The Human Brainnetome Atlas and its Applications in Understanding of Brain Functions and Disorders

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Outline

- The Brainnetome Atlas
- **Construction** of Brainnetome Atlas
- **Validation** of Brainnetome Atlas
- **Applications** of Brainnetome Atlas
- Summary and Perspectives
What is the Brainnetome?

- The **Brainnetome** (Brain-net-ome) takes brain network as basic research unit, which is consists two components: **Node** and **Connection**

- It can be studied on different scales from neuron to brain region
Brainnetome on Three Scales

The nodes and connections of Brainnetome can be defined at different scales and levels.

**Microscale**: neurons and their synaptic connections (~10^{11} neurons and 10^{15} connections)

**Mesoscale**: connections within and between minicolumns (~2×10^8 minicolumn)

**Macroscale**: anatomically distinct brain regions and inter-regional pathways (~250 regions in the cortex)
Research Themes of Brainnetome

- Topological Structure of Brain Networks *(Brainnetome Atlas & Connectome)*
- Dynamics and Characteristics of Brain Networks
- Network Manifestation of Functions and Malfunctions of the Brain
- Genetic Basis of Brain Networks
- Simulating and Modeling Brain Networks on Supercomputing Facilities


[www.brainnetome.org](http://www.brainnetome.org)
Brain Atlases: in vitro & in vivo Studies

Problems: Roughness, Lack of correspondence, Little sub-regional information and Variable relations between functional borders and macroscale landmarks

Zilles and Amunts, *Nat Rev Neurosci*. 2010;
Fan et al, *Cerebral Cortex*, 2016
Basic Ideas for Brainnetome Atlas

Brodmann’s Atlas 1909

Brainnetome Atlas

Parcellation Results
Outline

- The Brainnetome Atlas
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Methodologies of the Brainnetome Atlas

1. Anatomical connectivity
   - Rest of the brain
   - Connectivity matrix

2. Functional connectivity
   - Time Series
   - (15,000)
   - Clustering
   - Similarity matrix

3. Meta-analysis co-activation

4. Seed voxels
Area with Heterogeneous Cytoarchitectures

The parcellation results of posteromedial cortex could be well comparable to its complex cytoarchitectonic organization

Zhang et al., *Cerebral Cortex*, 2014
Connectivity Profiles Cross Species

Fiber tract patterns for 5 right PMC subregions

CoCoMac database

Zhang et al., *Cerebral Cortex*, 2014
Areas with Homogeneous Cytoarchitecture

Brodmann area 38

Fan et al., *Cerebral Cortex*, 2014
Connectivity Profiles of Sub-regions

Sub-regional connectivity patterns

Fan et al., *Cerebral Cortex*, 2014
Connectivity Based Parcellation of Human Brain

Wang et al., *Neuroimage* 2012; Fan et al., *Cerebral Cortex* 2014; Liu et al., *J Neuroscience* 2013; Li et al., *Neuroimage* 2013; Zhang et al., *Cerebral Cortex* 2014; Wang et al., *Human Brain Mapping* 2014; Zhang et al., *Brain Structure & Function*, 2014
The Human Brainnetome Atlas

- The Human Brainnetome Atlas: A New Brain Atlas Based on Connectional Architecture
- With 210 cortical and 36 subcortical sub-regions, provides a fine-grained, cross-validated atlas and contains information on both anatomical and functional connections

Fan et al., Cerebral Cortex, 2016
Open Resources of Brainnetome Atlas

ATPP pipeline: https://www.nitrc.org/projects/atpp

http://atlas.brainnetome.org

Brainnetome Atlas Viewer
https://www.nitrc.org/projects/bn_atlas/

Education
Fan et al., Cerebral Cortex, 2016
Available in Platforms and Popular Software

- Neuroinformatics Platform of Human Brain Project, International Neuroinformatics Coordinating Facility
- Popular Software: SPM, FSL
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Verification of the Brainnetome Atlas

Cross-modality Comparison

- Genetic Basis of Brain Parcellation
- Connectivity-Function Relationship
Criteria for Human Brain Parcellation

- Inputs: determine the information available to a region
- Outputs: determine the influence it can have on other brain regions

The connectivity plays a fundamental role in making a brain area distinct!

Comparison of Brainnetome Atlas with JuBrain

The topography of parcellation based on connectivity profiles is consistent with parcellation based on cytoarchitecture.
Multi-modal CBP of Superior Parietal Lobule and Dorsal Premotor Cortex

Superior parietal lobule (SPL) parcellation results using multimodal neuroimaging methods

Wang et al., Human Brain Mapping, 2015

Five left dorsal premotor (PMD) cortical modules were identified

Genon et al., Neuroimage, 2017
Posterior Boundary of Wernicke’s Area:  
Intraoperative Electrical Stimulation

Wang et al., Human Brain Mapping, 2015
2-cluster, termed shell-like and core-like divisions, provided the best description of the data and was consistent with earlier anatomical studies on shell-core organization.

Xia et al., *Human Brain Mapping*, 2017
Verification of the Brainnetome Atlas

- Cross-modality Comparison
- Genetic Basis of Brain Parcellation
- Connectivity-Function Relationship
Consistent Parcellation of Brain Regions

Brodmann Atlas — JuBrain Atlas

Cytoarchitectonics

Receptor-architectonics

Gyral / sulcal anatomy

Connectivity

Brainnetome Atlas

Broca’s area divisions
-- by receptor architectonics

Freesurfer DK Atlas

Topographic mapping

Motor and sensory homunculi

-- by connectivity-driven info

## Genes Influence Cortical Patterning

**Animal Studies**

<table>
<thead>
<tr>
<th>Signaling molecules (patterning centers)</th>
<th>Intrinsic mechanisms</th>
<th>Anatomically and functionally distinct areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fgfl8, Fgf17 (ANR, CoP)</td>
<td>Graded gene expression in VZ (dTel)</td>
<td>2/3</td>
</tr>
<tr>
<td>Wnts, Dmp (hem)</td>
<td></td>
<td>4/5</td>
</tr>
<tr>
<td>Shh</td>
<td></td>
<td>6/7</td>
</tr>
<tr>
<td>Anti-gen</td>
<td></td>
<td>8/9</td>
</tr>
</tbody>
</table>

- **Fgf8, Fgf17, Emx2 regulate frontal cortex subdivision patterning**

- **Cholfin et al., PNAS, 2007, J Comp Neurol, 2008**

**Human Studies**

<table>
<thead>
<tr>
<th>Whole Brain</th>
<th>4 divisions</th>
<th><strong>Chen et al., Neuron 2011</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar Level</td>
<td>12 divisions</td>
<td><strong>Chen et al., Science 2012</strong></td>
</tr>
</tbody>
</table>

- **Cortical areal development is controlled by the interplay of intrinsic and extrinsic mechanisms**

  - **O'Leary, et al., Neuron, 2007**

- **Fgf8, Fgf17, Emx2 regulate frontal cortex subdivision patterning**

  - **Cholfin et al., PNAS, 2007, J Comp Neurol, 2008**

**Fine-grained intrinsic genetic architecture of the cortex?**
The genetic correlations of morphology are estimated based on twin strategy, and built fine-grained genetic architecture.

Cui et al., Cerebral Cortex, 2016
Genetic subdivisions corresponded to fine-grained functional specializations.

Superior Medial Frontal Cortex

Frontal Pole

Inferior Frontal Gyrus

M1

Cui et al., Cerebral Cortex, 2016
Genetic correlation correlates with functional connectivity, which validates the genetic basis of the Brainnetome atlas.

Cui et al., *Cerebral Cortex*, 2016
Verification of the Brainnetome Atlas

- Cross-modality Comparison
- Genetic Basis of Brain Parcellation

Connectivity-Function Relationship
Why Anatomical Connectivity Profiles Can Be Used to Construct Brainnetome Atlas

Anatomical connectivity patterns predict face selectivity in the fusiform gyrus

- Whether anatomical connectivity can predict functional activations across different cognitive domains?
- Whether there exists regional difference in the connectivity-function relationship throughout the whole cortex are still unknown?
We used seven tasks from HCP to address the first question:

<table>
<thead>
<tr>
<th>Contrasts</th>
<th>Mean Similarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMOTION FACES</td>
<td>0.55</td>
</tr>
<tr>
<td>GAMBLING PUNISH</td>
<td>0.56</td>
</tr>
<tr>
<td>LANGUAGE STORY-MATH</td>
<td>0.59</td>
</tr>
<tr>
<td>MOTOR T</td>
<td>0.42</td>
</tr>
<tr>
<td>RELATIONAL REL</td>
<td>0.69</td>
</tr>
<tr>
<td>SOCIAL TOM</td>
<td>0.68</td>
</tr>
<tr>
<td>WM 2BK</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Wu et al., 2019, under review
Connectivity-function Relationship

- The connectivity-function relationship (CFR) was characterized by predicting activity from anatomical connectivity across the cortex.

- Whether there exists regional difference in the connectivity-function relationship throughout the whole cortex?
Spatial Distribution of CFR in Different Contrasts

The seven functional networks that represented the functional hierarchy of the cortex

Wu et al., 2019, under review
CFR Hierarchy was Correlated to Functional and Anatomical Hierarchy

Wu et al., 2019, under review
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Applications of Brainnetome Atlas

- Summary and Perspectives
Applications of Brainnetome Atlas

- Connectivity Profiles Reveal the Translation Subarea in the PHR
  - Sex-specific Neural Circuits of Emotion Regulation
  - New Paradigm for Diagnosis and Therapy of Brain Diseases
  - Cross-species Comparison of Nucleus Accumbens
Anterior PHR is an Imaging Marker for AD

Neuropathological staging of AD related changes

Patterns of grey matter atrophy identified at the time of progression from MCI to AD

Construction of the fine-grained PHR atlas will provide important imaging guidance for the early diagnosis of AD

In 2007, European Union has incorporated the gray matter atrophy of MTL based on MRI as the diagnostic markers

Lancet Neurology, 2007
Anatomy and Functions of PHR

Anatomy of lateral parahippocampal region

Two cortical systems for memory-guided behaviour

Ranganath, C. and Ritchey, M. (2012) *Nat Rev Neurosci*

Recent fMRI findings

Libby et al. (2014) *J Neuroscience*

Object coding
Location coding

Inconsistent!
Parcellation of PHR with Connectivity Profiles

A

Functional connectivity of left PHR subregions

B

C

Functional connectivity of PRCr, PRCc and PHC in the hippocampus and entorhinal cortex

Zhuo et al., *Journal of Neuroscience*, 2016
Revised Model Based New Findings

Zhuo et al., *Journal of Neuroscience*, 2016
Dynamic Damages in MCI and AD

Grey matter volume decrease degree in PHR associated with AD
Applications of Brainnetome Atlas

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**Significant Gender Difference in Depression**

- **There are gender differences in the incidence of depression:** The number of female patients with depression is much greater than that of male patients. Female depressive disorders are also reported to show more severe depressive symptoms than Male patients.

- **Dysfunction in emotion regulation is one of the main symptom of major depression**

- **Amygdala is the key brain region for emotion regulation.** Hence, investigating brain functional connectivity based on the sub-regions of amygdala generated from precise Brainnetome Atlas may reveal the underlying critical factors of why mood regulation ability exist remarkable gender differences.
Amygdala and Emotion Regulation

Laterobasal nuclei group (LB), centromedial nuclei group (CM), and the superficial nuclei group (SF)
Gender-specific Networks of Emotion Regulation in CM of Amygdala

Cognition Related Networks:
Connectivity between right CM and medial superior frontal gyrus (SFG)
Gender-specific Networks of Emotion Regulation in CM of Amygdala

Emotion Related Networks:
Connectivity between CM and insula and superior temporal gyrus (STG)

Wu, et al., Scientific Reports, 2016
Applications of Brainnetome Atlas

- Connectivity Profiles Reveal the Translation Subarea in the PHR
- Sex-specific Neural Circuits of Emotion Regulation
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- Cross-species Comparison of Nucleus Accumbens
Brainnetome Atlas Based New Paradigm for Diagnosis and Therapy of Brain Diseases

- Brainnetome Atlas Based Precision Targeting for Therapy of Parkinson Disease, Depression, Epilepsy, Disorders of Consciousness.

Brainnetome Atlas Based Precision Targeting for Therapy of Parkinson Disease

The therapy effectiveness of PD depends on precisely targeting the subregions of the subthalamus nucleus.
Precision Therapy Based on Brainnetome Atlas

<table>
<thead>
<tr>
<th></th>
<th>rTMS</th>
<th>Non-rTMS</th>
<th>NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>90</td>
<td>52</td>
<td>110</td>
</tr>
<tr>
<td>Baseline</td>
<td>85</td>
<td>43</td>
<td>105</td>
</tr>
<tr>
<td>Follow up</td>
<td>72</td>
<td>29</td>
<td>-</td>
</tr>
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Applications of Brainnetome Atlas

- Connectivity Profiles Reveal the Translation Subarea in the PHR
- Sex-specific Neural Circuits of Emotion Regulation
- New Paradigm for Diagnosis and Therapy of Brain Diseases
- Cross-species Comparison of Nucleus Accumbens
The ventral striatum, including two nucleus accumbens (Acb) subregions, the shell and core, differ in the patterns whereby they integrate signals from prefrontal and limbic areas of the brain.

The Shell-core Organization of Acb is Conserved across Species

Whether these shell and core subregions are homologous and, if so, what is the extent of that homology?

G.E. Meredith et al., *Journal of Comparative Neurology*, 1996
The shell- and core-like divisions of Acb, provided the best description of the data and was also consistent with earlier anatomical studies on shell-core organization.

Xia et al., *Human Brain Mapping*, 2017
Tractography-Based Parcellation of Monkey Acb

A Macaques: Parcellation results using MMDS1

B The averaged Cramer's V

C The probability maps and MPM

D Macaques: Parcellation results using MMDS2

E Macaques: Histological result

F Humans: Parcellation results

Xia et al., 2019, under review
Defining Human and Macaque Comparable OMPFC Areas

- Human OMPFC CBP-based parcellation
  - Neubert et al., 2015

- Monkey OMPFC cytoarchitecture-based parcellation
  - Paxinos et al., 2009; Calabrese et al., 2015

Roughly corresponding relationships for the human and macaque OMPFC target areas:

- 11, 11m, 13, 14m, 25, 32, and 47o
Redefining Target OMPFC Areas for Cross-Species Comparison

Delineated connectionally comparable targets areas in OMPFC
Cross-species Comparisons by Connectivity Fingerprints

connectivity ratio = \frac{RCV(\text{target} - \text{shell})}{RCV(\text{target} - \text{shell}) + RCV(\text{target} - \text{core})}

A subcortical target group
LH: anatomical connectivity fingerprints

B prefrontal target group
LH: anatomical connectivity fingerprints

C single connectivity [prefrontal targets]

Fingerprints [Humans — Macaques]  histograms [permutated value — observation — criterion]

Xia et al., 2019, under review
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Summary and Perspectives
Summary

- A new brain atlas – brainnetome atlas based on connectivity profiles, and its reliability were presented.
- With the brainnetome atlas, we could get insights into the brain function and the brand new knowledge on the pathophysiological mechanism of psychiatric and neurological disorders.
- It opens a new avenue to study the brain and its disorders.
Future in Brainnetome Atlas

Multimodal brainnetome atlas, new paradigm for the early diagnosis and therapy, and new models for brain-inspired computing.
Brainnetome Atlas

Individualized

Multi-modal

Multi-scale
The fasciculus is a bundle of axons that follow the same pathway, and with origins and terminations of the same brain regions. With Brainnetome atlas, the subcomponents in the main fiber bundles can be identified.
Framework of Fiber Bundle Segmentation

Whole Brain Tractography → FA Map → ROI Selected → Major Fiber Bundle → Similarity Matrix → Clustering

SLFII-1, SLFII-2, SLF/AF-1, SLF/AF-2, SLF/AF-3, SLF/AF-4, SLFIII-1, SLFIII-2, SLFIII-3, SLF/AF-5, SLF/AF-4

Cheng et al., Poster No. Th776
Subcomponents of SLF/AF

- SLF II-1
- SLF II-2
- SLF/AF-1
- SLF/AF-2
- SLF/AF-3
- SLF/AF-4
- SLF/AF-5
- SLF III-1
- SLF III-2
- SLF III-3

Cheng et al., Poster No. Th776
Subcomponents of Cingulum Bundle

Lateral view

Medial view

CB-1
CB-2
CB-3
CB-4
CB-5
CB-6

Cheng et al., unpublished, 2019
Multi-scale Brainnetome Atlas

Human Brainnetome Atlas
- Cohort with Brain Diseases
- Healthy Cohort

Monkey Brainnetome Atlas
- 9.4T MRI
- Animal Models
- Macro
- Meso

Mechanism
Translation

Ongoing
3-5 Years
5-10 Years
Multiscale Monkey Brainnetome Atlas

9.4T MRI

Connectivity Profiles

Cross-species Brainnetome Atlas

PS-OCT

Tracer Imaging

Lightsheet

Tissue Clearing

PS-OCT

Tracer Imaging

Lightsheet

Tissue Clearing

Two-Photon Imaging

Photoacoustic Imaging

Microendoscope

Optogenetics

Cortical Neuron Dynamic Imaging

Two-Photon Absorption

Photoacoustic Deep Imaging

Detection

Modulation

Monkey Brainnetome Atlas

Macroscopic

Mesoscale (Structure)

Mesoscale (Function)
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