States & Stability in Human Brain Networks

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The outer surface of the cerebral hemispheres is called cerebral cortex which consists of a densely folded strip of grey matter. The cerebral cortex displays a multi-layered organizational pattern. The architecture of the cortical layers varies across the brain. The majority of the cortex is six-layered (neocortex), and can be further parcellated in distinct areas or fields. The cytoarchitecture reveals variations in cell shape, size, and density; characteristics which are used as anatomical landmarks to divide the cortex into distinct areas. According to the work of individual groups and authors, the number of areas that are distinguished varies from a minimum of 17 to a maximum of 107. The most widely used maps are provided by Brodmann (Fig. 4.3) and his original atlas contained 52 areas. According to Brodmann's classification, the frontal lobe consists of eleven fields, which are grouped in five main regions: (1) Area 4 corresponds to the primary motor cortex, containing neuronal bodies, as well as cortico-spinal projection fibers which show a somatotopical organization; (2) Area six contains the premotor region and is subdivided into the lateral premotor cortex (PMC), and the pre-supplementary motor area (pre-SMA); (3) Area 44 and 45 correspond to Broca's area; (4) Area 8–10, and 46 include dorsolateral prefrontal areas, and 47 to the ventrolateral prefrontal cortex; (5) Finally, areas 11 and 47 represent the main parts of the orbitofrontal cortex. The parietal lobe is divided into four regions consisting of a total of nine separate fields by Brodmann: (1) Areas 1–3 correspond to the somatosensory cortex and its cytoarchitecture strongly resembles that of the primary motor cortex; (2) The more laterally located areas 5 and 7 together form the superior polymodal parietal cortex; (3) Areas 39 and 40 are located in the inferior polymodal parietal cortex, corresponding to the Geschwind's territory; (4) The medial parts of areas 31, 5, and 7 form the precuneus, and area 43 is considered a transition region of the fronto-parietal operculum.

B. U. Forstmann et al.

Fig. 4.3 Reproduction of the classical Brodmann map. (a) lateral view, (b) medial view. Individual numbers indicate Brodmann area numbers.
Control and Processing Systems

specified transformations: e.g., sensory, perceptual, semantic, motor

control

input

processing

output

e.g. Petersen & Posner, 2012
My Research

1. Control system functions

2. Modulation of processing by control systems

3. Networks & hubs

control

input

specified transformations: e.g., sensory, perceptual, semantic, motor

output
My Research

1. Control system functions
2. Modulation of processing by control systems
3. Networks & hubs

- Specified transformations: e.g., sensory, perceptual, semantic, motor
- Input
- Control
- Output
functional Magnetic Resonance Imaging (fMRI)

Blood Oxygen Level Dependent (BOLD) Signal

Heeger & Ress, 2002
Functional Connectivity (FC): measuring relationships across brain regions

Van Dijk et al., 2010, J Neurophysiol

Introduction

1.0 correlation (FC)

during a resting state
FC: A way to map brain organization

Introduction

Regions

Correlation (FC)

-0.4  0.0  0.4  0.8  1.0

BOLD signal

Time (min)

L MOT  L VIS

r = 0.06
FC: A way to map brain organization

Correlation (FC)

-0.4

1.0

[Brain map and correlation matrix diagram]
Mapping functional brain networks with fMRI

Gordon et al., 2017, Neuron
Braga et al., 2017, Neuron
Laumann et al., 2015, Neuron
Poldrack et al., 2015, Nat Commun
The Promise of Functional Connectivity

- Brain damage and disease
- Individual differences
- Development and aging
- Cognitive demands
How do functional brain networks vary over different timescales?

How does Parkinson’s disease affect functional brain networks?

Recent work: Characterizing individual variation in brain networks
How do functional brain networks vary over different timescales?

How does Parkinson’s disease affect functional brain networks?

Recent work: Characterizing individual variation in brain networks
Stabile or State Dependent?

Two hypotheses:
1. Functional networks are primarily stationary
2. Functional networks reconfigure substantially with ongoing cognition, mood, etc.
Timescales of variation in functional brain networks

How variable are functional brain networks?

- Moment-to-moment variation (seconds)
- Changes with brain states (minutes)
- Circadian/slow changes (hours, days)
- Changes with extensive experience (weeks, years)
- Stable in an individual
- Invariant
On the **stability** side

Group depictions of FC networks are similar across sites, subjects, and techniques

*Power et al., 2011, Neuron*  
*Yeo et al., 2011, J Neurophys*
On the **state-dependence** side

We examined how brain networks vary across diverse **task states**

- **Semantic Task**
  - Noun/verb judgment
- **Mental Rotation Task**
  - Same/mirror judgment
- **Coherence Task**
  - Yes/no coherence

N = 28 (N = 25 for individual tasks)

*Gratton* et al., 2016, *Cell Reports*

See also: Cole et al., 2014, *Neuron*; Krienen et al., 2014, *Phil Trans*
On the state-dependence side

Functional networks vary systematically and consistently between task and rest

These changes are related to **topological** and **functional** properties of brain networks.

*Gratton et al., 2016, Cell Reports*
On the state-dependence side

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Gratton et al., 2016, Cell Reports
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Task - Rest

Gratton et al., 2016, Cell Reports

WashU

Harvard

Power et al., 2011

Yeo et al., 2011
Timescales of variation in functional brain networks

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What are the relative contributions of these effects to functional brain networks?

- Magnitude
- Anatomical distribution
MSC data is well-suited to addressing this question

We use Midnight Scan Club (MSC) data to address this question:

10 subjects, 10 sessions each

dataset from Dr. Nico Dosenbach & WUSTL MSC group

See:
Gordon et al., 2017, Neuron
High sampling permits high-precision mapping of individual brain networks

Gordon et al., 2017, Neuron; Laumann et al., 2015, Neuron; Poldrack et al., 2015, Nat Commun
MSC data is well-suited to addressing this question

We use **Midnight Scan Club (MSC)** data to address this question:

10 subjects, 10 sessions each

- **GUITAR**
- **TONGUE**

Separate effects:
- **Common** across the full group
- Selective to individual **subjects**
- Selective to individual **sessions**
- Selective to individual **task states**

*dataset from Dr. Nico Dosenbach & WUSTL MSC group*

*See: Gordon et al., 2017, Neuron*

*Gratton et al., 2018, Neuron*
Single subjects showed examples of each effect.

We measured functional networks from each subject for each state and session.

1. States & Stability

![Correlation Matrices]

- Rest
- Coherence
- Semantic
- Motor
- Memory

Correlation (z) scale:

-0.4 0 1.0
Individual-level effects dominate early dimensions
State-level divisions appear at higher dimensions
Quantification of the similarity among functional brain networks

1. States & Stability

MSC01
Coherence Task
Session 1

MSC09
Semantic Task
Session 2
Quantification of the similarity among functional brain networks

1. States & Stability
Quantification of the similarity among functional brain networks

Functional Network Similarity

MSC01  MSC02  MSC03  MSC04  MSC05  MSC06  MSC07  MSC09  MSC10

Task: Rest, Coherence, Semantic, Motor, Memory

networks, matched on property $P$
Quantification of the similarity among functional brain networks

**Functional Network Similarity**

<table>
<thead>
<tr>
<th>MSC01</th>
<th>MSC02</th>
<th>MSC03</th>
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</table>

**Task:** Rest, Coherence, Semantic, Motor, Memory

networks, matched on property $P$
Effects differ by functional system

1. **Individual-specific** effects are stronger in **control** systems
2. **Cross-subject** effects are stronger in **processing** systems
States & Stability: Summary & Conclusions

- **Moment-to-moment variation (seconds)**
- **Changes with brain states (minutes)**
- **Circadian/slow changes (hours, days)**
- **Changes with extensive experience (weeks, years)**
- **Stable in an individual**
- **Invariant across a group**

Gratton et al., 2018, Neuron
States & Stability: Summary & Conclusions

These findings are important for:
1. Understanding potential neurobiological contributions to functional networks
2. Interpreting functional network comparisons between groups and states
3. Developing functional network-based medical therapeutics

Gratton et al., 2018, Neuron
How do functional brain networks vary over different timescales?

Functional networks are primarily stable, with moderate state-based effects

How does Parkinson’s disease affect functional brain networks?

Recent work: Characterizing individual variation in brain networks
Talk Outline

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Parkinson’s Disease (PD)

2nd most common neurodegenerative disorder
- ~1 million cases in the US
- ~20 new cases/100,000/yr.

Clinical manifestations:
- Motor
- Cognitive
- Psychiatric
- Sleep disturbances, etc.
Parkinson’s Disease (PD)

Neuropathology:
- ascending α-synuclein deposition (Lewy bodies)
- Substantia nigra/striatal dopamine pathophysiology
- Impacts nuclei from multiple neurotransmitter systems

How does PD disrupt function across distributed brain networks?

We address this question by using resting-state functional connectivity to map networks across the brain
Our study

- A large and well-characterized dataset of non-demented PD and age-matched healthy controls (PD N=107, HC N=46)

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>PD</th>
<th>HC</th>
<th>PD vs. HC p-value</th>
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<tbody>
<tr>
<td><strong>N</strong></td>
<td>107</td>
<td>46</td>
<td>-</td>
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<tr>
<td>Sex (% male)</td>
<td>56.1</td>
<td>30.4</td>
<td>0.003*</td>
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<tr>
<td>Age</td>
<td>65.2 (7.3)</td>
<td>63.8 (11.0)</td>
<td>0.37</td>
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<td>Years of Education</td>
<td>16.2 (2.6)</td>
<td>14.8 (2.7)</td>
<td>0.002*</td>
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<td>MMSE</td>
<td>28.6 (1.6)</td>
<td>29.0 (1.1)</td>
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<td>Disease Duration (Years)</td>
<td>6.3 (4.2)</td>
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<tr>
<td>Age Onset of PD</td>
<td>59.0 (7.6)</td>
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<td>UPDRS-III OFF Total</td>
<td>23.1 (8.5)</td>
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<td>LEDD</td>
<td>792 (545)</td>
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</table>
Our study

- A large and well-characterized dataset (PD N=107, HC N=46)
- Well-sampled cortex and subcortex

What is the relative magnitude and specificity of network-level effects in PD?
Network organization was similar in PD and HC.
PD was characterized by **block-specific** FC deficits

- **Within and between networks**
- **Cortical and subcortical networks**
We used multi-dimensional techniques to measure these differences.

La Rosa et al., 2016, Stat Med; La Rosa et al., 2012, PLoS One
Large differences were found within and between sensorimotor, thalamic, and cerebellar networks.

block p(FDR) < 0.05

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mean abs. correlation difference (z)

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<th>.02</th>
<th>.04</th>
<th>.06</th>
<th>.08</th>
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z = 3  x = -28  y = 6
Differences reflect **weakened magnitude** of positive and negative connections.

**2. Networks in PD**

block p(FDR) < 0.05

**positive** connections

**negative** connections

<table>
<thead>
<tr>
<th>Mean abs. correlation difference (z)</th>
<th>Correlation (z) difference PD - HC</th>
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<tbody>
<tr>
<td>.02 .04 .06 .08 0.1</td>
<td>-0.2 -0.1 0 0.1 0.2</td>
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</table>
Spring embedding depicts weakening of systems
Networks in PD: Summary and Conclusions

- PD is characterized by selective deficits in functional networks
  - Respect known **network divisions**
  - Diminished magnitude suggests a **breakdown** of affected networks

- Differences were within and between cortical and subcortical systems
  - Emphasizes the need for a **brain-wide “connectome” perspective**
  - Striatal connectivity was less affected – thus network effects were **downstream of primary pathology**

- **Functional network effects in PD are complex and emergent**
  - Findings may be important for understanding clinical manifestations in PD

*Gratton et al., 2018, Cerebral Cortex*
Talk Outline

How do functional brain networks vary over different timescales?
Functional networks are primarily stable, with moderate state-based effects

How does Parkinson’s disease affect functional brain networks?
Parkinson’s disease selectively impacts blocks of network-to-network connections, remote from primary pathophysiology

Recent work: Characterizing individual variation in brain networks
Talk Outline

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Recent work: Characterizing individual variation in brain networks
Identification of “network variants”

3. Network variants

- Group networks
- MSC06 networks

Overlap of variants across individuals

Ben Seitzman

Seitzman*, Gratton*, et al., under review
Network variants are stable

![Brain scans and correlation plot showing stability of network variants across sessions.]

- **All sessions from MSC02**
  - Session 1
  - Session 2
  - Session 3
  - Session 4
  - Session 5
  - Session 6
  - Session 7
  - Session 8
  - Session 9
  - Session 10

- **Intraclass Correlation**
  - Axes: Spatial R (ranging from -0.2 to +0.8)
  - Data points for subjects MSC01 to MSC10

- **Characteristics**
  - Spatial variation in network connectivity
  - Reliability measured through intraclass correlation

- **Implications**
  - Consistency in network structure across repeated sessions
  - Importance of stable network markers for individual identification
Network variants are frequently associated with control-related networks.
Task activations in network variants shift toward new network profile

MSC02 variants over typical networks

How are network variants related to individual variation in behavior?

Task Activation (z)

-3 0 3

t(8) = 7.68, p<0.001

DMN variant DMN variant loc within subject within others
Network Variants: Summary and Conclusions

- Network variants
  - Are reliable
  - Frequently associated with control-related systems
  - Show task activations shifted toward their new network profile

Individual differences in brain networks are stable, systematic, and related to function

Seitzman*, Gratton*, et al., under review
Summary & Conclusions

**How do functional brain networks vary over different timescales?**
Functional networks are primarily stable, with moderate state-based effects

**How does Parkinson’s disease affect functional brain networks?**
Parkinson’s disease selectively impacts blocks of network-to-network connections, remote from primary pathophysiology

**Recent work: Characterizing individual variation in brain networks**
Individual network “variants” are stable and systematic
Functional network measures are well-suited to tracking slow, stable brain processes such as traits and disease.

These measures can provide detailed images of individuals.

Individual differences are most pronounced in control-related brain systems, with implications for studying their function.
Overarching Conclusions
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