Sex classification by resting state connectivity

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Introduction

- **Cognitive sex differences** well documented in **behavioral and functional brain imaging** (fMRI).
- Structural MRI has identified a **structural sexual dimorphism** of the human brain (3).
- **Sex differences** are also found in **resting state** (RS) brain **connectivity** (e.g. 8, 11).

Aims of the present study:

1. Employ a **machine learning approach** on RS data to address generalizability of previous findings to independent samples.
2. Delineate **regionally specific brain networks** underlying successful classification of novel subjects' sex.
3. Further understanding of a possible **sexual dimorphism of the RS connectome.**

Methods

Samples:
- Two mutually exclusive samples of unrelated subjects constructed of Human Connectome Project data (HCP S1200 release, (7)).
- Sample 1: 434 subjects (217 males, age range: 22-37, mean age: 28.6 years),
- Sample 2: 310 subjects (155 males, age range: 22-36, mean age: 28.5 years).
- Males and females matched for age, twin-status and education within each sample.

Functional imaging data:
- Resting state (RS): 1200 volumes per subject.
- Siemens Skyra 3T scanner (TR=720ms).
- Standard realignment and normalization.
- FSL-FIX denoising (5).
- Individual RS connectomes extracted for 436 ROIs based on (6) .

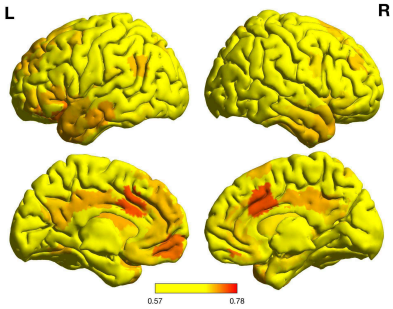
Sex Classification:
- Linear SVM (LibSVM toolbox, (1)) model for classification of subjects' sex from RS connectome.
- Nested optimization of cost parameter.
- 10 repetitions of a 10-fold cross-validation.
- Across sample classification: fitting of the model on sample 1 and testing it on sample 2.

Whole brain vs. ROI based classification:
- (1) Whole brain connectome.
- (2) Each individual ROI's connectivity profile (436 parcels).

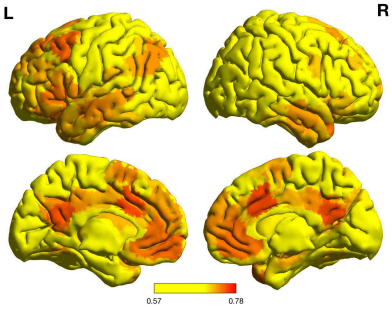
Result Summary:
- ROI based analyses performed separately for each sample and conservatively characterized by minimum across the two samples.

Results

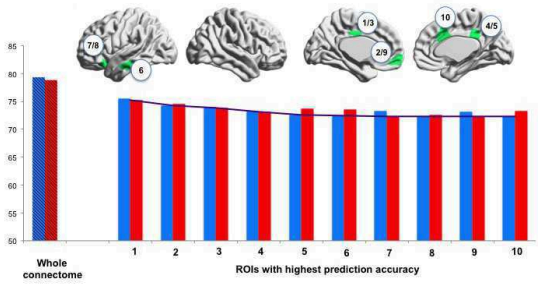
1 ROI based minimum classification accuracy across both samples



2 ROI based classification accuracy for between-sample classification



3 Classification accuracy for the whole connectome analysis and the ten ROIs with highest classification accuracy across sample 1 and sample 2



1) L Cingulate Gyrus, BA 24 (75.52%, 75.29%)
2) L Ant Cingulate, BA 32 (74.32%, 74.56%)
3) L Ant Cingulate, BA 24 (73.25%, 73.80%)
4) R Cingulate Gyrus, BA 31 (73.25%, 73.19%)
5) R Caudate (72.52%73.70%)
6) L Inf Temporal G, BA 20 (72.38%, 73.60%)
7) L Inf Frontal G, BA 47 (73.27%, 72.32%)
8) R Inf Frontal G, BA 47 (72.32%, 72.60%)
9) L Med Frontal G, BA 11 (73.13%, 72.31%)
10) R Ant Cingulate, BA 24 (72.29%, 73.32%)

Whole Brain Connectome

- 10-fold cross-validation performance for whole brain connectome:
  - Sample 1: 79.3%
  - Sample 2: 78.8%.
- Across sample classification performance:
  - 81.4%.

  (possibly due to larger training set)

Whole brain RS connectome allows for the prediction of an unknown subject's sex at ~ 80% accuracy!

Regional Connectivity

- ROI based analyses identified regions for which the connectivity profile differentiated most strongly between the sexes.
- Highest regional accuracies:
  - Medial brain regions in anterior cingulate and cingulate gyrus.
  - Left lateralized inferior frontal gyrus and inferior temporal gyrus
- Regions displaying top classification accuracies highly similar for within-sample and between-sample classification.

Classification accuracies for top ROIs are only marginally lower than whole connectome analyses!

Discussion

- Both within- and between-sample cross-validation allowed reliable classification of unknown subjects' sex from RS connectivity profiles ➔ **robust sexual dimorphism of the resting state connectome.**
- Predictive power of local brain connectivity almost as high as whole brain connectivity ➔ **regionally specific effects.**
- Within- and between-sample prediction based on highly similar brain regions ➔ **reliability of findings.**
- Regions with top prediction power are mainly located along **(anterior) cingulate cortex.**
- Cortical regions with top prediction accuracies are **left lateralized.**
- Left inferior frontal **inter-hemispheric connectivity** has been shown to **vary across the menstrual cycle in women**, but to remain **stable in men** (9).
- Similar frontal regions reported in relation to **differing cognitive strategies between the sexes** (10).
- Sex differences in cingulate cortex reported in connection with **emotional reactivity and cognitive control of emotion** (2,4).
- Regions most clearly differentiating between the sexes are related to **cognitive control of behaviour and emotion.**
- Findings might help explain why **sex differences** are mostly found **in cognitive strategies** employed by men and women, but not in behavioural performance per se.
- Results substantiate a **sexual dimorphism in RS connectivity** ➔ male and females differ not only in brain structure, but also in functional brain organization.

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