#3840

Connectome-based classification of *BDNF* Met allele carriers

Ziegler E.[1], Foret A.[1], Mascetti L.[1], Muto V.[1], Le Bourdiec-Shaffi A.[1], Stender J.[1], Balteau E.[1], Dideberg V.[2], Bours V.[2], Maquet P.[1,3], **Phillips C.**[1,4]

[1] Cyclotron Research Centre, [2] Department of Human Genetics, [3] Department of Neurology CHU Sart Tilman, [4] Department of Electrical Engineering & Computer Science; University of Liège, Belgium

Background

BRAIN-DERIVED NEUROTROPHIC FACTOR

- Protein essential for brain development and long-term potentiation
- Associated gene (*BDNF)* regulates activity-dependent release of BDNF protein **[1]**
- Alleles: G encodes Valine, A encodes Methionine
- Common single-nucleotide polymorphism known as Val66Met. Prevalence varies: 0.55% in Sub-Saharan Africa, 19.9% in Europe, and 43.6% in Asia **[2]**
- Carrying the Met allele reduces activity-dependent secretion of BDNF **[1]**
- BDNF facilitates pruning of silent axonal branches during development **[3,4]**
- Two large (n > 400) studies have found increases in fractional anisotropy (FA) in Met carriers, relative to Val homozygotes **[5,6]**

EXPERIMENTAL DESIGN

- Population (n = 36, 15 Met carriers, 21 Val homozygotes
- Highly regulated young healthy subjects (18-25y)
- High-resolution T1 MPRAGE (1 x 1 x 1 mm^3 voxels)
- Diffusion-weighted MRI (61 directions, b=1000, 2.3 x 2.3 x 2.3 mm^3 voxels)

Connectome Mapping & Classification

CONNECTOME MAPPING

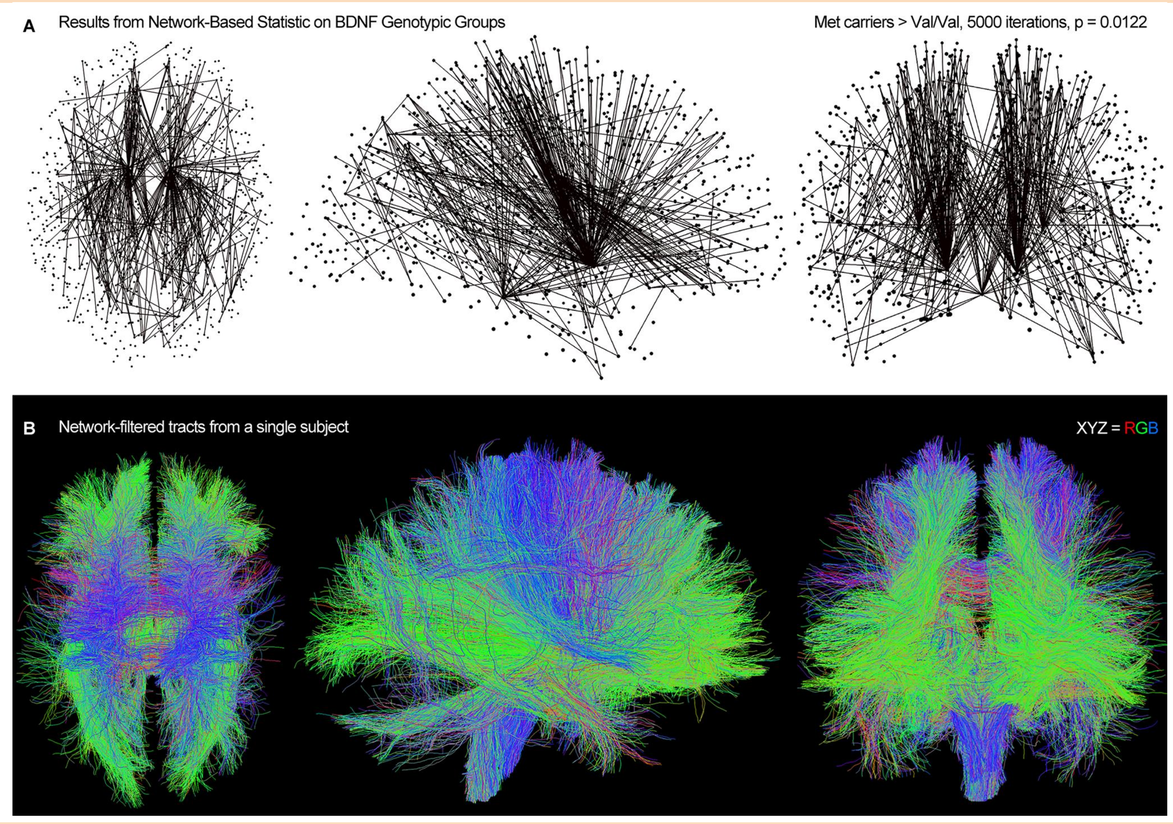
- Whole-brain Probabilistic Tractography
  - Non-negativity constrained spherical deconvolution to obtain orientation distribution functions **[7,8]**
  - 300,000 fibers, seeded from randomly placed points in the white matter
- Anatomical Parcellation of T1-weighted image
  - Segmentation to Desikan-Killiany atlas (83 regions) **[9]**
  - Parcellation to Lausanne 1015-region atlas **[10,11]**
- Connection matrix incremented any time a fiber crossed two regions
- Freely available online as Nipype Advanced Connectivity Tutorial (MRtrix) **[12]**

STATISTICS & CLASSIFICATION

- Non-parametric test via "Network-Based Statistic" (5000 permutations, *t* thresh. = 3) **[13]**
- Machine learning classification with Gaussian Processes using the Pattern Recognition Toolbox for Neuroimaging **[14]**
  - Classifier uses connectivity matrices (edge weights only, no spatial or network topological information)
  - Leave-one-out cross-validation procedure
  - Statistical significance assessed by permutation (n=1000)

Results (significant at FDR p<.05)

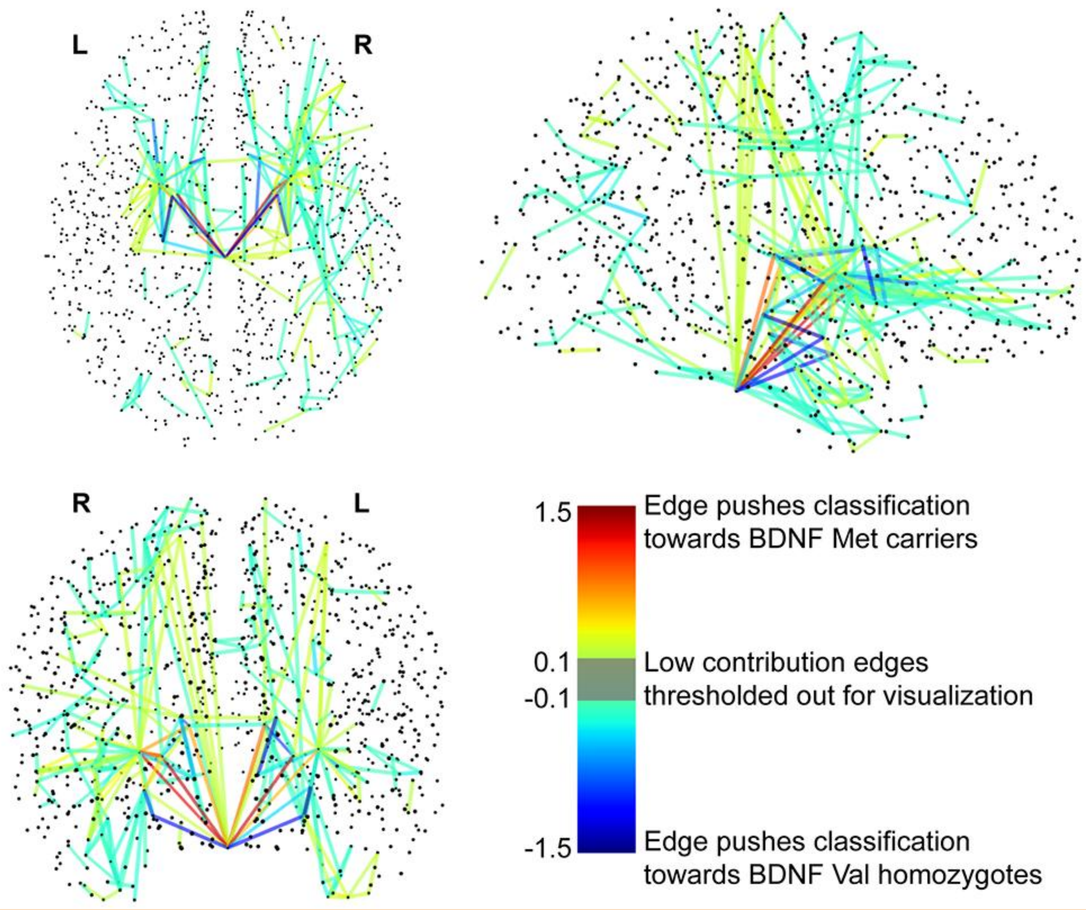
1. Apparent increases in connectivity for Met carriers



2. Genotype accurately classifiable from brain connectivity

- **Balanced accuracy: 87.14%** (p<.001)
- **Predictive Value** (for ValVal & Met carriers)**: 94.4%** & **77.8%**

Spatial representation of classifier weights (thresholded for display purpose only!)



3. No significant difference or classification for either gender or adenosine deaminase (ADA) genotype

Conclusions

- *BDNF* Met carriers prune less axonal arbors during brain development
- Resulting tracts stay in the brain
  - Seem to provide little or no benefit
  - May protect against age-related deficits
- Extraneous tracts are found as increases in fractional anisotropy
- Various connections have increased fiber count in Met carriers:
  - Connections 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.

REFERENCES

[1] Egan MF, 2003, Cell 112: 257–269. **[2]** Petryshen TL, 2010, Mol Psychiatry 15: 810–815. **[3]** Singh KK, 2008, Nat Neurosci 11: 649–658. **[4]** Cao L, 2007, Curr Biol 17: 911–921. **[5]** Chiang, MC, 2011, NeuroImage 54, 2308–2317. **[6]** Chiang MC, 2011, Neuroimage 55: 448–454. **[7]** Tournier JD, 2004, Neuroimage 23: 1176–1185. **[8]** Tournier JD, 2007, Neuroimage 35: 1459–1472. **[9]** Desikan RS, 2006, Neuroimage 31: 968–980. **[10]** Hagmann P, PLoS Biol 6: e159. **[11]** Daducci A, 2012, PLoS One 7: e48121. **[12]** Gorgolewski K, 2011, Front Neuroinform 5: 13. **[13]** Zalesky A, 2010, Neuroimage 53: 1197–1207. **[14]** Schrouff J, 2013, Neuroinformatics .

ACKNOWLEDGEMENTS & SPONSORS

Le Fonds de la Recherche Scientifique (FNRS), the University of Liège, the Queen Elisabeth Medical Foundation, the Léon Fredericq Foundation, the Belgian Inter-University Attraction Program, the Welbio program, and the Marie Curie Initial Training Network in Neurophysics (PITN-GA-2009-238593).

CYCLOTRON RESEARCH CENTRE | http://www.cyclotron.ulg.ac.be | erik.ziegler@ulg.ac.be & c.phillips@ulg.ac.be