States and Stability in Human Functional Brain Networks

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Mapping functional brain networks with fMRI

Van Dijk et al., 2010, J Neurophysiol

Introduction

- slow (0.01 – 0.1 Hz)
- large-scale
- “functional”
Mapping functional brain networks with fMRI

Unlabeled
SM
SM (lat)
CO
Auditory
DMN
Memory
Visual
FP
Salience
Sub-cortex
Ventral Attn
Dorsal Attn
Cerebellum

Power et al., 2011, Neuron
Yeo et al., 2011, J. Neurophys
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

Introduction
Talk Outline

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
Talk Outline

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
Timescales of variation in functional brain networks

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Laumann, et al., 2016, Cerebral Cortex
Gratton et al., 2016, Cell Reports
Power et al., 2011
Yeo et al., 2011
How variable are functional brain networks?

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

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

See: 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:

- **Semantic Task**: noun/verb judgment
- **Separate effects**: - Common across the full group - Selective to individual subjects - Selective to individual sessions - Selective to individual task states
- **Incidental Memory**: faces, scenes, words
- **Rest**: eyes open, fixation

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

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

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

<table>
<thead>
<tr>
<th>Subject</th>
<th>MSC01</th>
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<th>MSC03</th>
<th>MSC04</th>
<th>MSC05</th>
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Task: Rest, Coherence, Semantic, Motor, Memory

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

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

network similarity: \( z(r) \)

networks, matched on property \( P \)
1. States & Stability

Variance in human functional brain networks attributable to:

- Group
- Individual
- Individual & Task
- Individual & Session
- Task

Stability and sensitivity to individual differences suggests utility in precision medicine.

- 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
1. States & Stability

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
**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?**

**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.

slides courtesy of Bob Knight
Parkinson’s Disease (PD)

Neuropathology:
- Ascending α-synuclein deposition (Lewy bodies)
- Substantia nigra/striatal dopamine pathophysiology
- Impacts nuclei from multiple neurotransmitter systems
  - e.g., see Aarsland et al., 2002, Neurology

**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.
Previous studies of functional connectivity in Parkinson’s Disease

- Focused primarily on single seeds/systems, especially in the striatum

- A handful of studies have looked at networks, primarily focused on cortex
  - Main findings: involvement of motor, visual, and association systems
  - BUT
    - Almost none do any rigorous motion correction
    - Most are ON med
    - Most do not systematically sample subcortical structures
Our study

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

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<th>HC Mean (SD)</th>
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<td>Sex (% male)</td>
<td>56.1</td>
<td>30.4</td>
<td>0.003*</td>
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<td>Age (Years)</td>
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Gratton et al., 2018, Cerebral Cortex
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?
Our study

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

This allowed us to examine 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
These findings replicate across split-half samples.

Half 1, $G_{PD}^* - G_{HC}^*$

Half 2, $G_{PD}^* - G_{HC}^*$

$p = 0.02$

$p < 0.001$
Large differences were found within and between sensorimotor, thalamic, and cerebellar networks

block p(FDR) < 0.05

mean abs. correlation difference (z)

z = 3
x = -28
y = 6
Differences reflect **weakened magnitude** of positive and negative connections

**positive** connections

**negative** connections

**correlation (z) difference**

**PD - HC**

-0.2  -0.1  0   0.1  0.2
Spring embedding depicts **weakening** of systems.
A subset of block FC is related to motor and cognitive performance.
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
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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

Seitzman*, Gratton*, et al., in review
Network variants are **stable** and **systematic**

**How are network variants related to individual variation in behavior?**
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.
Summary & Conclusions

Functional network measures are well-suited to tracking slow, stable brain processes.

These measures can provide detailed images of individual differences.

Functional network effects can be complex and emergent, occurring at locations remote from primary pathology.
Acknowledgments

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Annie Nguyen

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Thank You!
EXTRA SLIDES
On the **stability** side

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

**WUSTL**

Power et al., 2011, Neuron

**Harvard**

Yeo et al., 2011, J Neurophys
On the **stability** side

Functional networks do not vary substantially from moment-to-moment at rest

![Real vs Simulated States](image)

Similar states to **static** noisy simulations

![Frame Censoring](image)

Minimal kurtosis (**variance of covariance**) once motion is accounted for

Laumann, Snyder, Mitra, Gordon, Gratton, et al., 2016, Cerebral Cortex
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

**GUITAR**

N = 28 (N = 25 for individual tasks)

**Rest**

Eyes open, fixation

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*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 share substantial similarity across task and rest states...

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

... but FC varies 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

... but FC varies 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*
Pattern is **consistent** across individuals and tasks.
Pattern is consistent across subjects and tasks, when data quantities are matched.
Modeling variation per network connection
Individual effects remain when using individual parcellations.
Clusters are reused, yielding on average a 32% shorter description for this network. The codes naming the modules and the codes used to indicate an exit from every node in the network. The Huffman code illustrated here is an efficient way to do so. The 314 bits shown under the network describe the sample trajectory. Reporting only the module names, and not the locations within the modules, provides an efficient coarse graining of the network.

We want to describe the trajectory of a random walk on each module, starting with 1111100 for the first node on the walk in the upper left corner, 1100 for the second node, etc., and ending with 00011 for the last node on each module are shown to the left and the right of the arrows under the network, respectively. Using this code, we can describe the walk in the lower right corner. (Rosvall and Bergstrom, 2008, PNAS)
Nodal Role relationships, Task and Rest
Supplemental Figure 2: Infomap in PD and HC participants

(A) Data-driven clustering solutions (using Infomap [REF]) for large-scale networks in this group of HC participants. Different colors represent different networks, shown for 0.01 – 0.1 density thresholds. Gray colors represent a lack of assignment.

(B) The same plot, but for PD participants. Note substantial similarity between PD and HC participants.
Supplemental Figure 3: Analysis of FC differences between PD and HC

(A) The absolute magnitude of differences between PD and controls; decreases in magnitude are shown in blue colors, increases in magnitude are shown in red colors, and changes in direction are shown in black.

(B) FC for each connection in the correlation matrix for HC and PD participants, plotted against the unity line. Note that PD is associated with a flattening of FC, with negative values being elevated toward 0 and positive values being diminished toward 0, and thus tending to appear more in the yellow triangles. This was especially true of edges within the significant blocks (red) relative to other edges (gray) which stayed closer to the unity line.
Supplemental Figure 4: PD and HC matched groups for subject number, sex, age, and years of education

The PD group was subsampled to approximately match the HC group for sex, years of education, and participant numbers (note that age was already approximately matched; see table above). The figure shows the G* difference map between groups (G*_{PD_match} - G*_HC; p<0.001). Notably, the differences between the two groups were quite similar to those reported in the main manuscript.

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<td>Sex (% male)</td>
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<td>0.77</td>
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<td>65.3 (7.7)</td>
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<td>Years of Education</td>
<td>14.9 (2.0)</td>
<td>14.8 (2.7)</td>
<td>0.82</td>
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Supplemental Figure 5: Consistency of findings across split-half samples of data
(A) Distribution of p-values from OODA run on 50 split-half samples of PD and HC data (mean+/-SD: p=0.02 +/- 0.03; median: p=0.008).
(B) G* difference matrices from the two halves of a split-half sampling are plotted (this iteration was selected as it had the median p-value outcome of split-half samples). G* difference matrices were largely similar between the two halves, and were both significant (p<0.05).

These are from median p-value split-half run (run = 23)
Heterogeneous sample with a range of motor and cognitive impairments typical of PD

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<td>0.65 (0.65)</td>
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<td>0.41 (0.74)</td>
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<td>Cog Total</td>
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*Normalized by large general sample (Z)*
A closer look at **motor FC**: Diminished sensory, increased association FC
A closer look at **motor FC**: Subcortical effects differ by sub-region

**HC**

**PD**

**PD - HC**

$y = -54$

$z = 12$

$z = 6$

$z = 0$
A closer look at **thalamic FC**: Frontal thalamic sub-regions show large PD effects.
A closer look at **striatal FC**: Striatal effects are similar to previous publications.
A subset of block FC is related to motor and cognitive performance
Network variants are stable in individuals.
Network variants appear in characteristic locations from one association network to another. Networks default mode, fronto-approach the group assignment (W data network) and the temporo-parietal junction, and sensorimotor and posterior cingulate cortex (MSC (left) and HCP (right) datasets) locations across individuals. Figure 3.

We implemented a modified winner-take-all approach to which the majority of variants were assigned to N networks (error bars = SEM). W Gordon and colleagues observed low overlap between mean dice assignments (error bars = SEM) for each individual. We observed that each variant typically takes on the default mode (red), lateral frontal cortex and insula, and often assigned to the network variants often "switch" at variant ns. The overlap of is displayed in Fig 3B. We observed that each variant typically takes on the default mode (red), lateral frontal cortex and insula, and often assigned to the network variants often "switch" at variant ns. The overlap of is displayed in Fig 3B.
Functional activations of network variants

A. mean (de-)activation across MSC individuals

B. MSC02 de-activations (t<0)

Group-average functional networks with MSC02 variants overlaid (black lines)

Task/rest variant mis-alignment across subjects

 MSC02, 02  MSC02, 03  MSC02, 04  MSC02, 05  Group
Subgroups of individuals with similar network variants

Figure 5: Separable groups of individuals via network associations of variants. The figure displays 3 groups of individuals in the (A) MSC and (B) HCP dataset clustered by the network associations of their variants.