Growth Charting of Brain Connectivity Networks and the Identification of Attention Impairment in Youth

Published in JAMA Psychiatry, 2016 (Kessler, Sripada, & Angstadt)

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Outline

Motivation

Pediatric Growth Charts

- Long history for height, weight, etc

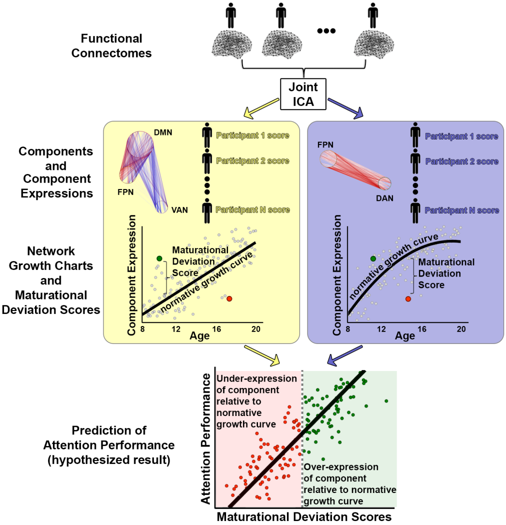
Intrinsic Connectivity Networks

- Attention & ADHD connection
- DMN vs TPN balance

Background

- Focus today: processing pipeline, modeling, and analysis
- Slides: linked from `http:dankessler.me`
- Paper: Kessler, Angstadt, & Sripada. JAMA Psychiatry 2016

Method Overview



Sample

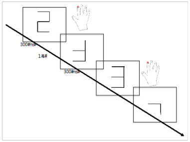
Rueben Gur

Raquel Gur

1000 youth

519 youth after quality check exclusions

Resting State fMRI
5 minute 20 seconds



Penn Continuous Performance Task
300 trials, 7 minutes

- Philadelphia Neurodevelopmental Cohort
- Resting state fMRI
- Penn Continuous Performance Task
- N = 519 (after QC & exclusions)

Task: PCPT

- Penn Continuous Performance Test
- 1s to respond
- "Go" on digit/letter (varies by phase)
- Measure: Acc (corrected for age with quadratic model)

Clinical Interview

- Assesses psychopathology dimensions
- ADHD Module
- Symptom endorsement -> pseudo ADHD "diagnosis"

MRI Measures

- T1-weighted image (structural contrast)
- Resting State fMRI

T1 Image

- Structural contrast
- Ventricles are black, "gray matter" is darker, "white matter" is brither

Resting state fMRI

- 4D Image (Multiple "Volumes"): X*Y*Z*time
- T2* contrast captures BOLD (blood oxygenation, coupled to neural activity)

fMRI Prepocessing Overview

Lots of quality-control steps throughout

1. Slice-time Correction
2. Motion Correction
3. Normalization
4. Smoothing

Preproc: Slice-time Correction

- Each fMRI volume is acquired sequentially in slices
- Volume not acquired simultaneously
- Correct (through interpolation) s.t. all slices w/in volume temporally aligned

Prepoc: Motion Correction

- Participants move their head over the scan
- Estimate affine realignment to common volume (e.g. V_0)
- Alignment is progressive (rigid body transforms)
    - realign V_1 to V_0 using affine matrix Q_1
    - align V_2 to V_0, initialize solution with Q_1
    - and so on
- Store Q_i
- Process Q_i's to capture summary displacement information for each frame
    - this will be used later in preproccessing

Preproc: Normalization

- Everybody's brain is unique
- This is problematic for group analyses
- Standard Brain/Space: MNI (Montreal Neurological Institute)
- Steps
  1. Rigid body registration of T1 scan to T2* scan
  2. Estimate nonlinear warp (affine + splines) b/w T1 and MNI template
  3. Apply estimated warp to each volume of T2* scan

Preproc: Smoothing

- Normalization isn't perfect
- Brains are plastic and diverse even when perfectly aligned anyway
- Smooth with Gaussian kernel (3D, 8mm FWHM)

Resting Processing & Connectome Generation

Processing

- Linearly detrended
- COMPCor: PCA-based nuisance regression (CSF & WM)
- Bandpass Filtering (0.01 to 0.1 Hz)
- Motion Scrubbing: Delete volumes with large displacement/motion

Connectome Generation

- Isomorphic grid, 12mm spacing
- 1068 Regions of Interest (ROIs)
- Calculate pairwise correlation, then R-to-Z transform
- Vector embedding: Each participant contributes $\binom{1068}{2}$ edges

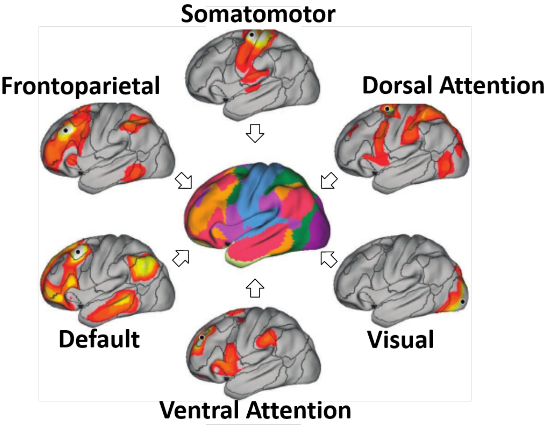
Data Cleansing

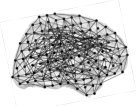
- Intersubject nuisance effects may manifest at edge level
- e.g.: left handers have > connectivity at edge i
- Concatenate vector embeddings into matrix X
- estimate with OLS $X = Y\hat{\beta} + \hat{\epsilon}$
- Reestimate data as $X^{\dagger} = Y^{\dagger}\hat{\beta}$
- Y is ideal design matrix where nuisance fx are flat
- Induce eigenvector selection through augmentation: add $\hat{\beta}$ for fx of interest at each edge

Independent Components Analysis

- reduce rows of $X^{\dagger}$ through PCA (DX) (retain top 15 eigenvectors)
- ICA-decomposition using FastICA $X = AS$
- A: mixing matrix 15 by 15
- S: source matrix: 15 by $\binom{1068}{2}$
- Unreduce $A^{\dagger} = D^{-1}A$
- $A^{\dagger}$ is # of subjects by 15
- The i,j element indicates the expression of component j for subject i

Network Assignment & Visualization



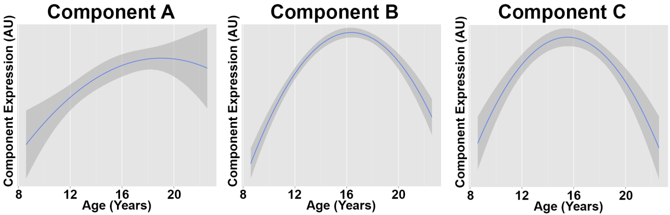


Network Growth Charting Analyses

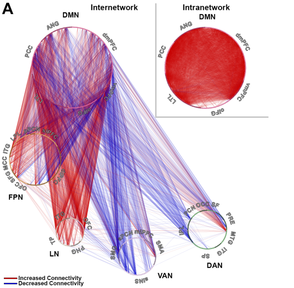
- Growth charts obtained from OLS population-level estimates
- Predict each column of A with OLS $A_i^\dagger = age + age^2$
- Residuals from these models are deviation scores reflecting over- or under- expression of a component relative to age
- Use deviation scores to predict
    - Accuracy on PCPT (age-corrected)
    - ADHD status

Network Growth Charting to Predict Task Accuracy

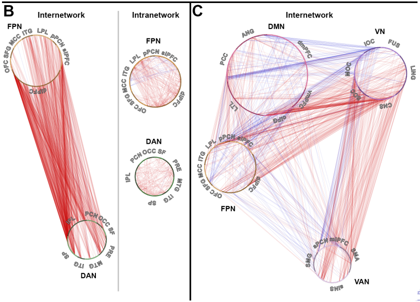
- Deviation scores predict accuracy very well ($R^2 = 0.287$)
- A subset of just 6 components' deviation scores do most of the work ($R^2 = 0.240$)
- Of these, 5 show vigorous maturational profiles
- Split half analysis, OLS with all 15 deviation scores: $R^2 = 0.176$



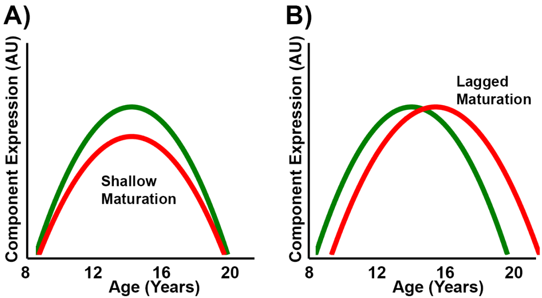
DMN-TPN Shifts in Maturing Components



Abbreviation	*Region Name*
VN	**Visual Network**
FUS	Fusiform Gyrus
LING	Lingual Gyrus
CNS	Cuneus
SOC	Superior Occipital Cortex
MOC	Middle Occipital Cortex
IOC	Inferior Occipital Cortex
SMN	**Somatomotor Network**
SMA	Supplementary Motor Area
PRE	Precentral Gyrus
POST	Postcentral Gyrus
STG	Superior Temporal Gyrus
DAN	**Dorsal Attention Network**
SF	Superior Frontal
PRE	Precentral Gyrus
MTG	Middle Temporal Gyrus
ITG	Inferior Temporal Gyrus
SP	Superior Parietal
IPL	Inferior Parietal Lobule
PCN	Precuneus
OCC	Occipital Cortex
VAN	**Ventral Attention Network**
mlPFC	Middle Lateral Prefrontal Cortex
SMA	Supplementary Motor Area
aINS	Anterior Insula
SMG	Supramarginal Gyrus
aPCN	Anterior Precuneus
LN	**Limbic Network**
OFC	Orbitofrontal Cortex
PHG	Parahippocampal Gyrus
TP	Temporal Pole
ITG	Inferior Temporal Gyrus
FPN	**Frontoparietal Network**
slPFC	Superior Lateral Prefrontal Cortex
dlPFC	Dorsolateral Prefrontal Cortex
OFC	Orbital Frontal Cortex
SFG	Superior Frontal Gyrus
MCC	Mid Cingulate Cortex
ITG	Inferior Temporal Gyrus
LPL	Lateral Parietal Lobule
pPCN	Posterior Preceneus
DMN	**Default Mode Network**
dmPFC	Dorsomedial Prefrontal Cortex
vmPFC	Ventromedial Prefrontal Cortex
oIFG	Orbital Inferior Frontal Gyrus
LTL	Lateral Temporal Lobe
PCC	Posterior Cingulate Cortex
ANG	Angular Gyrus



Shallow vs Lagged Dysmaturation and Task Accuracy



Shallow Dysmaturation

Dysmaturation yields consistent underexpression of components

Lagged Dysmaturation

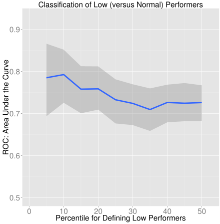
Dysmaturation yields comparable, but right-shifted, peak

Strong Evidence for Shallow Dysmaturation over Lagged

Likelihood Ratio $> 10^{26}$

Biomarker of Attention Dysfunction from Network Growth Charting

- Goal: Binary Classification of Attention Dysfunction
- Binarize task performance into *low* and *normal* performers (split by %ile cutoff)
- Vary %ile cutoff for binning
- LOOCV of Logistic Regression, performance assessed with ROC AUC, error bars from permutations



Biomarker of ADHD from Network Growth Charting

- Goal: Binary Classification of Pseudo ADHD Diagnosis
- Logistic regression predicting dx using 6 components IDed earlier
- Model is significant, but effect size weak compared to attention prediction
- $\chi^2_6 = 13.00; P = 0.043$

Discussion

- Recent review paper calls for developmental approaches to connectomic imaging
- We link dysmaturation of ICN topology to attention dysfunction
- DMN-TPN intra- and inter-relationships implicated
- Shallow vs lagged dysmaturation provides better predictive fit

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