Neuroimaging in Clinical Practice

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Disclosures

“Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.”
Fragile Power of the Human Brain
Neurodevelopmental Lottery

- Dyslexia – 5-17% of children
- ADHD – 11% of children
- Autism/ASD – 1.5% of children (1/42 boys)
- Depression – 2.5% children (8.3% adolescents, 6.7% adults)
- Bipolar Disorder – 4% of children (2.6% adults)
- Schizophrenia - 1% adults

All children - 5%-20% (more to less severe)
All adults - 50% evident childhood roots

Education – 1/8 children receive special education
Neuroimaging

grey matter structure (MRI)

white matter structure (DTI)

grey matter function (fMRI)
Neuropsychiatric Diseases & Neuroimaging

• MRI studies 1995-2015 (PubMed)
  schizophrenia – 5081
  depression – 4935
  anxiety – 2303
  autism – 1475
  ADHD – 1029
  dyslexia – 591
  and ERP, PET, MEG ….
Neuropsychiatry & Neuroimaging & Genetics
NEUROIMAGING 1.0

• *Neuroimaging & Neuropsychiatry 1.0*
  - visualize and quantify brain differences associated with disorders
  - visualize and quantify brain plasticity associated with effective treatment
NEUROIMAGING 2.0

- Neuroimaging & Neuropsychiatry 1.0
  - visualize and quantify brain differences associated with disorders
  - visualize and quantify brain plasticity associated with effective treatment

- Neuroimaging & Neuropsychiatry 2.0
  - translation from description and correlation of brain differences to knowledge that helps people
  - diagnosis ✓
  - prognosis ✓
  - understanding of which person will benefit from which treatment ✓
  - better early identification ✓
OUTLINE

• Adult ADHD
  - Is there a biomarker for current diagnosis vs. remission of ADHD?

• Social Anxiety Disorder
  - Are there biomarkers that predict who will benefit from behavioral therapy?

• Familial Risk for Depression
  Are there biomarkers that suggest risk for depression?

Functional magnetic resonance imaging (fMRI)
Background

• Default Mode Brain Network
• Resting State Functional Networks
Default-Mode Brain Network

• fMRI task activation studies compare activation differences between two conditions
• what is *more* active in the brain when people are doing nothing (no task) than doing most tasks?
Default Mode of Brain Functioning
Raichle et al., 2001, *PNAS*

Medial prefrontal cortex (MPFC); Posterior cingulate cortex (PCC)
Default-Mode Brain Network

• Default-Mode regions are deactivated during many tasks; activated during rest

• What activates Default-Mode Regions?

Default Self Overlap

also thinking about our past, our future, other people
Resting-State Functional Networks

• Intrinsic functional networks may be revealed by temporal correlations between fMRI (BOLD) signals in the resting brain
Resting-State Functional Networks

contralateral motor areas in a network

ipsilateral motor and visual areas not in a common network
Adult Attention Deficit Hyperactivity Disorder (ADHD)

• DSM-IV Criteria for ADHD
  
  6 or more symptoms for 6 months for **inattention** and/or **hyperactivity/impulsivity**

• tailored for children – what about adults?
  
  *Persistent Adult ADHD =* 
  
  more than half (4 or 5) of symptoms all other criteria (e.g., childhood onset)
Adult ADHD: Decreased Positive Correlations Between PCC-MPFC

- 20 ADHD participants (mean age = 34.9; 16 male)
  - Ascertained retrospectively
- 20 Controls (mean age = 31.2; 14 male)

Castellanos et al., 2008
Neurobiology of Persistent vs. Remitted Adult ADHD

Is there a neurobiological distinction between persistent ADHD and remitted ADHD?
Neurobiology of Persistent vs. Remitted Adult ADHD

- 17 Controls (mean age = 28.7; 11 male)
- 20 Remitted ADHD (mean age = 27.5; 8 male)
- 10 Persistent ADHD (mean age = 28.3; 10 male)
  - Full DSM-IV criteria: 6 or more symptoms and all other diagnostic requirements (e.g., age of onset)
  - Subthreshold DSM-IV criteria: more then half but less than full diagnostic criteria (4 or 5 active symptoms) and all other diagnostic requirements

Mattfeld et al., *Brain*, 2014
Neurobiology of Persistent vs. Remitted Adult ADHD

No significant differences between Persistent & Remitted ADHD on 9 other neuropsychological tests or childhood severity of ADHD

PASGAF = Past Global Assessment of Functioning Scale; BRIEF = Behavior Rating Inventory of Executive Function
Neurobiology of Persistent vs. Remitted Adult ADHD

- Controls
- Persistent ADHD
- Remitted ADHD?
- Remitted ADHD?
Neurobiology of Persistent vs. Remitted Adult ADHD

Controls

Persistent ADHD

Remitted ADHD?
Reduced MPFC-PCC Coupling Reflects Current Diagnostic State of ADHD

Mattfeld et al., *Brain*, 2014
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*Functional magnetic resonance imaging (fMRI)*
Choice of Therapy
Individuality & Variability

• most interventions (behavioral, pharmacological) help some people (≈ 50%) but not others

• can we do better to match people to interventions that will really help them (personalized medicine, precision medicine)?

• example of how imaging might help
Social Anxiety Disorder

- excessive and unreasonable fear of social situations
- common disorder – in U.S., 15 million adults; 6.8% in a given year (NIH)
- chronic, disabling, associated with substantial impairment, decreased quality of life, psychiatric comorbidity, twice the rate of unemployment vs. other anxiety disorders and depression
Social Anxiety Disorder (SAD)

- *treatments* – cognitive behavioral therapy (CBT) and/or pharmacology
- *effectiveness* – about 50% of patients substantially helped
- no evidence basis for choice of treatment
- poor prediction of treatment outcome
Social Anxiety Disorder (SAD)

- study with 51 SAD patients before and after CBT treatment
- does brain imaging before treatment predict outcome?
  - activation fMRI
  - resting-state fMRI
- outcome = gain on Liebowitz Social Anxiety Scale (LSAS) $r = +.38$
Social Anxiety Disorder (SAD)

fMRI Tasks

Emotional Scene (15 s) + Emotional Face (15 s) + Neutral Face (15 s) + Neutral Scene (15 s) + …

Emotional > Neutral Scenes
Emotional > Neutral Faces

Doehrmann et al., 2013, *JAMA Psychiatry*
Social Anxiety Disorder (SAD):
Correlation Between Baseline fMRI & Treatment Outcome

$r = +.71$

$r = + .68$

Doehrmann et al., 2013, JAMA Psychiatry
Social Anxiety Disorder (SAD): Predicting Treatment Outcome

*predicts better outcome*  
*predicts worse outcome*
Connectomics

• Structure
  - Diffusion Tensor Imaging (DTI) measures white-matter microstructure

• Function
  - functional connectivity (fMRI) spontaneous, correlated fluctuations in fMRI signal during the resting state identify intrinsic functional neural networks
Amygdala Functional Connectivity

Amygdala seed cluster predicting outcome

Whitfield-Gabrieli et al., *Molecular Psychiatry*, 2015
Whole-Brain Multi-Voxel Pattern Analysis (MVPA)

Empirically defined seeds

Cluster predicting outcome

Whitfield-Gabrieli et al., *Molecular Psychiatry*, 2015
Right Inferior Longitudinal Fasciculus
Diffusion Weighted Imaging of Right Inferior Longitudinal Fasciculus

Whitfield-Gabrieli et al., Molecular Psychiatry, 2015
Social Anxiety Disorder (SAD): Predicting Treatment Outcome

Prediction from diffusion tensor imaging and resting-state fMRI

Whitfield-Gabrieli et al., *Molecular Psychiatry*, 2015
Categorical Analysis

- LSAS improvement > 50% vs. < 50%
- logistic regression with initial LSAS, 3 connectomic measures
- 81% accuracy, 84% sensitivity, 78% specificity

Whitfield-Gabrieli et al., *Molecular Psychiatry*, 2015
Neuroprognosis

Can brain measures predict future behavior and future response to treatment better than other currently available measures?

*Personalized Medicine*
Neuroimaging & Prognosis

• prognosis for depression
  (Canli et al., 2005)

• response to CBT or medications in depression
  (Mayberg et al., 1997; Pizzagalli et al., 2001; Davidson et al., 2003; Fu et al., 2004; Siegle et al., 2006, 2012, Chen et al., 2007; Costafreda et al., 2009; Forbes et al., 2010)

• response to medication in anxiety
  (Whalen et al., 2008)

• response to CBT in schizophrenia
  (Premkumer et al., 2009, 2010; Kumrai et al., 2009)

• relapse in methamphetamine dependence (37/40)
  (Paulus et al., 2005)

• rearrest for adult offenders
  (Aharoni et al., 2013)
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*Functional magnetic resonance imaging (fMRI)*
Depression

- lifetime prevalence – 16.5% (Kessler et al., 2005)
- increased risk if parent has depression – 3x
  (Weissman et al., 2006)
Children Ages 8-14 at Familial Risk for Depression

• **At-Risk Children**
  - no current depression
  - N = 38; mean = 11.1 years
  - at least one parent with depression

• **Control Children**
  - N = 25; mean = 10.6 years
  - no parental history of depression

Chai et al., *NeuroImage Clinical*, 2016
fMRI Task

FEARFUL

HAPPY

NEUTRAL

OBJECTS
Brain Activation Differences in Children at Risk for Depression

**Decreased** Response to Happy Faces in At-Risk Children

Control > At-Risk

**Increased** Response to Fearful Faces in At-Risk Children

At-Risk > Control
Multiple Differences in Resting State Connectivity of the Brain in At-Risk Children

Chai et al., *Biological Psychiatry*, 2016
Multiple Differences in Resting State Connectivity of the Brain in At-Risk Children

- pattern of resting state connectivity highly accurate in differentiating at-risk from control children, child by child

** brain = 79% accuracy, 81% sensitivity, 78% specificity

**clinical rating scale (CBCL) = 64% accuracy, 80% sensitivity, 27% specificity

Brain imaging more accurate than behavioral rating

Chai et al., *Biological Psychiatry*, 2016
OUTLINE

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• Familial Risk for Depression
  Are there biomarkers that suggest risk for depression? **YES**

*Functional magnetic resonance imaging (fMRI)*
Collaborators

• ADHD
  Joseph Biederman
  Aaron Mattfeld
  Thomas Spencer
  Ariel Brown
  Elana Kagan

• Social Anxiety Disorder
  Stefan Hofmann
  Mark Pollack
  Oliver Doehrmann
  Satrajit Ghosh
  Frida Polli

• Childhood Risk for Depression
  Joseph Biederman
  Dina Hirshfeld-Becker
  Jenny Chai

• all studies
  Susan Whitfield-Gabrieli