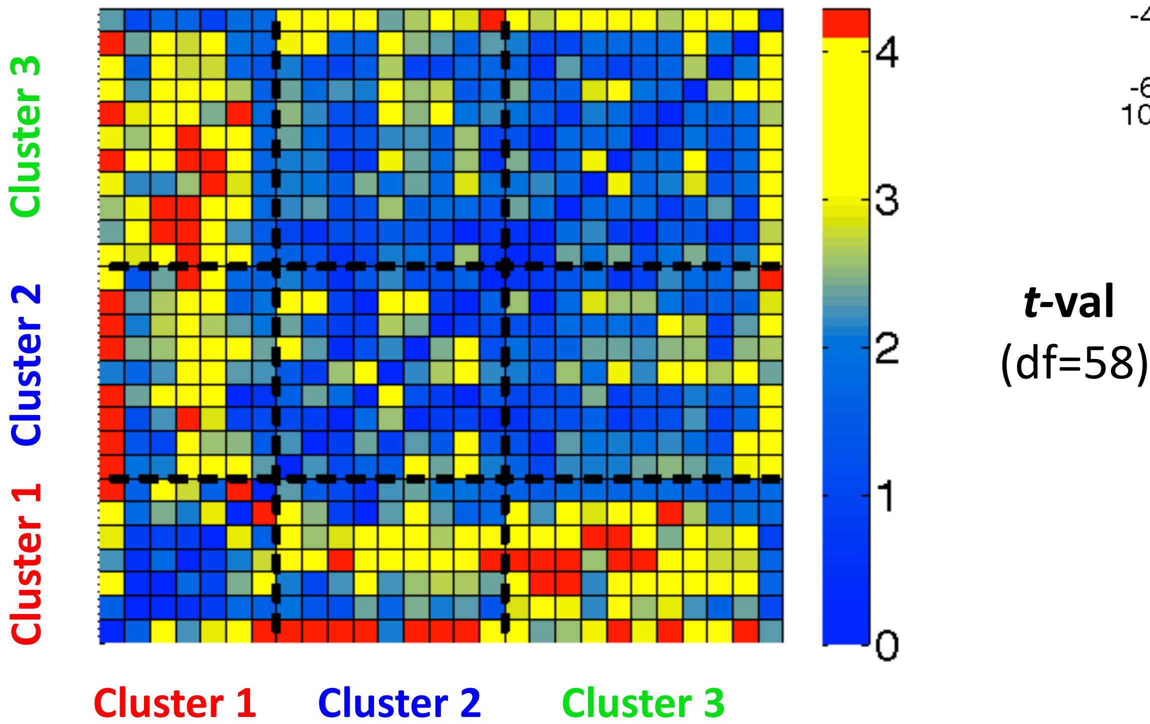
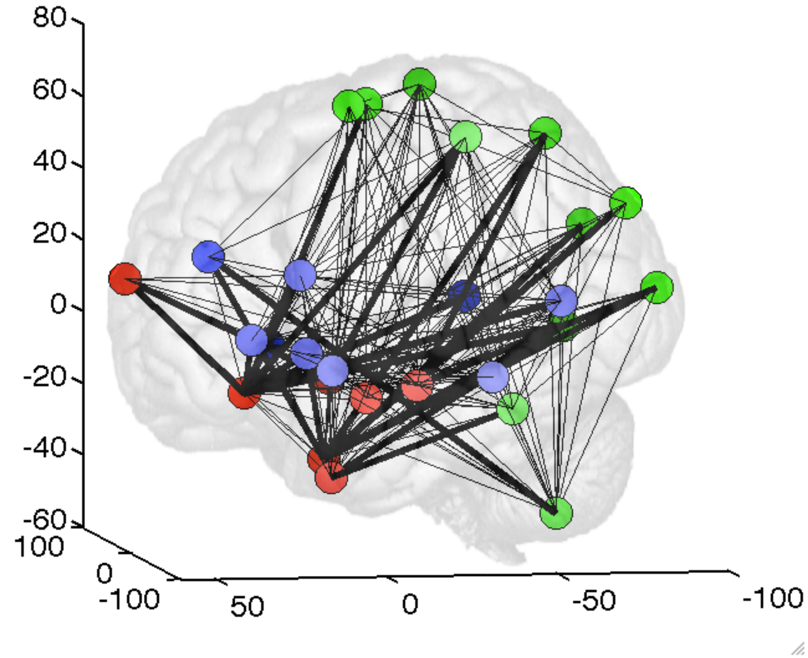
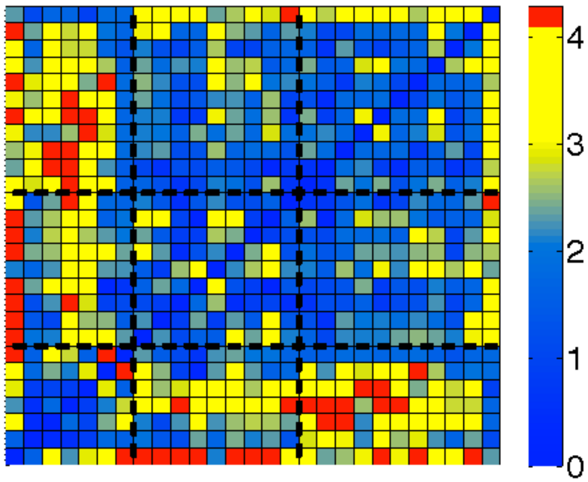
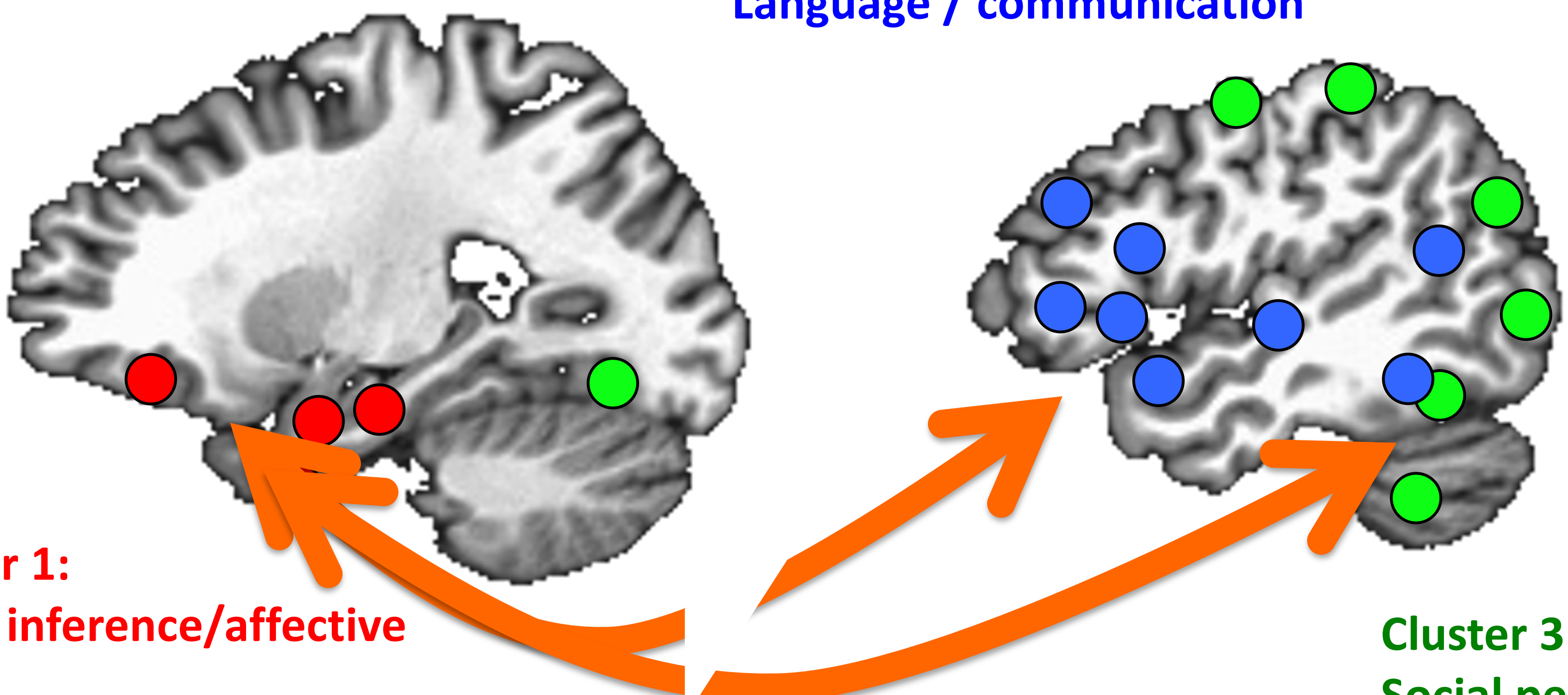






Is this clinically relevant?

Cluster 2:
Language / communication



Cluster 1:
Social inference/affective

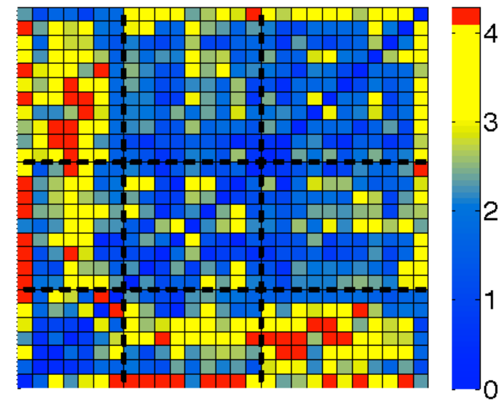
Cluster 3:
Social perception
Form / action

'Functional decoupling'

Correlations of **Social Responsiveness Scale (SRS)** ROI x ROI correlations in ASD sample alone (N=29)

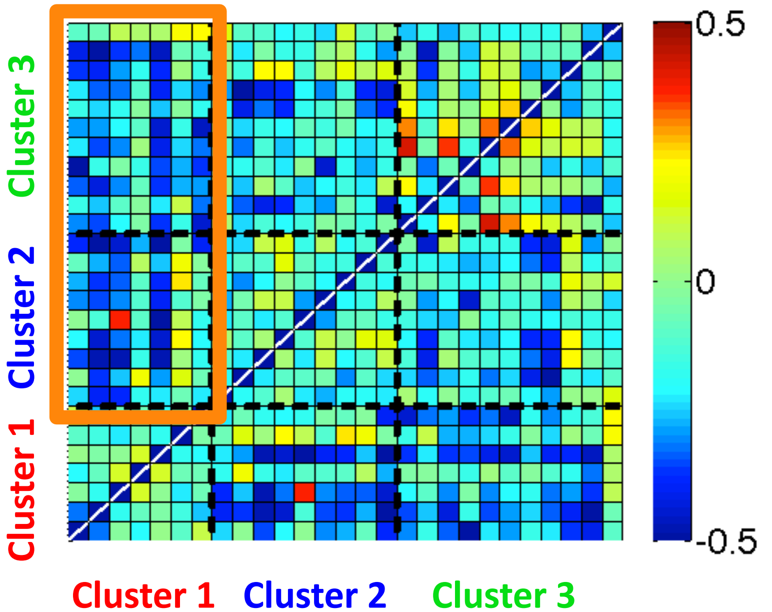
TD > ASD

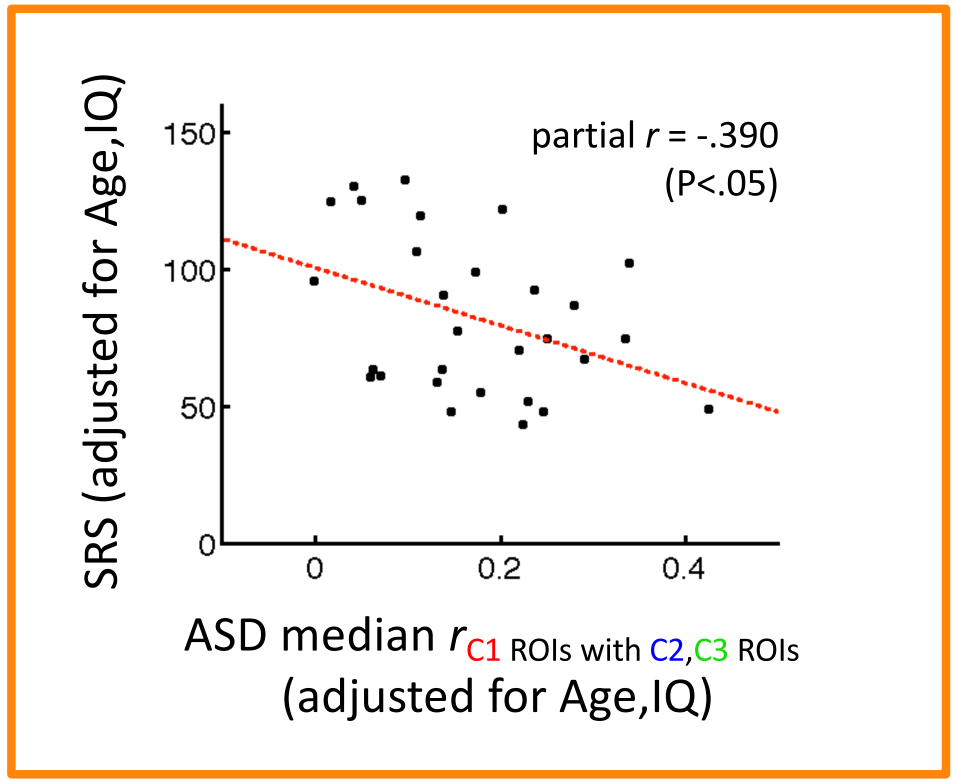
***t*-val**
(df=58)

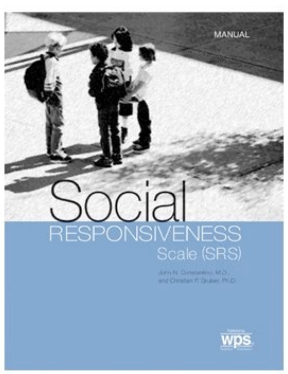


ASD: Correlation with **SRS**
(adjusted for Age,IQ)

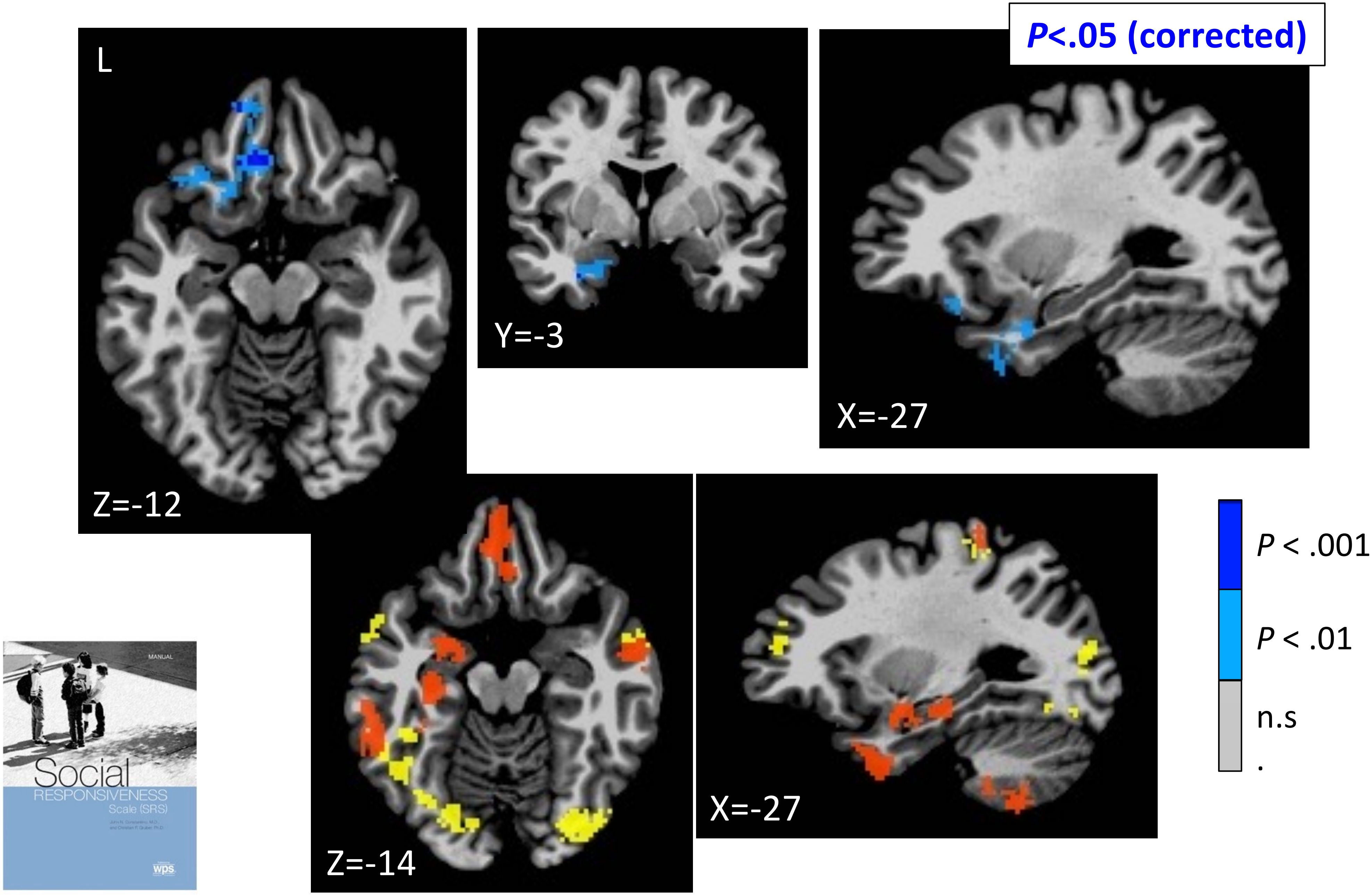
partial *r*
(df=25)





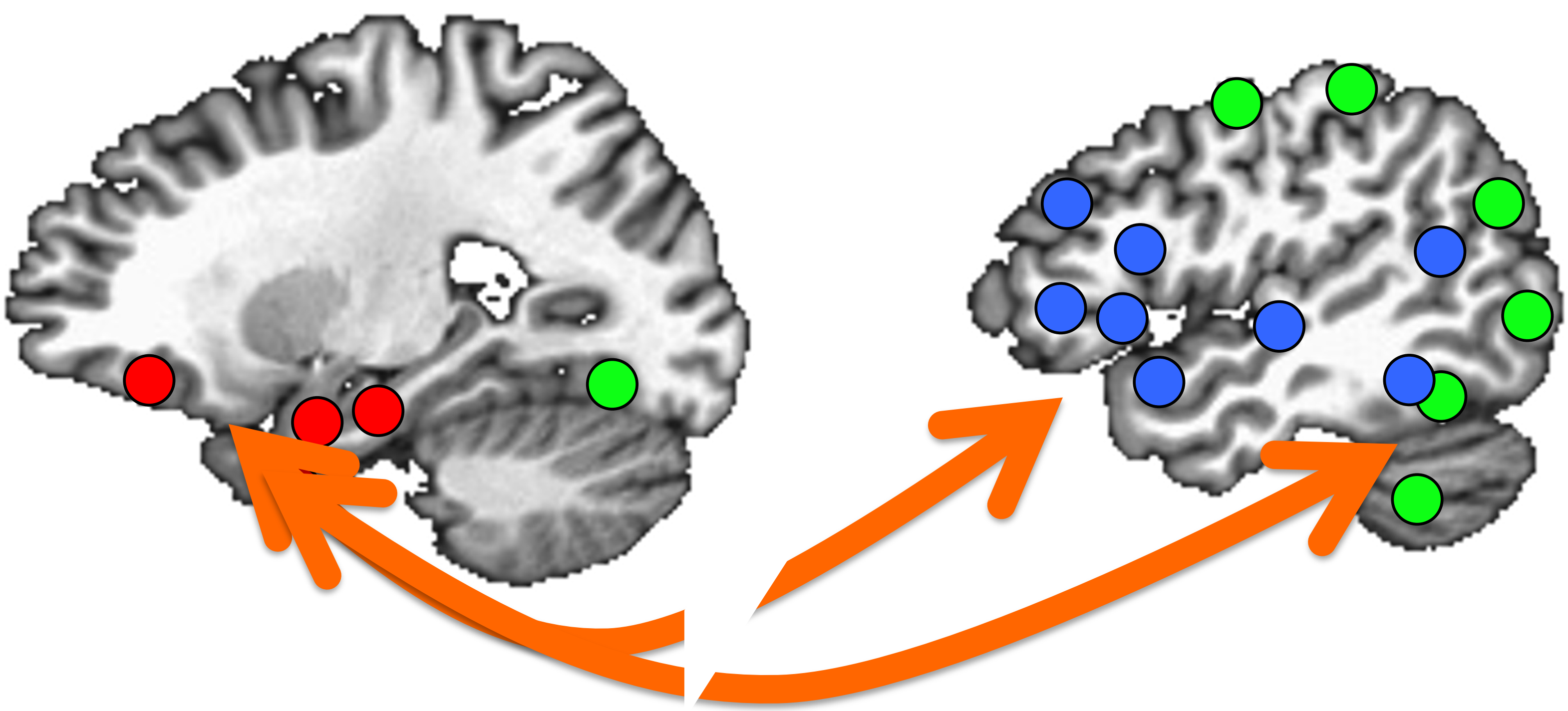


Correlations of **Social Responsiveness Scale (SRS)** with Connectedness in ASD sample alone (N=29)



Summary for ASD Study

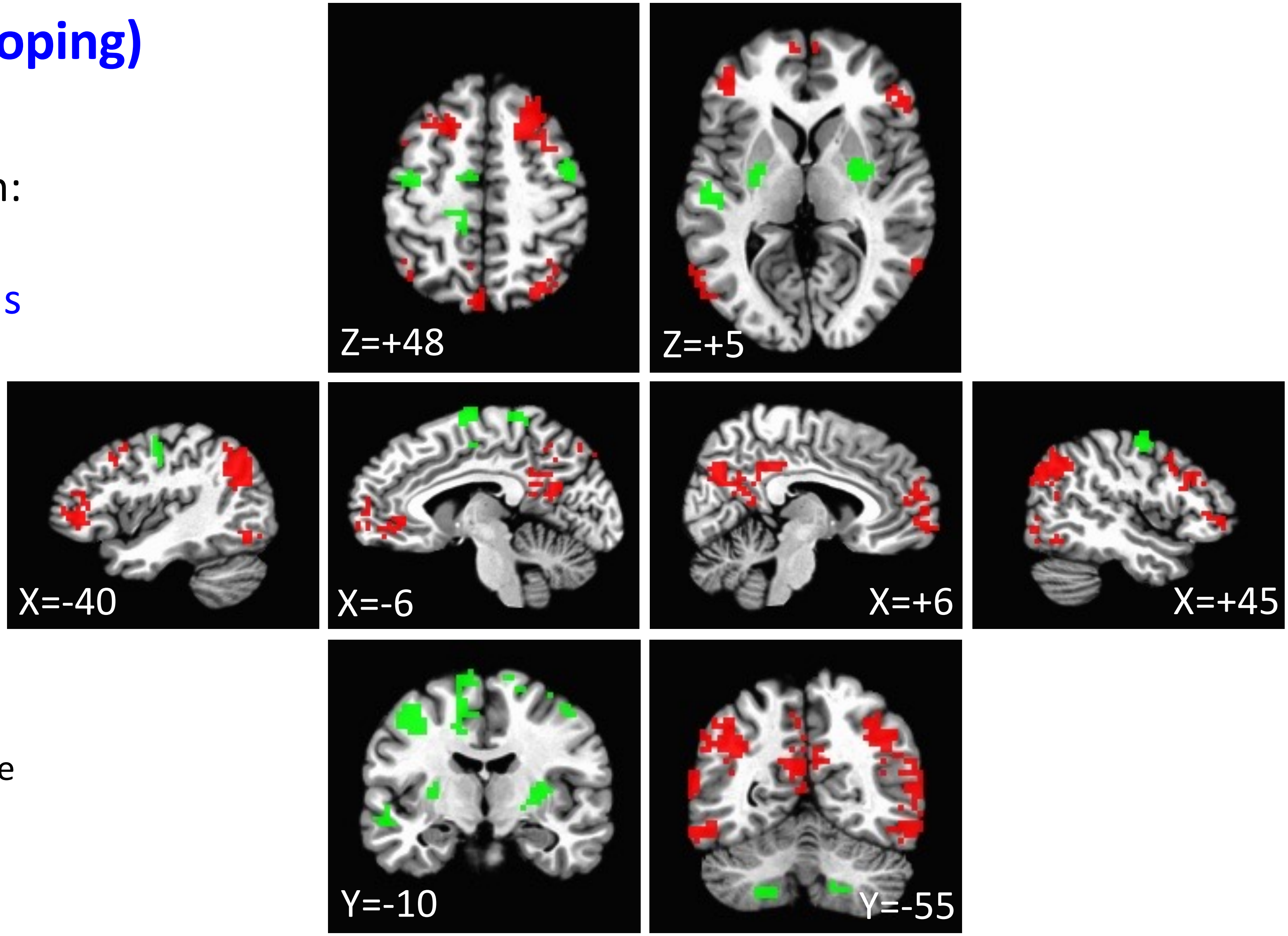
- At least for high-functioning ASD subjects, the largest differences in correlation were concentrated among regions of the 'social brain'
- We observed a fractionation of social brain circuits into two parts
- Social/affective component (Cluster 1) was 'functionally' decoupled from language and visuomotor components



Applying the same method to Childhood Onset Schizophrenia (vs. Typ. Developing)

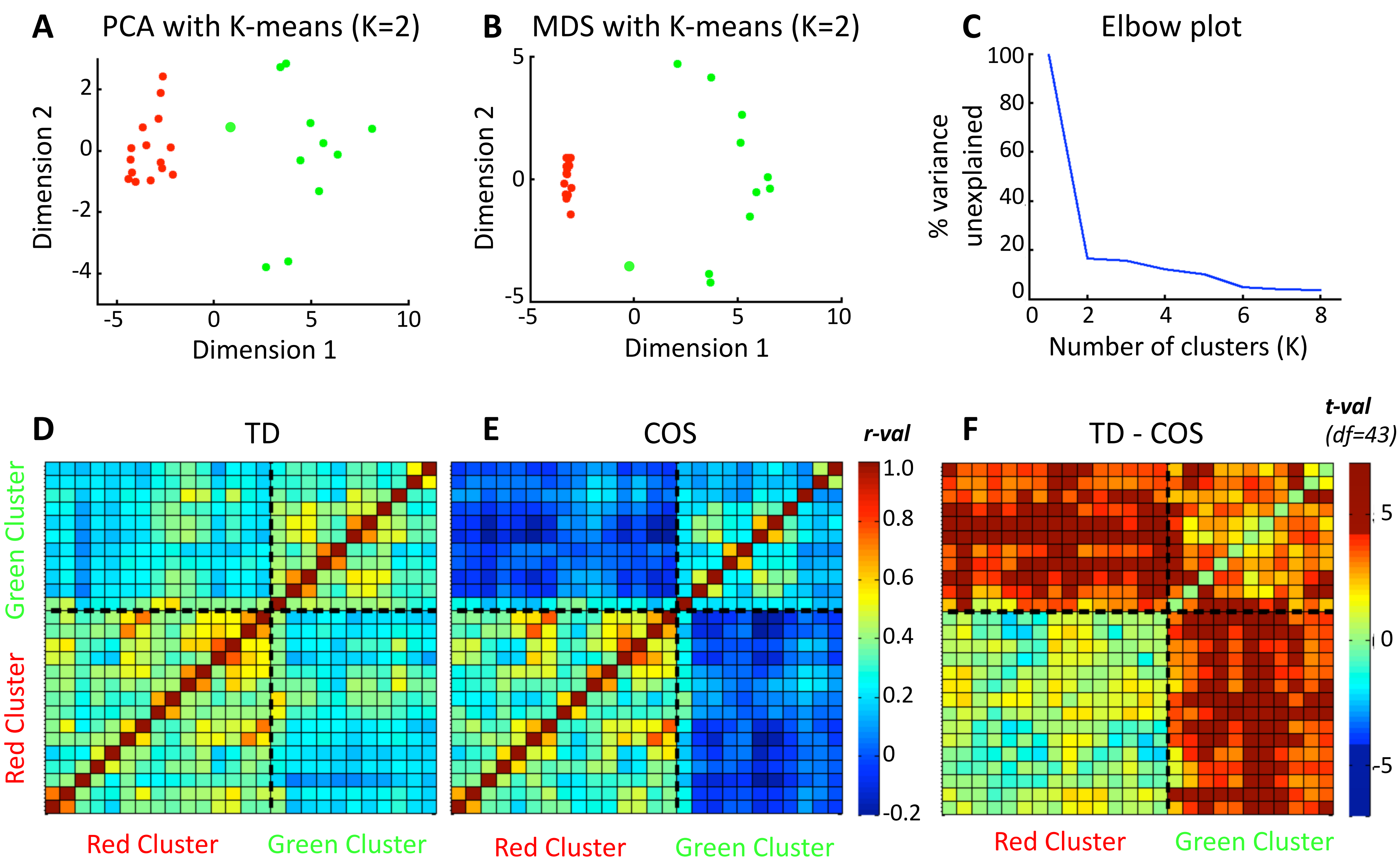
Collaboration with:

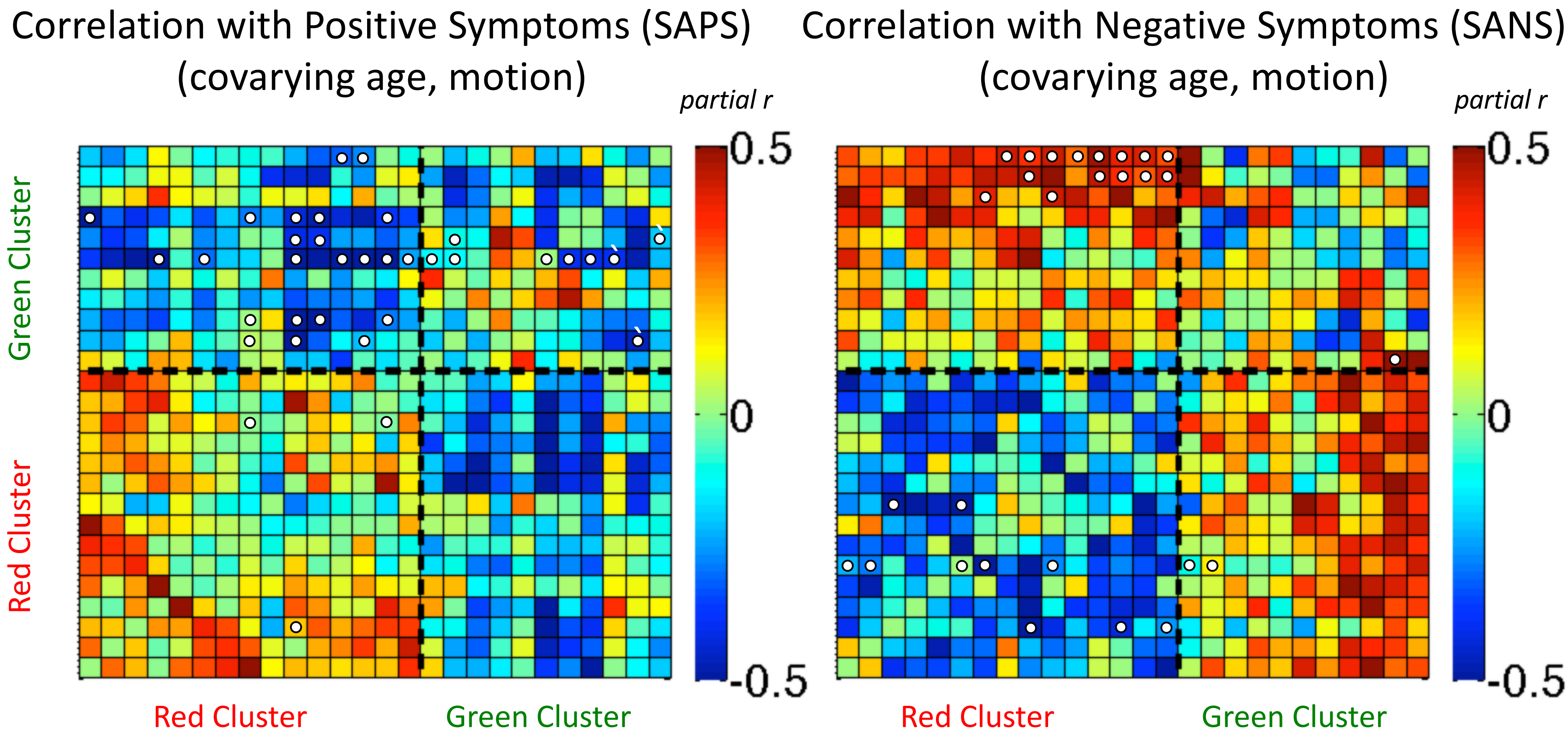
Becky Berman
Harrison McAdams
Nitin Gogtay
Judy Rapoport
et al.



Red cluster: Social-cognitive

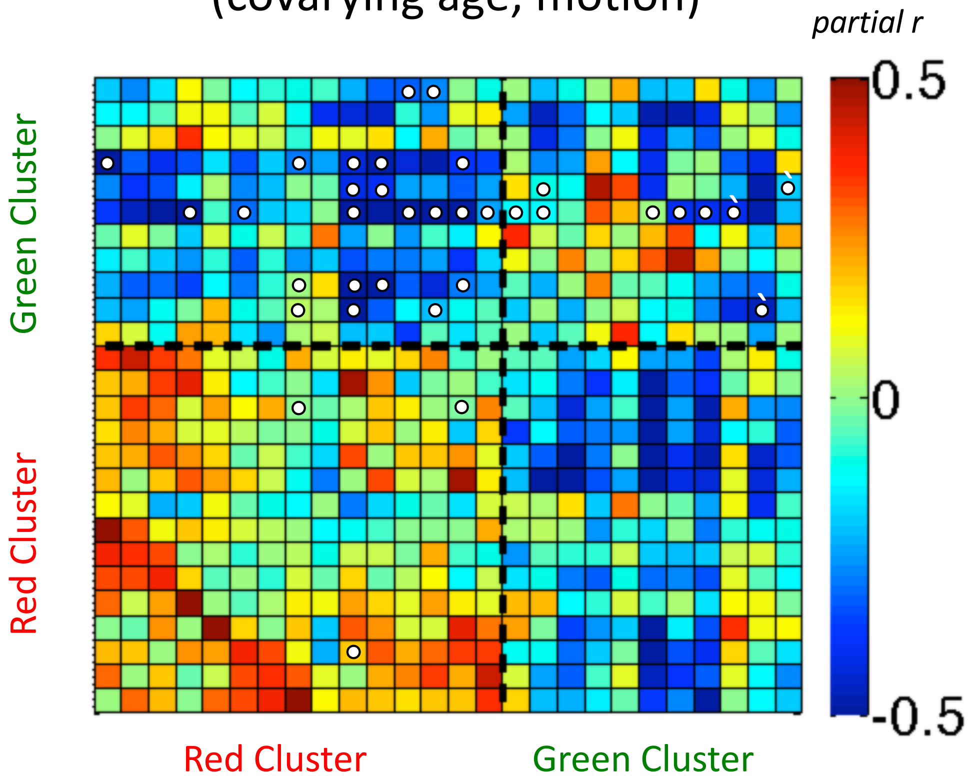
Green cluster: Sensorimotor


A
PCA with K-means (K=2)
Dimension 2
Dimension 1
B
MDS with K-means (K=2)
Dimension 2
Dimension 1
C
Elbow plot
% variance unexplained
Number of clusters (K)
D
TD
E
COS
r-val
F
TD - COS
t-val
(df=43)
Green Cluster
Red Cluster
Red Cluster
Green Cluster
Red Cluster
Green Cluster
Red Cluster
Green Cluster

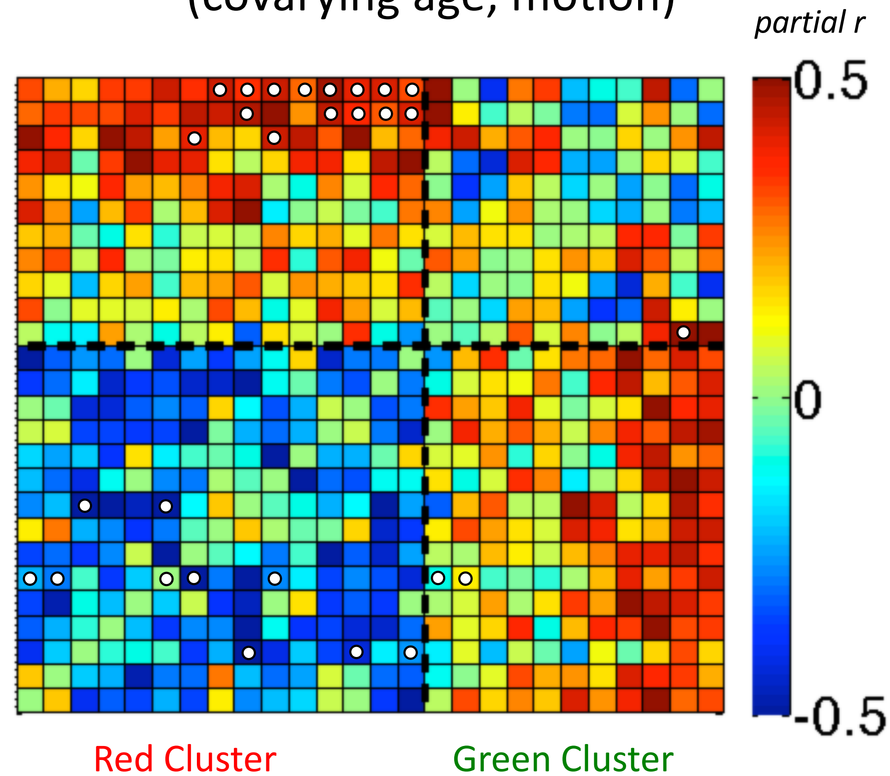


○ spatial overlap with seed-based symptom correlation analyses (p<.05, corrected by cluster size)

Correlation with Positive Symptoms (SAPS)
(covarying age, motion)



Correlation with Negative Symptoms (SANS)
(covarying age, motion)



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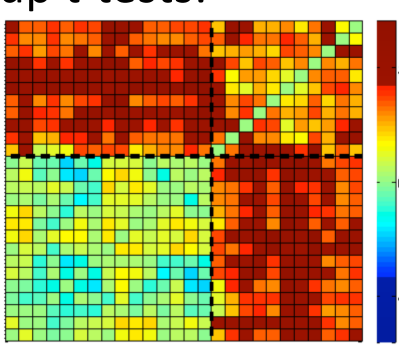
Group t-tests:



Increased Resting Correlations in Primary Lateral Sclerosis (PLS)

Collaboration with Mary Kay Floeter (NINDS) and Avner Meoded (Johns Hopkins):

NeuroImage: Clinical 7 (2015) 288–296

Contents lists available at ScienceDirect

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NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

NeuroImage: CLINICAL

Cerebro-cerebellar connectivity is increased in primary lateral sclerosis

CrossMark

Avner Meoded[a,1], Arthur E. Morrissette[a,2], Rohan Katipally[a,3], Olivia Schanz[a], Stephen J. Gotts[b], Mary Kay Floeter[a,*]

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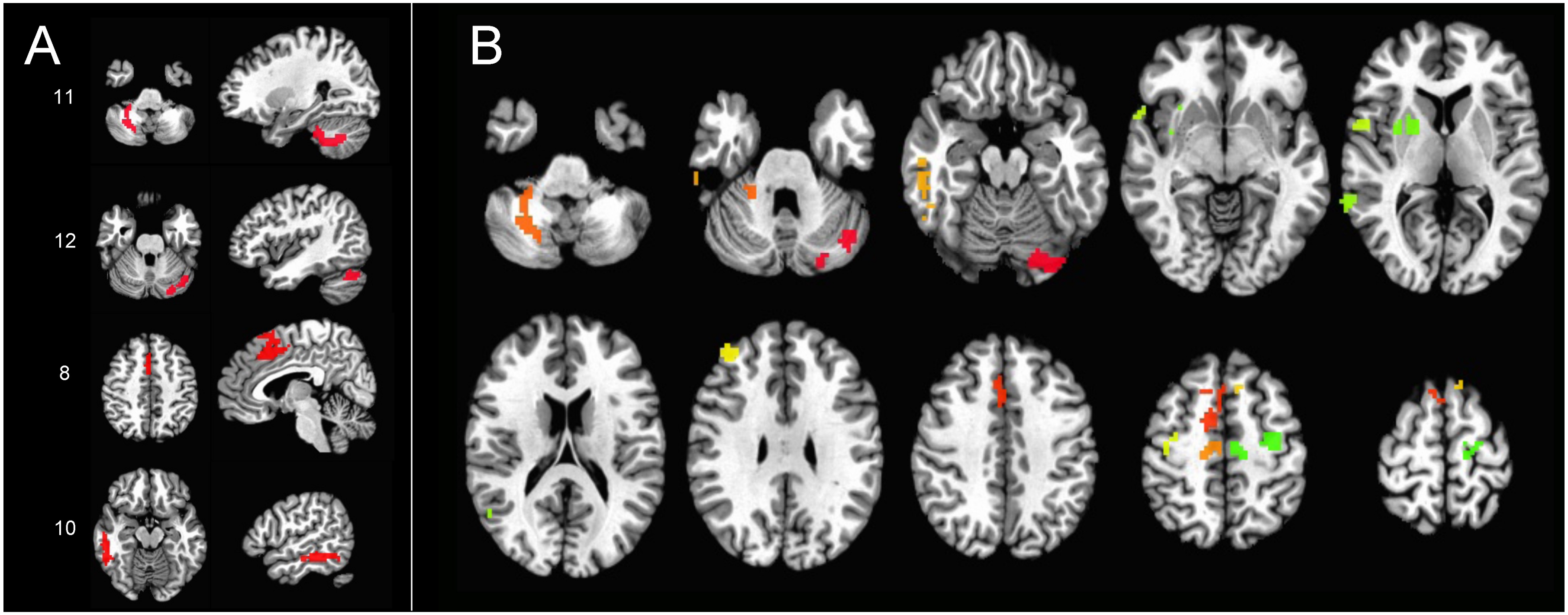
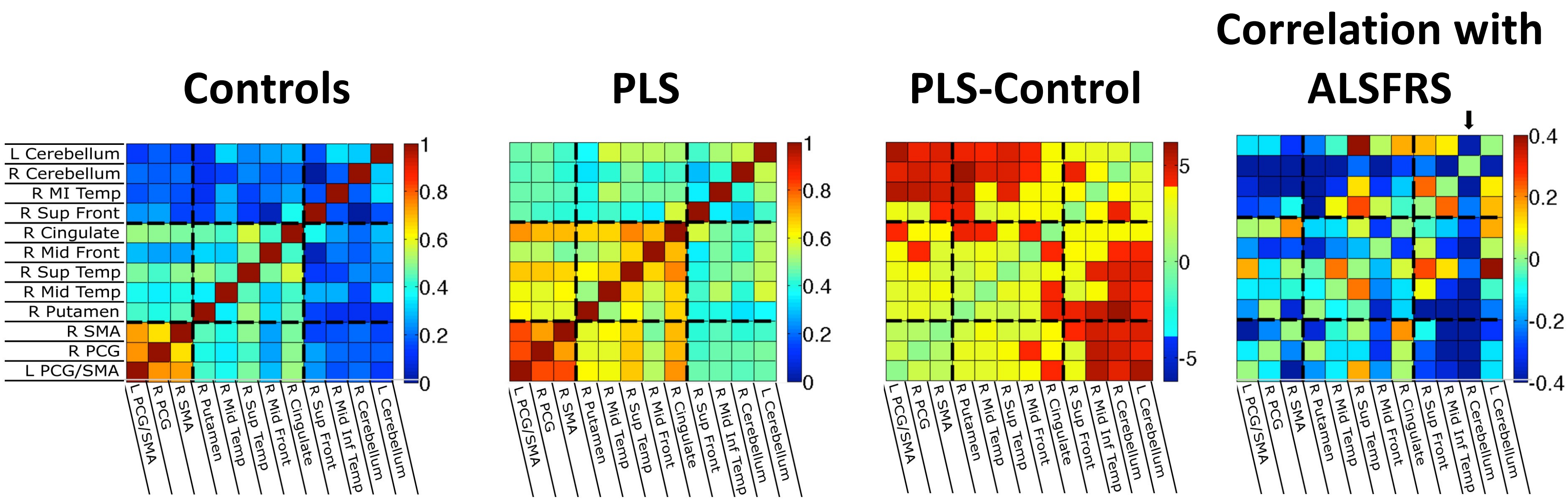
Increased Resting Correlations in Primary Lateral Sclerosis (PLS)

Collaboration with Mary Kay Floeter (NINDS) and Avner Meoded (Johns Hopkins):





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However, it's still not clear that everything is being detected:

- problem of mixtures that cancel
- spatially restricted effects can fail to be detected

Testing Every Voxel as a Seed

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- Do same tests on actual data using these critical thresholds to find corrected results

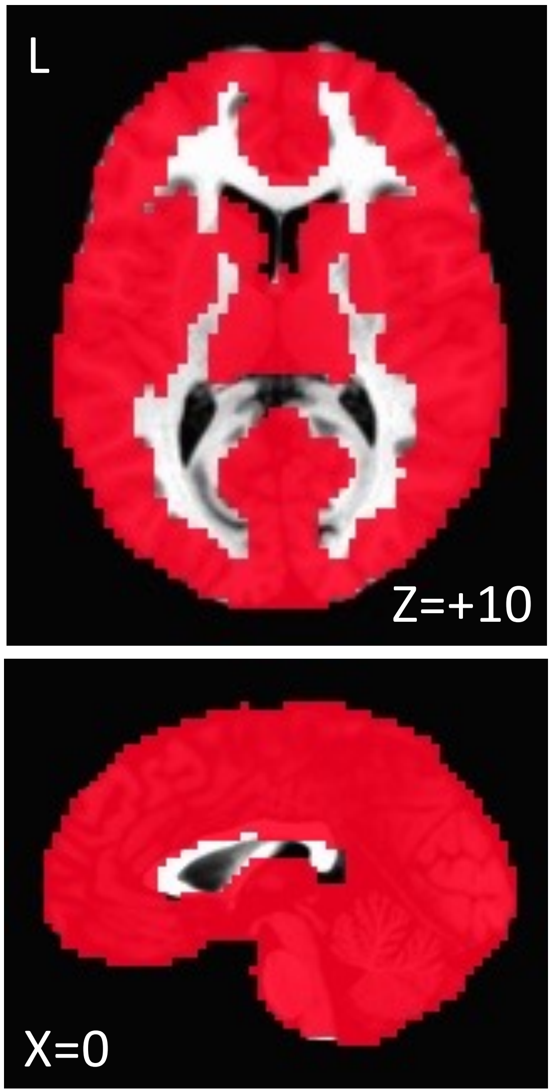
Larger ASD/TD Dataset (Martin lab)

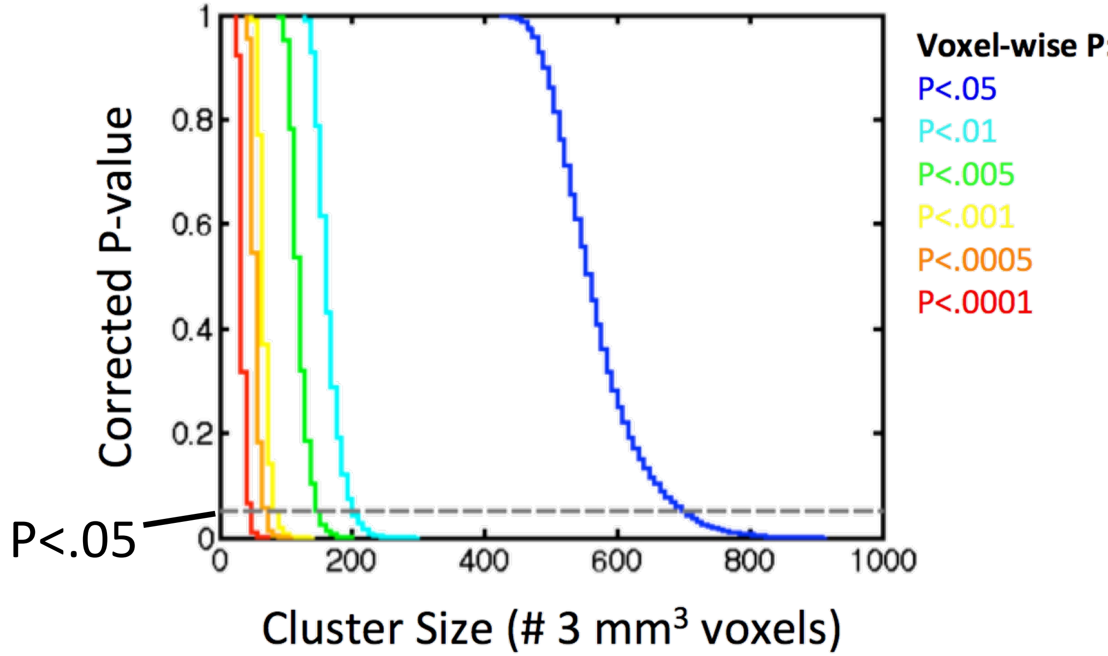
56 ASD, 62 TD, separated into two independent sets (Sets 1 and 2: 28 ASD, 31 TD each) that are matched for Motion and Age ($P>.1$ for all)

All voxel-wise t-tests also include Motion and Age as covariates (AFNI's 3dttest++, with common median centering)

Cluster-size Thresholds from Monte Carlo Simulations (5000 iterations)

Analysis Mask
(85% of Both ASD/TD Groups)





Voxelwise P-value	1 test	Test All Voxels	Factor of Expansion
P<.05	288	704	2.44
P<.01	73	200	2.74
P<.005	49	152	3.10
P<.001	22	88	4.00
P<.0005	16	72	4.50
P<.0001	8	48	6.00
P<.00005	6	40	6.67

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TD > ASD (ranging from $P<.05$ down to $P<.00005$, corrected):

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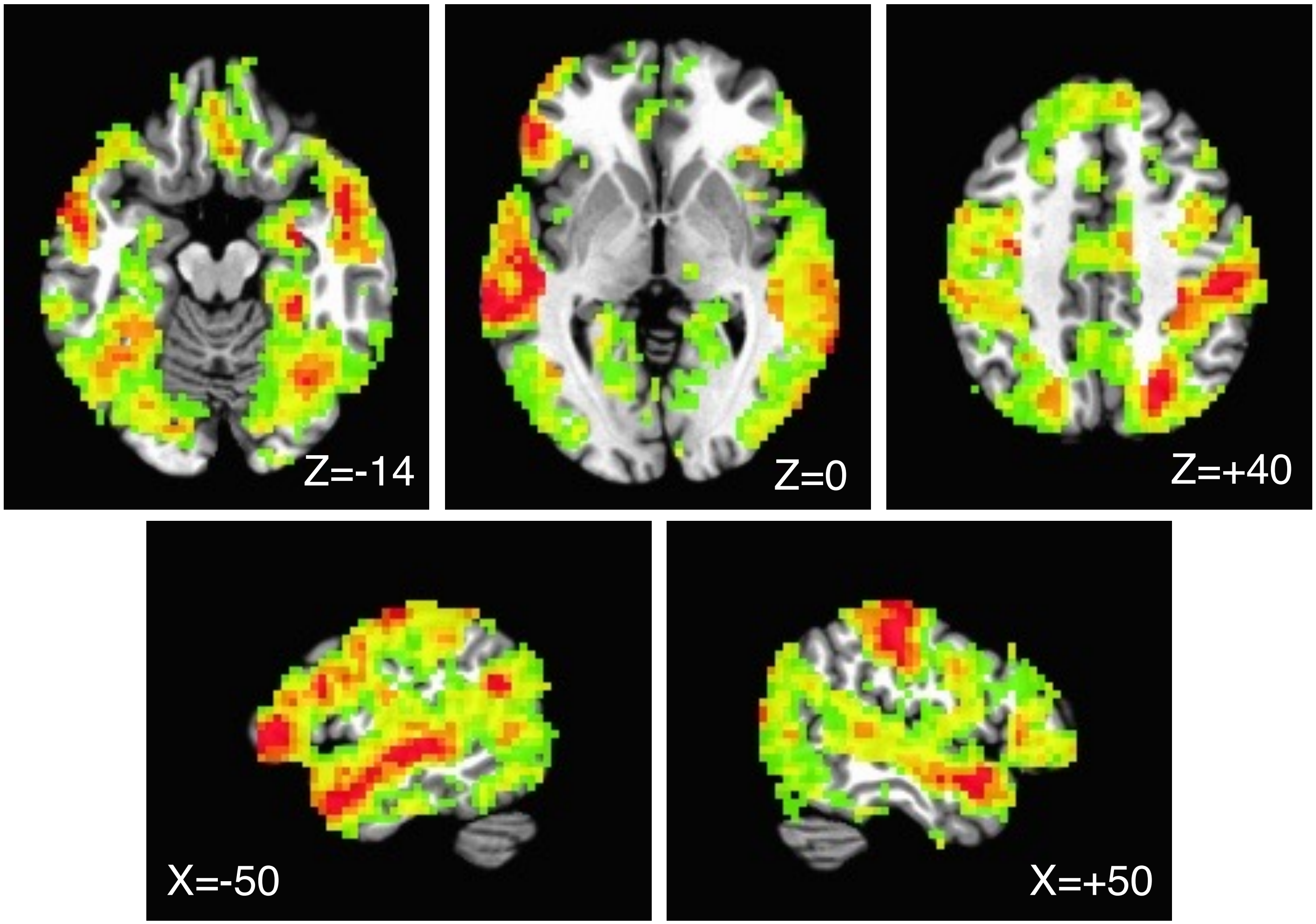

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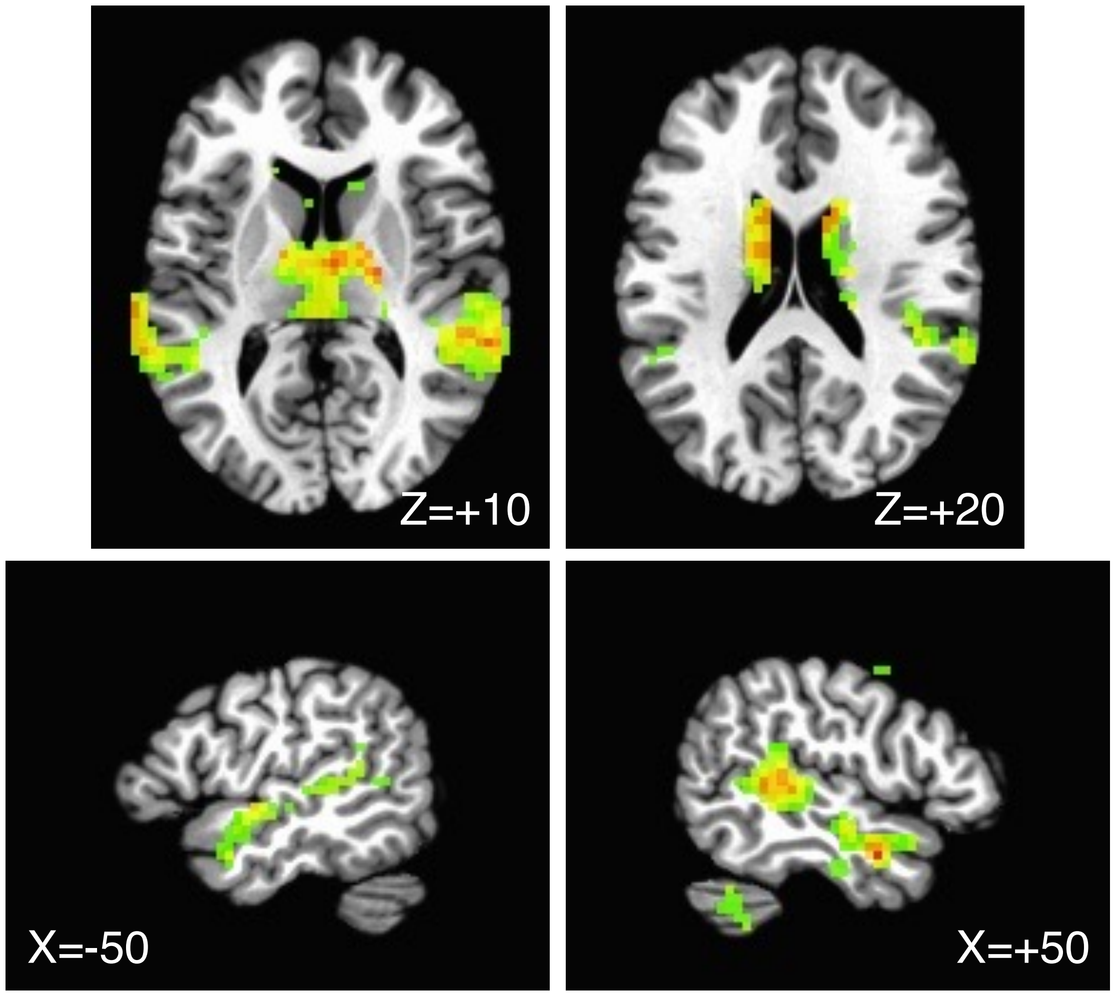


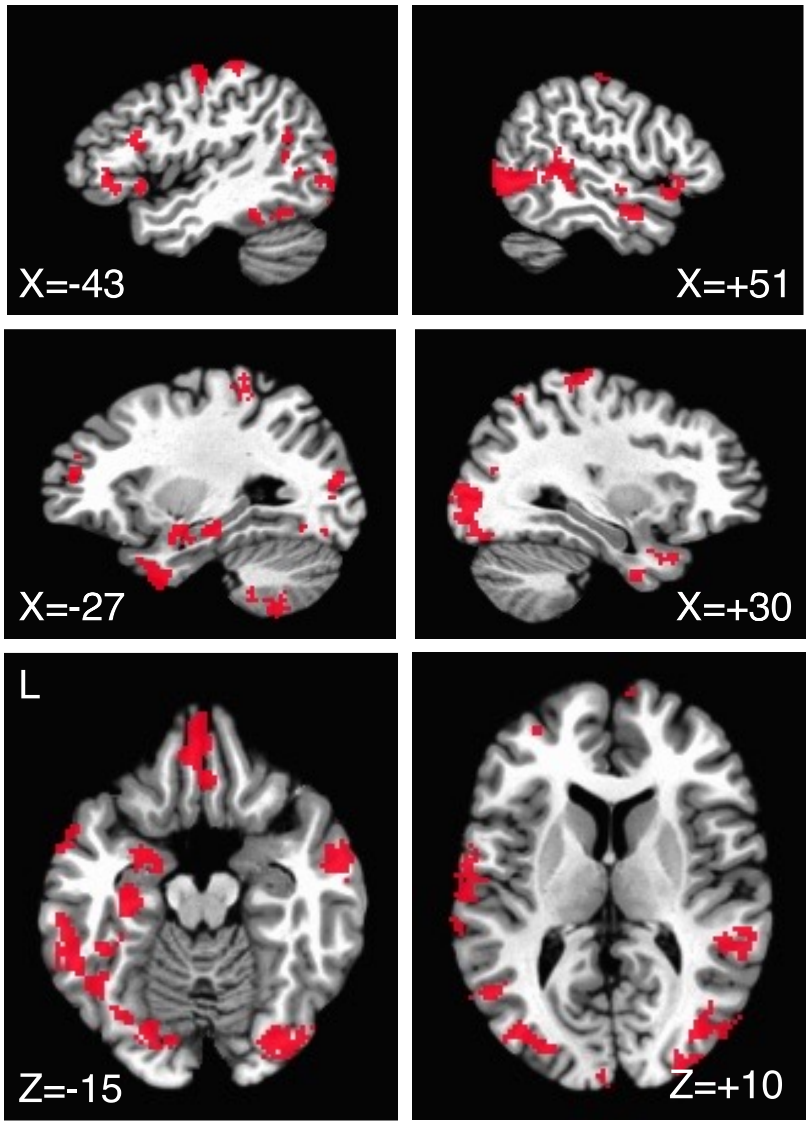
What is the relationship to Connectedness comparisons?

... and the previously reported results? (Brain 2012)

Brain 2012 ROIs

(31 ASD, 29 TD)

27 ROIs (ANATICOR)



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Connectedness Tests (TD-ASD),
P<.05, uncorrected (>100 voxels)

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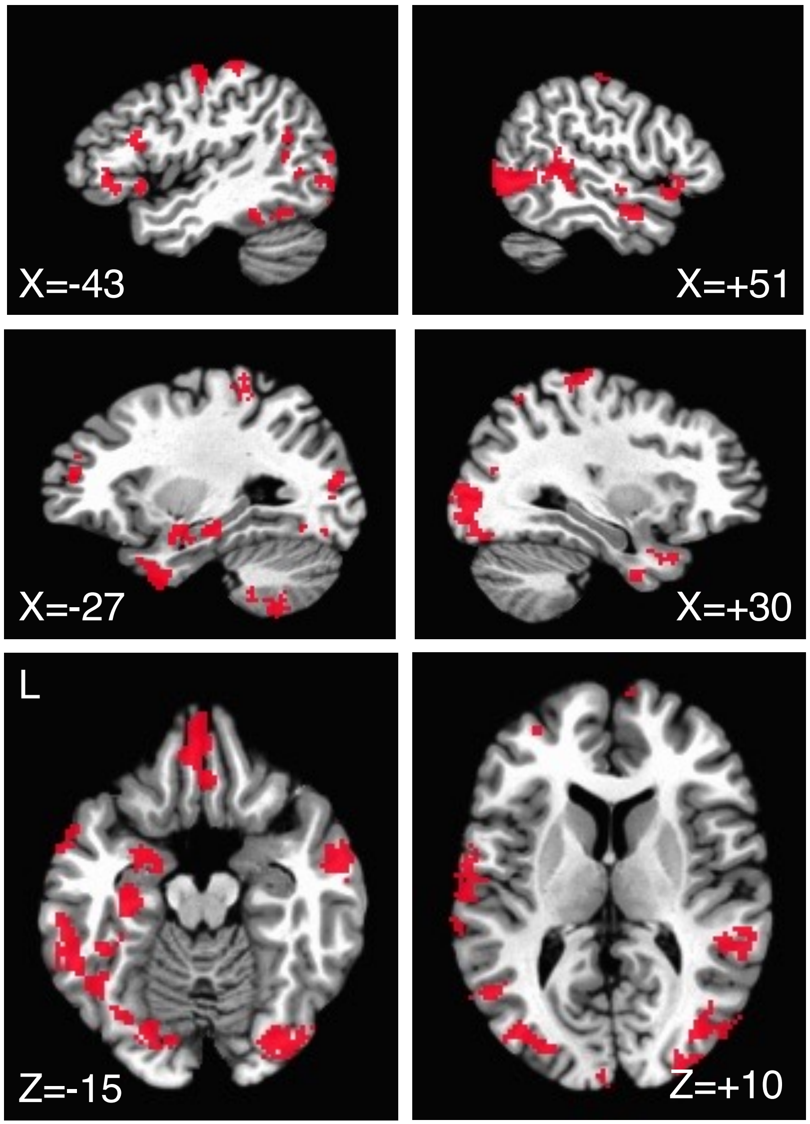

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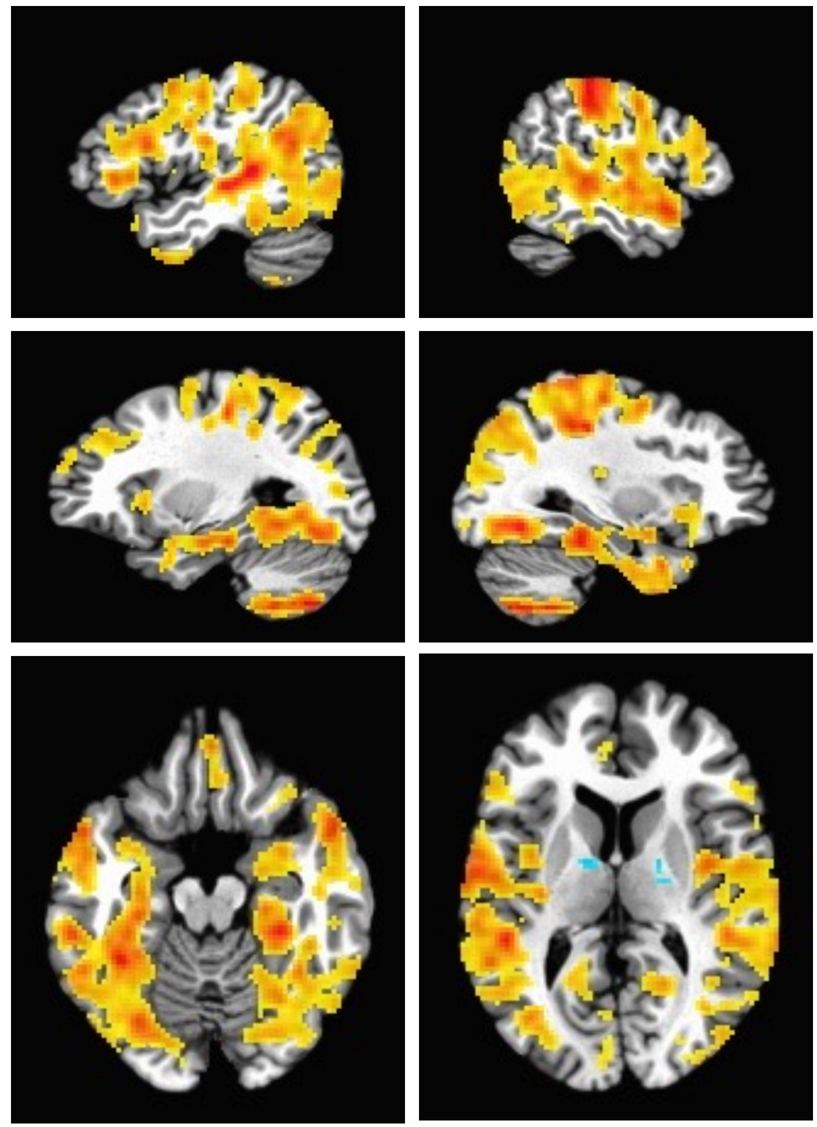

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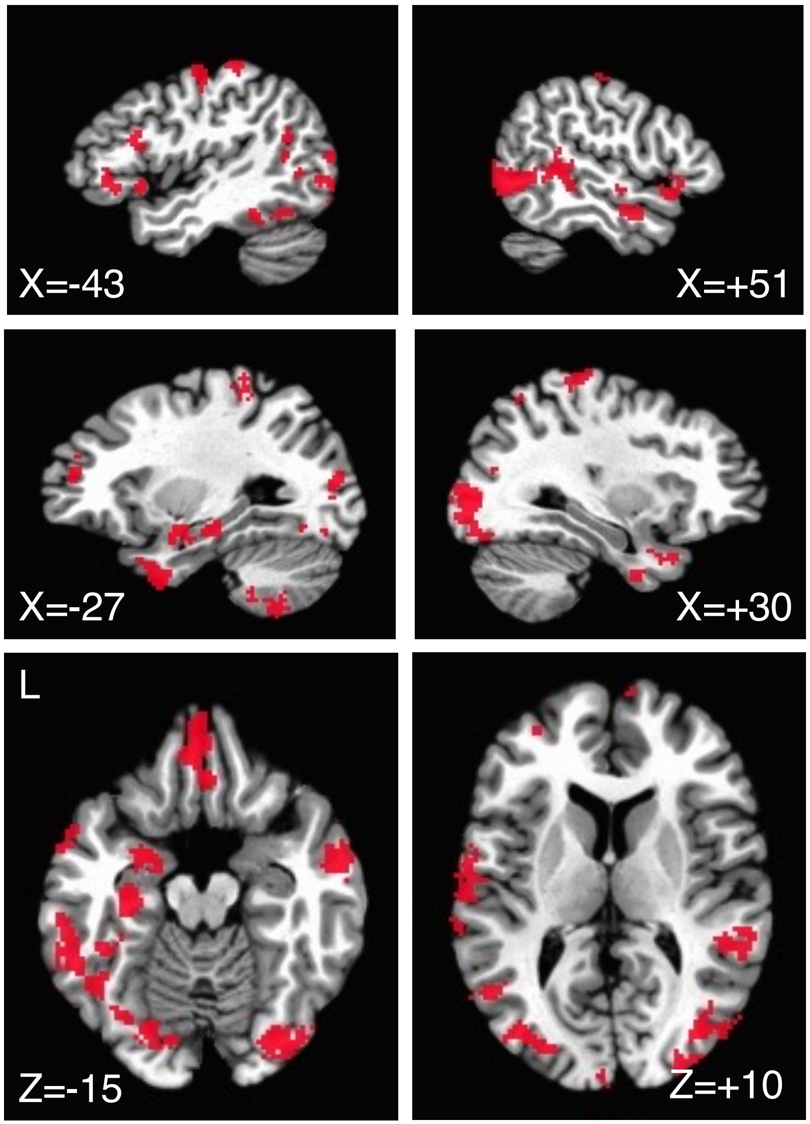

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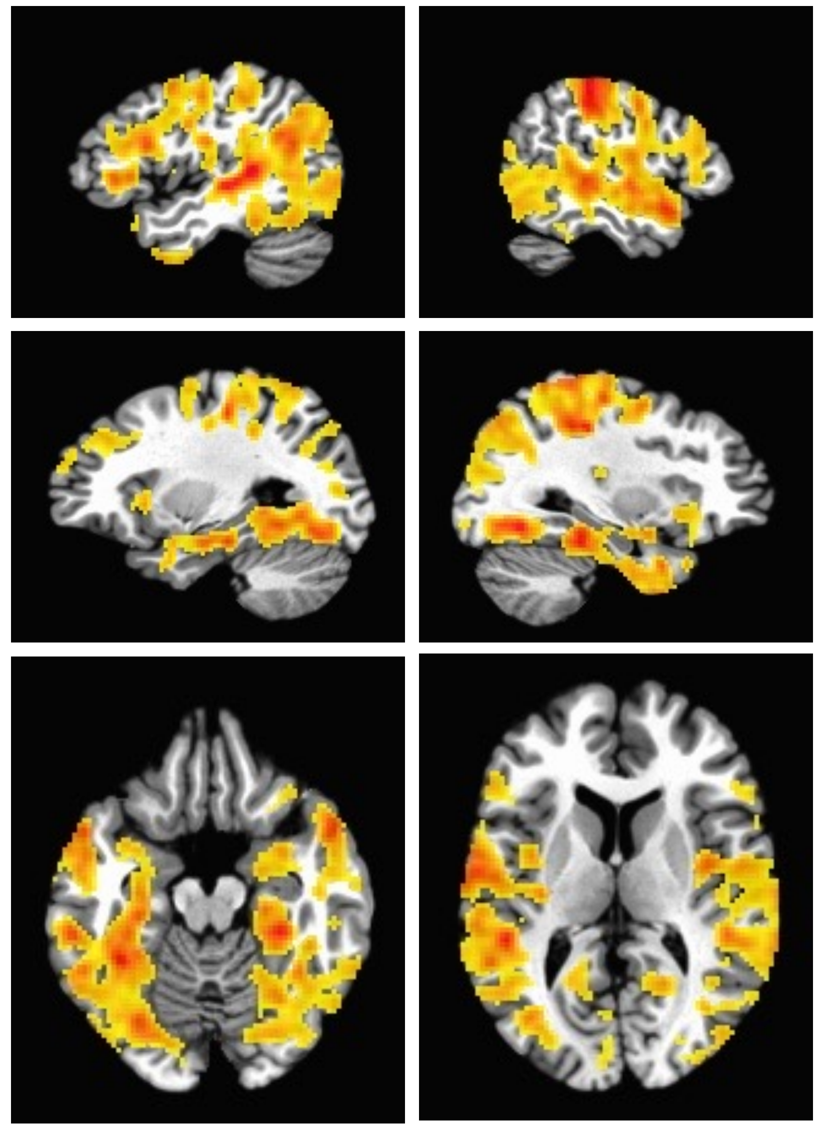

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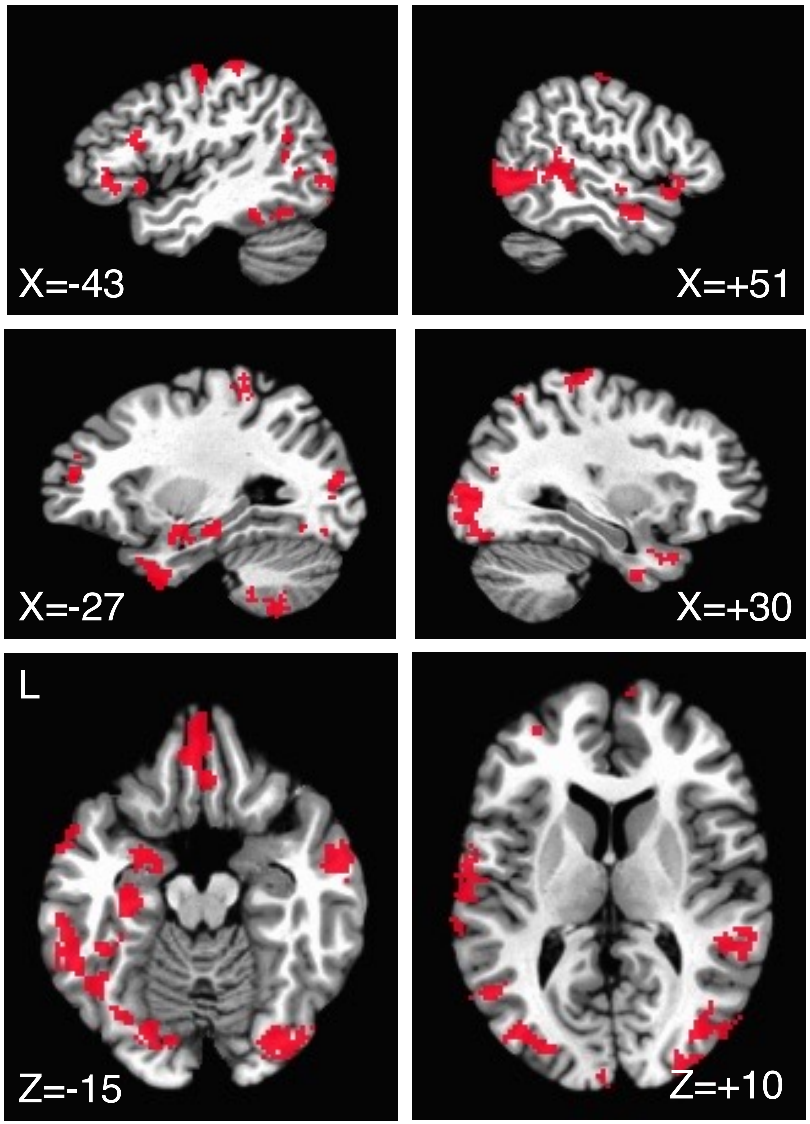

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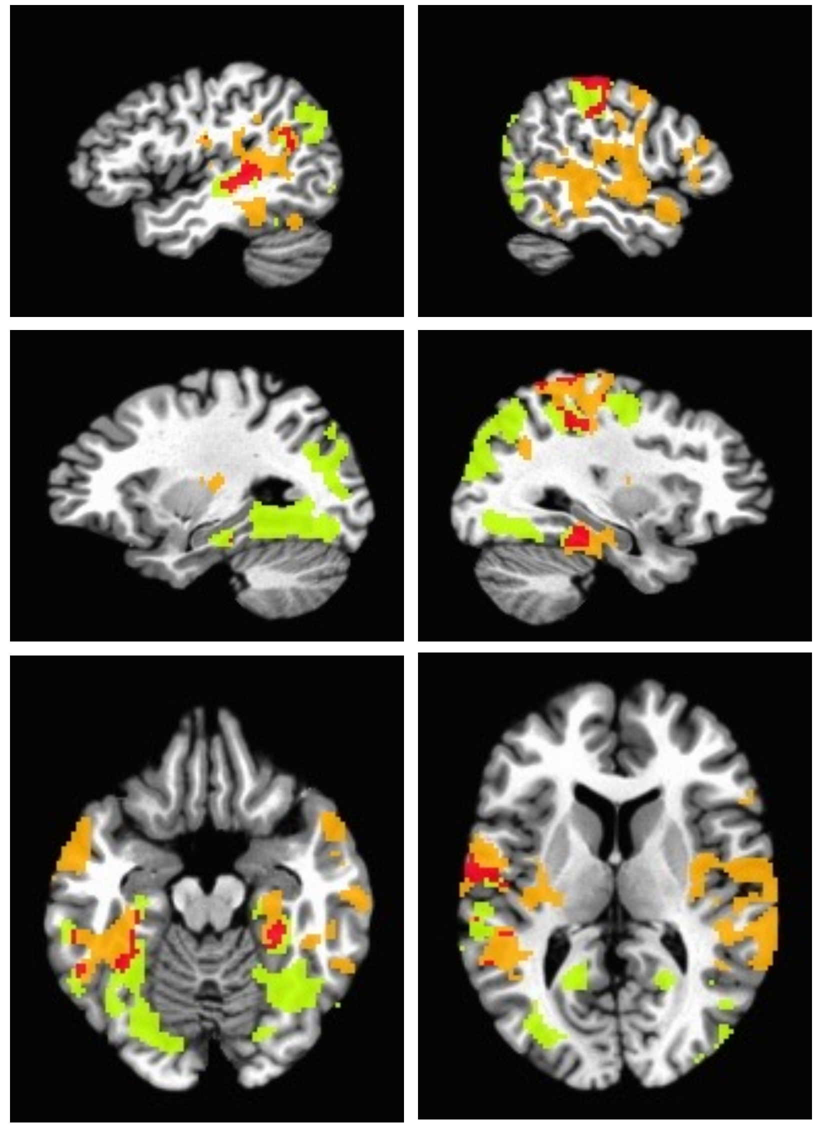

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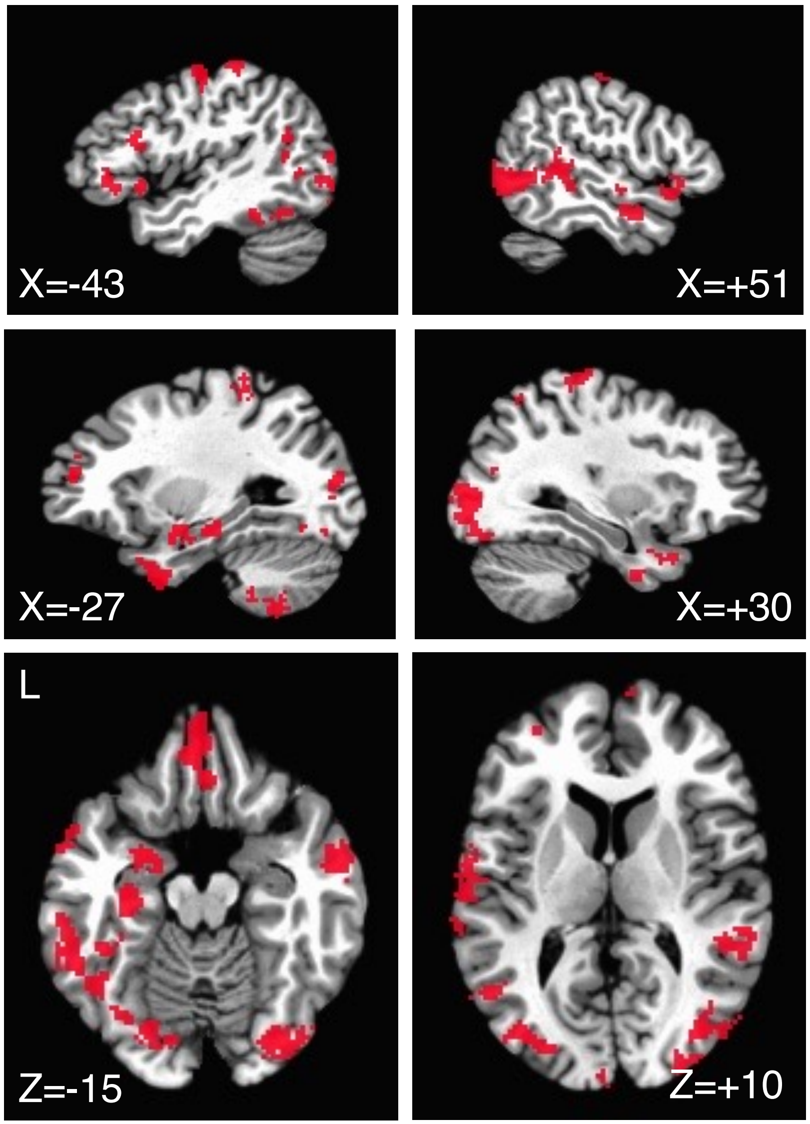

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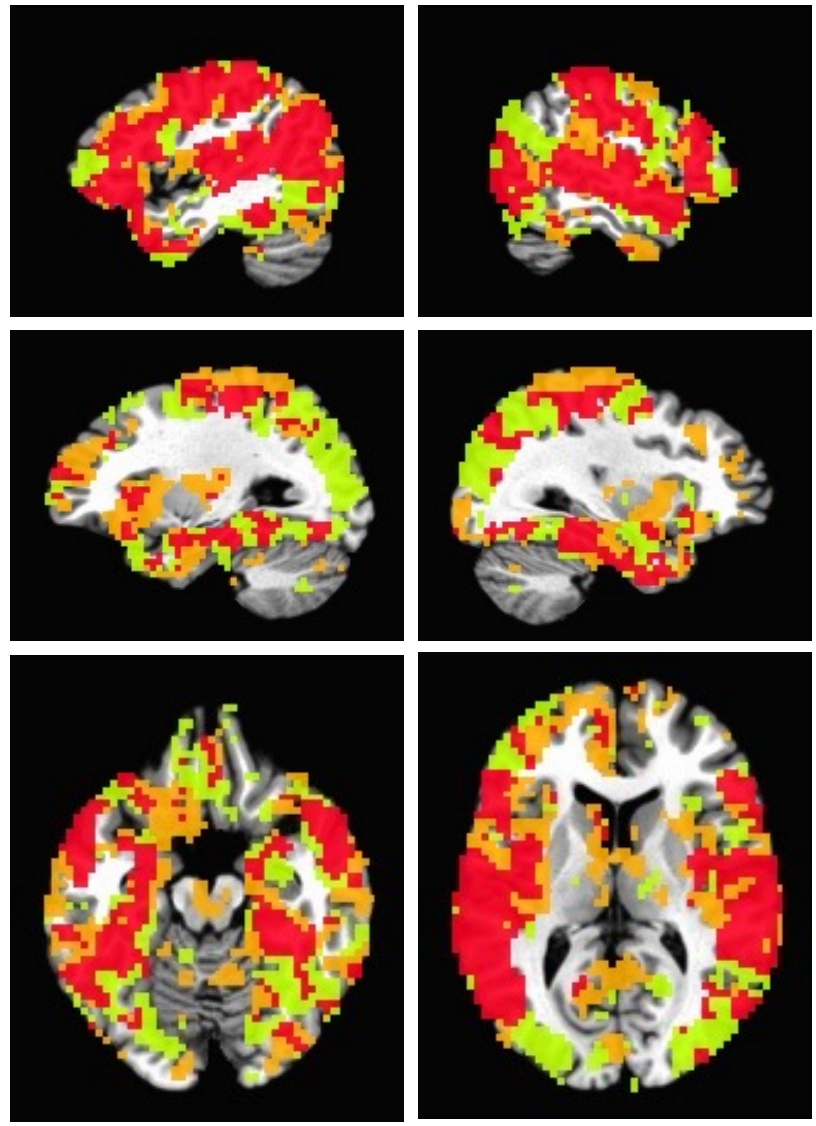
Testing All Voxels as Seeds (TD-ASD), Replication Across Two Sets, P<.05, corrected



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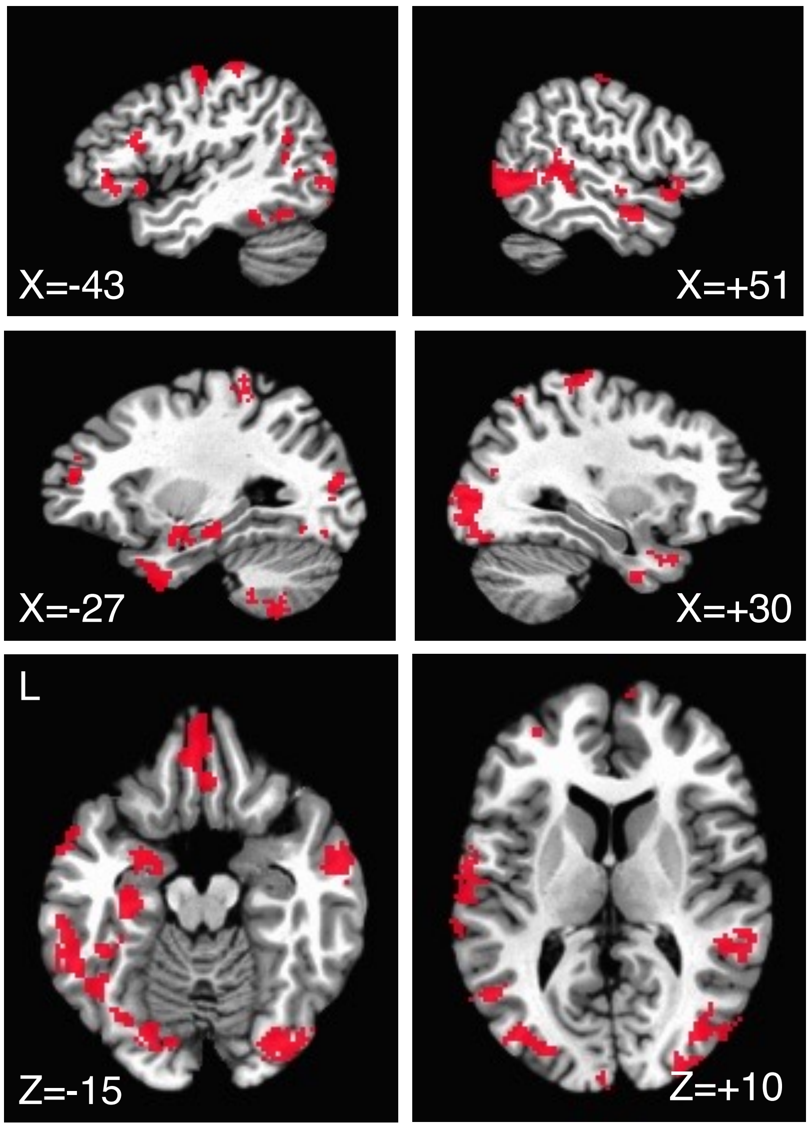

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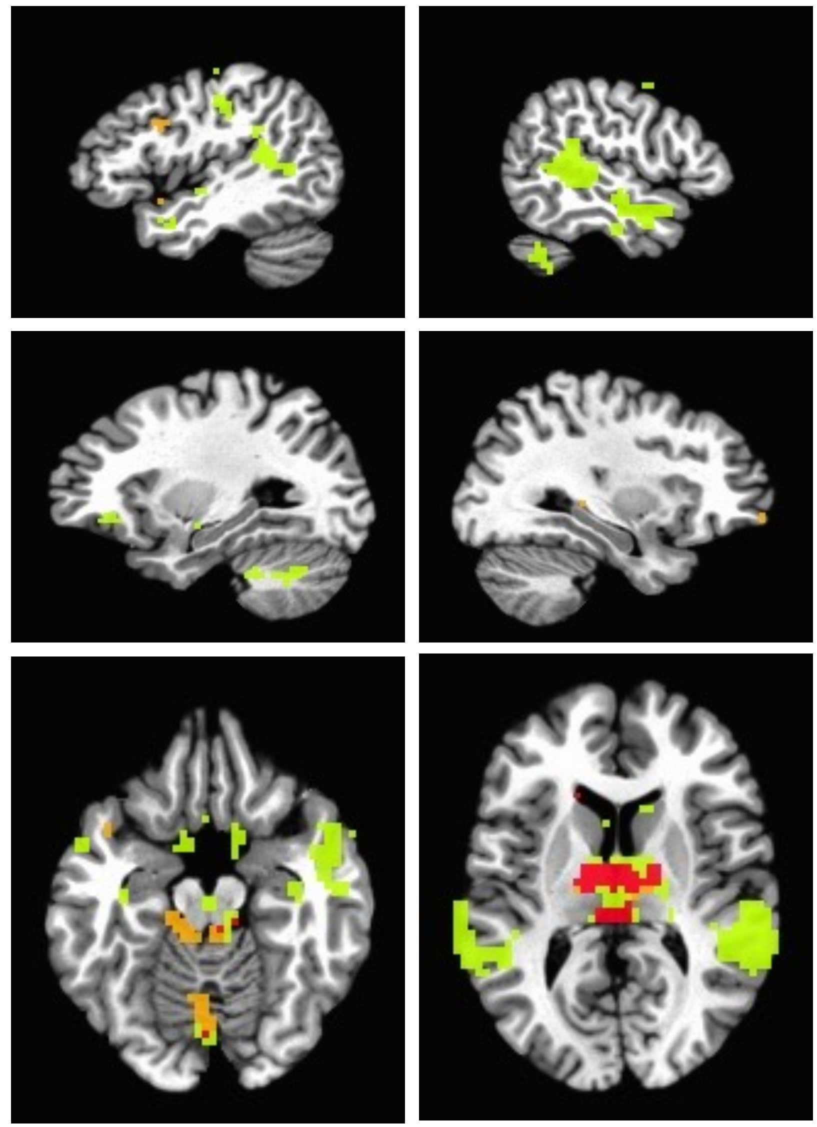

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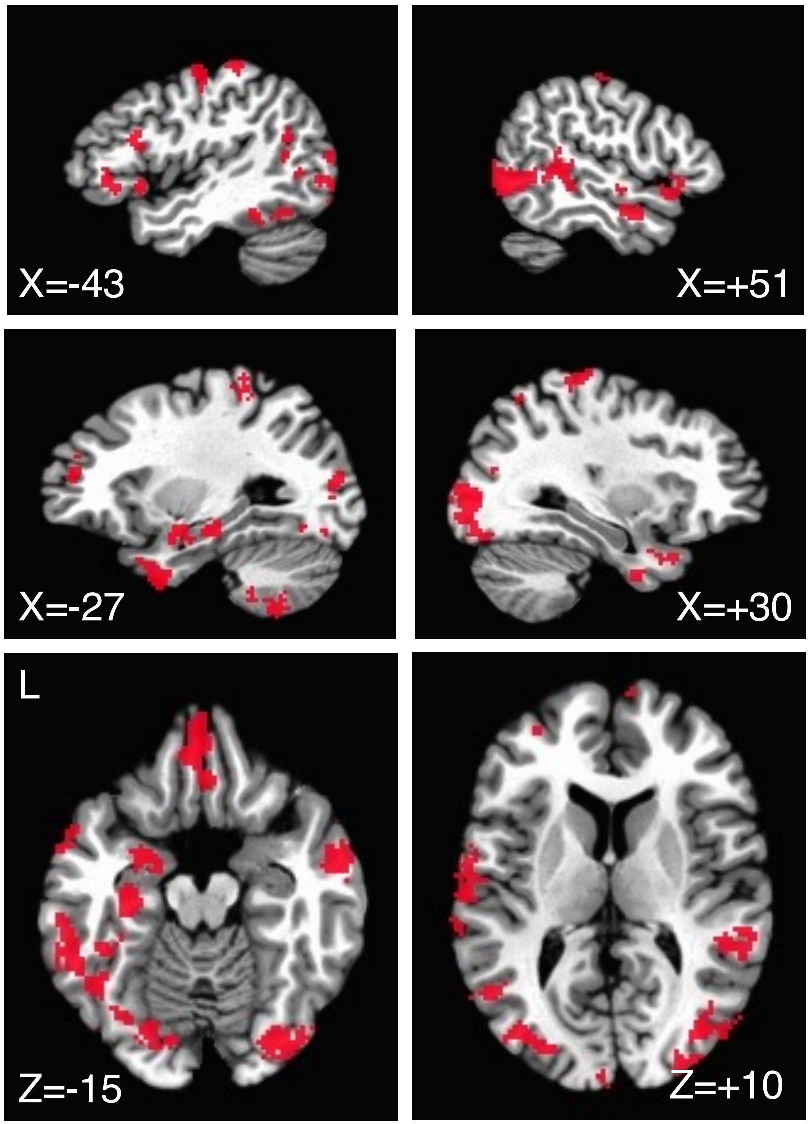

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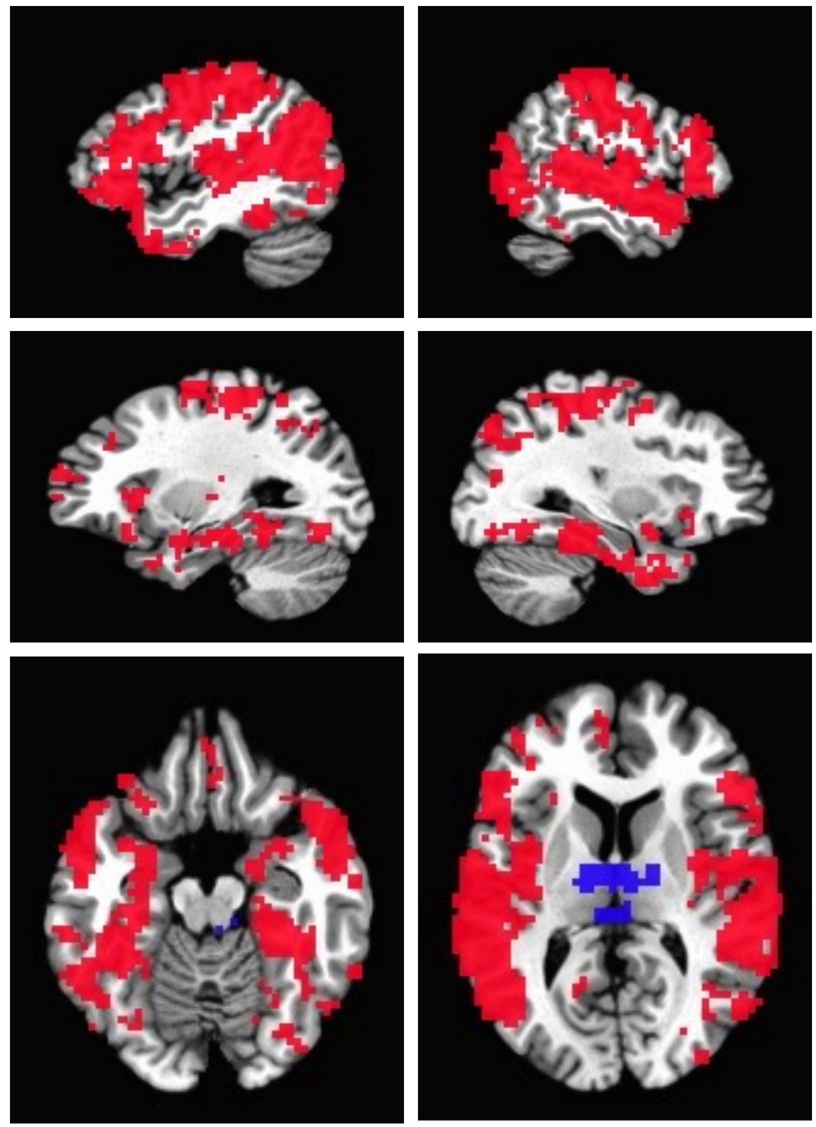

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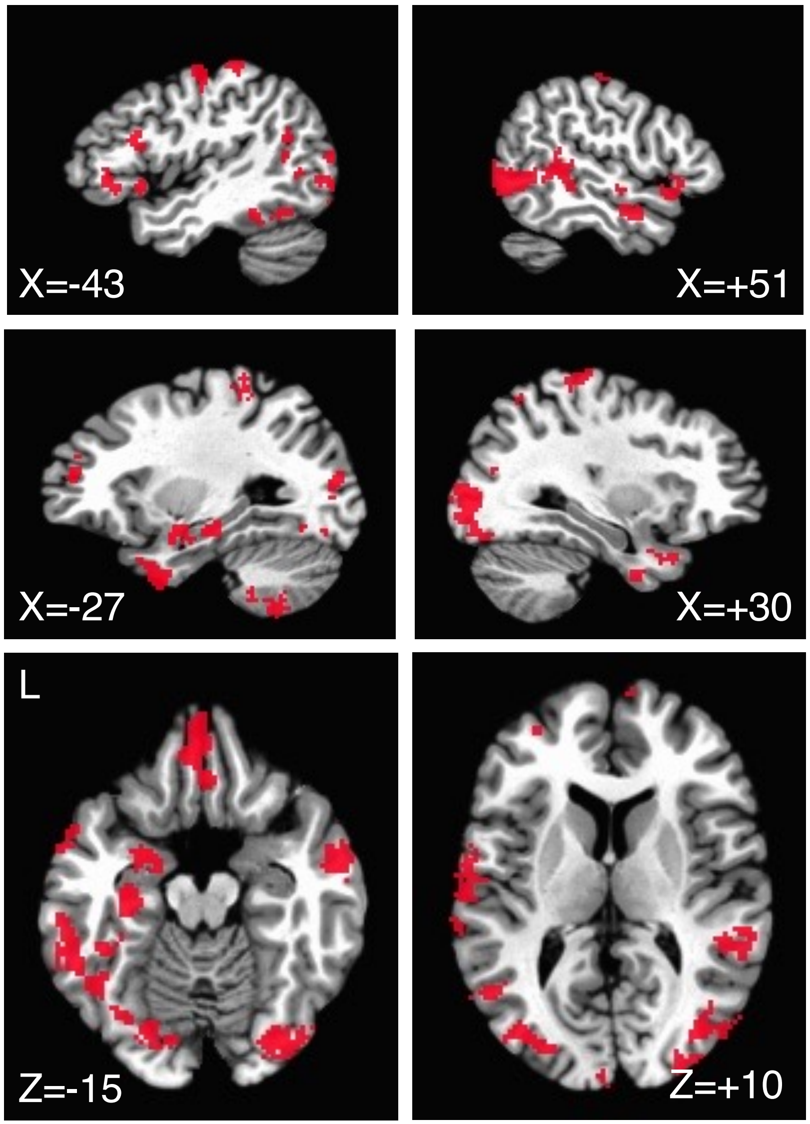

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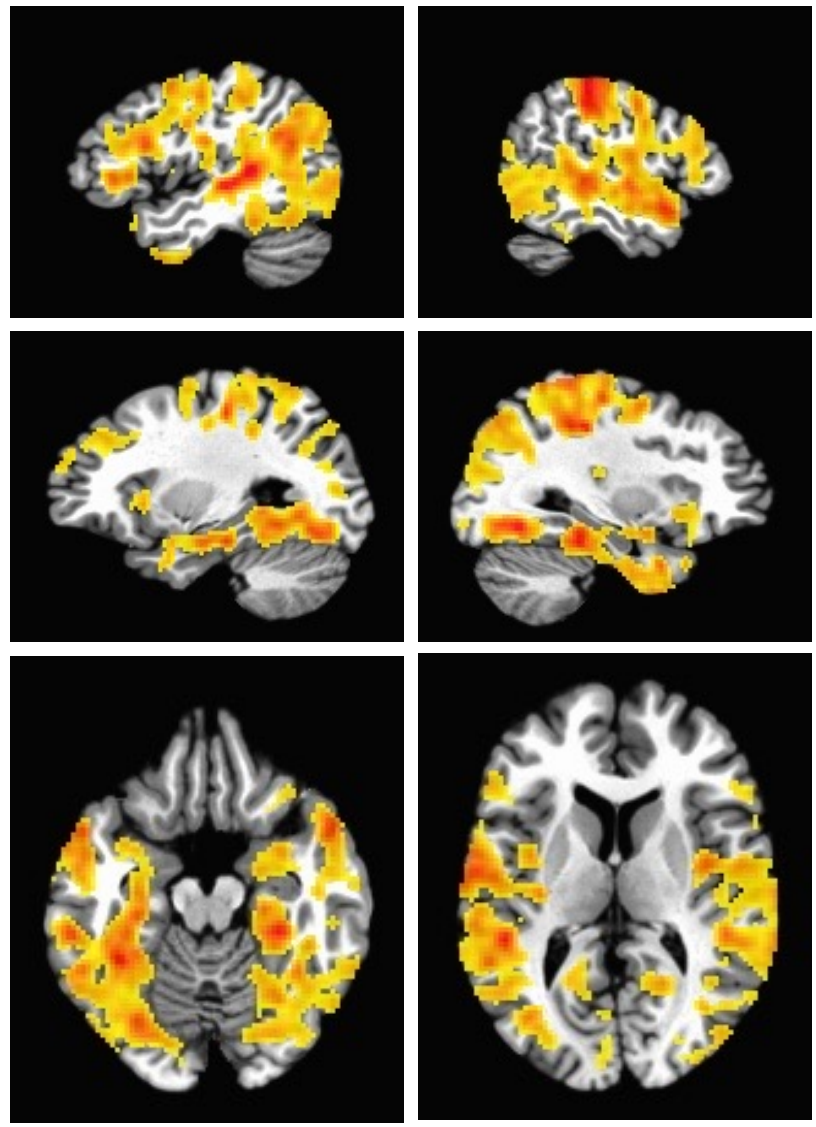

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- Voxel-wise seed testing does a better job than connectedness tests at identifying locations with mixed results (TD>ASD and ASD>TD), although results are not radically different
- Such tests do not require a priori assumptions about common network structure in control and clinical groups (as group ICA methods commonly do)
- Searches are possible for any type of test statistic for which p-values can be calculated (e.g. correlation with behavioral measures, more complex ANOVAs, etc.)

Acknowledgements:

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