Connectome based classification of BDNF Met allele carriers

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WHAT IS BDNF?

Brain-derived neurotrophic factor

- Protein essential for brain development & long term potentiation

Associated gene, BDNF

- Regulates the activity-dependent release of the BDNF protein
- Alleles: G encodes Valine, A encodes Methionine
- Common single-nucleotide polymorphism (SNP): Val66Met = swap Val for Met at codon 6,6
SO WHAT?

• Carrying MET allele
  ➔ reduced BDNF activity-dependent secretion in the brain

• BDNF role
  ➔ pruning of silent axonal branches during brain development

Egan MF, 2003, *Cell*

Singh KK, 2008, *Nat Neurosci*

Cao L, 2007, *Curr Biol*
**STUDY DATA**

- **Population** (n=36)
  - 15 Met carriers, 21 Val homozygotes
  - Highly regulated young healthy subjects (18-25y)

- **MR acquisition**
  - High-resolution T1 MPRAGE (1mm$^3$ isotropic voxels)
  - Diffusion-weighted MRI
    - 7 unweighted (b=100) images
    - 61 directional (b=1000) images
    - 2.3 x 2.3 x 2.3 mm$^3$ isotropic voxels
• Probabilistic Tractography
  – Spherical deconvolution → ODFs
  – 300,000 fibers, randomly seeded in WM

Tournier JD, 2004 & 2007, Neuroimage
CONNECTOME MAPPING

Network-filtered tracts from a single subject

XYZ = RGB
CONNECTOME MAPPING

• Probabilistic Tractography
  – Spherical deconvolution ➔ ODFs
  – 300,000 fibers, randomly seeded in WM

Tournier JD, 2004 & 2007, *Neuroimage*

• Anatomical segmentation & parcellation
  – Desikan-Killiany atlas (83 regions)
  – Lausanne 1015-region atlas

Desikan RS, 2006, *Neuroimage*
CONNECTOME MAPPING

1015 ROI
CONNECTOME MAPPING

- **Probabilistic Tractography**
  - Spherical deconvolution \(\rightarrow\) ODFs
  - 300,000 fibers, randomly seeded in WM
  
  Tournier JD, 2004 & 2007, *Neuroimage*

- **Anatomical segmentation & parcellation**
  - Desikan-Killiany atlas (83 regions)
  - Lausanne 1015-region atlas

  Desikan RS, 2006, *Neuroimage*

- **Connectome** = 1015 x 1015 matrix
  - 1 fiber crossing 2 regions \(\rightarrow\) +1 connection
CONNECTOME MAPPING
Compare connectivity matrices with

- **Network-based statistics (NBS)**
  - Non-parametric test using NBS

Zalesky A, 2010, *Neuroimage*
NBS Results

Increased fibers in Met carriers

Top view

Lateral view

Number of Fibers (Met / Val/Val)

20x

8.6x

4x

2.25x

1.5x
NBS Results

Fibers not present in Val homozygotes

Top view

Lateral view

Number of Fibers
• Some connections only in Met carriers

• Increased connection strength in Met carriers:
  – between bilateral thalami and brainstem
  – sensorimotor areas of parietal and frontal cortex
  – ventromedial prefrontal cortex (anterior forceps)
  – occipital, posterior parietal, and temporal areas also differ to a lesser extent.
STATISTICAL ANALYSIS

Compare connectivity matrices with

• **Network-based statistics (NBS)**
  – Non-parametric test using NBS

• **Multivariate statistics**
  – Gaussian Processes classification
  – Leave-one-out cross-validation procedure
  – Permutation testing

Zalesky A, 2010, *Neuroimage*

Rasmussen CE, 2006
Schrouff J, 2013, *Neuroinformatics*
CLASSIFICATION RESULTS

- **Balanced accuracy**: 87.1% (p<.001)
- **Class predictive values** (ValVal & Met-carrier): 94.4% & 77.8%
Classification Results

Grouping according to

- adenosine deaminase (ADA) genotype:
  Classification of G/A (n=16) vs. G/G (n=20)
  ➞ accuracy 58.3% (n.s.)

- gender:
  Classification of male (n=18) vs. female (n=18)
  ➞ accuracy 63.9% (n.s.)

No significant classification for ADA nor gender!
• **BDNF** Met carriers prune less axons during brain development

• Resulting tracts stay in the brain
  – Seem to provide little or no benefit at young age
  – May protect against age-related deficits

• Extraneous tracts are found as increases in fractional anisotropy

Harris SE, 2006, *Mol Psychiatry*
Gajewski PD, 2011, *Neurobiol Aging*

Chiang MC, 2011a and 2011b, *Neuroimage*
CONCLUSIONS

• *BDNF* genotype (allelic group) can be predicted based on brain connectivity

• Longitudinal *BDNF* studies are needed to cover youth-adult brain development

• Differences between Val66Met and Met66Met polymorphisms should be examined
Open-source software:

- Nipype/Nibabel/Dipy http://nipy.org
- ConnectomeViewer http://cmtk.org
- PRoNTo http://www.mlnl.cs.ucl.ac.uk/pronto/

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Thank you for your attention!