Variations of brain structure in healthy people: structural MRI investigations

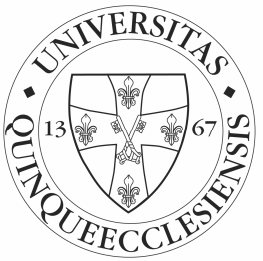
Ph.D. thesis

Gábor Perlaki

Supervisors:
Prof. József Janszky, M.D., D.Sc.
Attila Schwarcz, M.D., Ph.D.

Leader of Doctoral Program:
Prof. József Janszky, M.D., D.Sc.

Leader of Doctoral School:
Prof. Sámuel Komoly, M.D., D.Sc.



University of Pécs
Doctoral School of Clinical Neuroscience
PÉCS, 2014

1. Introduction

Until recently, the structural bases of individual differences have been studied primarily in postmortem examinations or in patients with brain lesions. However, with the advent of structural magnetic resonance imaging (MRI) techniques, such as MRI volumetry or diffusion imaging, it has become possible to investigate the macro- and microstructural bases of individual differences in healthy subjects or in patients without brain lesions as well. While initially these methods were very time-consuming and biased by manual, subjective drawing of the examined structures, recent developments like automated MRI volumetry, voxel-based morphometry (VBM) or voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics (TBSS) have allowed the macroscopic and microscopic structural variations to be probed in an objective, automated, time-saving manner. These refined automated methods are now sensitive enough to reveal meaningful structural differences even within relatively homogeneous groups (e.g. healthy controls).

Taking the advantage of structural MRI techniques, a series of studies tested inter-individual differences in brain structure within a population or structural differences between different populations. Both macro- and microstructural measures have been found to be related to a wide range of factors, such as age, gender, handedness, caffeine intake, body mass index, navigation experience, cognitive abilities or language functions. These studies provide evidence that variations in brain structure may be associated with various functional, behavioral, demographic, nutritional, environmental and biological indices in both clinical patient and healthy population groups.

With the availability of more sophisticated analysis techniques, recently it has become popular to move beyond simple group comparisons

of subjects at the extreme ends of the scale (e.g. patient vs. normal populations) and test for structural differences within more homogenous populations (e.g. healthy controls). Even within a healthy adult population there are considerable differences in the brain structure, which may carry functional and behavioral consequences. Investigating the structural variations of healthy subjects may extend our understanding of normal patterns, which represents an essential step before starting to search structural abnormalities in diseased groups.

2. Objectives

The aim of this thesis was to examine macro- and microstructural brain variations in healthy normal volunteers using the latest image processing methods such as automated MRI volumetry, voxel-based morphometry (VBM) or voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics (TBSS).

Our first experiment targeted consistent left-handers to examine the relationship between white matter microstructure and language lateralization in a combined analysis of diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) data. Unlike previous studies, this experiment provides insights into the microstructural correlates of language lateralization at the whole-brain level – without any pre-specification of regions of interest – using the novel voxel-based TBSS approach.

The second experiment aims to address the question of sexual dimorphism in hippocampal volume by automated MRI volumetry and VBM using both general linear model (GLM) and proportion head-size correction strategies. Previous studies on sexual dimorphism in hippocampal volume did not always yield consistent findings. Our

hypothesis is that one reason for the diversity of earlier results might lie in different types of head-size correction methods, a fact that is largely neglected, but is of great importance in morphological studies.

3. Materials and methods

White-matter microstructure and language lateralization in left-handers: A whole brain MRI analysis

Sixteen healthy, left-handed women aged 20-25 were included in the study. Left-handers were targeted in order to increase the chances of involving subjects with atypical language lateralization. Language lateralization was determined by fMRI using a verbal fluency paradigm. Tract-based spatial statistics analysis of DTI data was applied to test for white matter (WM) microstructural correlates of language lateralization across the whole brain. Fractional anisotropy (FA) and mean diffusivity (MD) were used as indicators of WM microstructural organization.

Are there any gender differences in the hippocampus volume after head-size correction? A volumetric and voxel-based morphometric study

T1-weighted MR images were collected in 99 healthy, Caucasian, university students (66 women and 33 men; mean age: 22.9 ± 2.2 and 23.5 ± 2.4, range: 19 to 31 and 20 to 30 years respectively). Sexual dimorphism in hippocampus was investigated by automated MRI volumetry and voxel-based morphometry (VBM) using both general linear model (GLM) and proportion head-size correction strategies.

4. Results

White-matter microstructure and language lateralization in left-handers: A whole brain MRI analysis

TBSS analysis showed significant relationship between functional language lateralization and white matter microstructure. Right-hemispheric language dominance was associated with reduced microstructural integrity (lower FA and higher MD) of the left superior longitudinal fasciculus and left-sided parietal lobe WM.

Are there any gender differences in the hippocampus volume after head-size correction? A volumetric and voxel-based morphometric study

Absolute hippocampal volumes were larger in men than women. After adjusting for head-size, the proportion method indicated larger hippocampi in women than men, while no gender differences were found using the GLM approach. Significant inverse correlation was observed between intracranial volume and hippocampus to intracranial volume ratio, demonstrating the inability of proportion method to completely remove the effect of head size. Investigating absolute hippocampal volumes in 15 head-size matched pairs of males and females indicated no gender differences.

5. Conclusions

White-matter microstructure and language lateralization in left-handers: A whole brain MRI analysis

In left-handed women, we found strong support that atypical cerebral dominance for language is associated with variations of white-matter microstructure in the left superior longitudinal fasciculus and left-sided parietal lobe white matter. The work included in this thesis contributes to

the existing literature on structural-functional relationships in the language network by emphasizing the importance of individual variations in healthy populations. Based on our data, it can be hypothesized that reduced white-matter integrity in the left-sided language related tracts are closely linked to the development of right hemispheric language dominance. The dependence of the right-sided language lateralization on the integrity of left-hemispheric pathways but not the right-hemispheric ones might be a useful reference for further investigations on how atypical language dominance develops. Our results may offer new insights into language lateralization and structure-function relationships in human language system.

Are there any gender differences in the hippocampus volume after head-size correction? A volumetric and voxel-based morphometric study

Using different methodological approaches to examine gender differences in hippocampal volumes of normal subjects, we found that GLM and proportion head-size adjustment techniques yield dissimilar results, ranging from no gender differences in hippocampi to larger hippocampi in females. We suggest that there is no sexual dimorphism in hippocampal size and the apparent gender differences found by the proportion method may have more to do with head-size than sex. The importance of the present findings about the fundamental differences between GLM and proportion approaches is mostly related to scientific reproducibility across MRI volumetry or VBM studies. Using the agreement/disagreement among proportion and GLM methods as an indication of stronger/weaker support of a hypothesis is dangerous, given that they are not representing the same phenomenon. Our results may have clinical importance, when adjusted hippocampal volumes are considered as diagnostic tools of disease severity in neurological and psychiatric illnesses.

6. Publications

6.1 Articles related to the thesis

G. Perlaki, G. Orsi, E. Plozer, A. Altbacker, G. Darnai, S.A. Nagy, R. Horvath, A. Toth, T. Doczi, N. Kovacs, P. Bogner, A. Schwarcz, J. Janszky, Are there any gender differences in the hippocampus volume after head-size correction? A volumetric and voxel-based morphometric study, Neurosci Lett 570 (2014) 119-123. **IF : 2.055 (in 2013)**

G. Perlaki[*], R. Horvath[*], G. Orsi, M. Aradi, T. Auer, E. Varga, G. Kantor, A. Altbacker, F. John, T. Doczi, S. Komoly, N. Kovacs, A. Schwarcz, J. Janszky, White-matter microstructure and language lateralization in left-handers: a whole-brain MRI analysis, Brain Cogn 82 (2013) 319-328. **IF : 2.683**

[*]Equal contribution in first authorship

6.2 Articles unrelated to the thesis

A. Altbacker, E. Plozer, G. Darnai, **G. Perlaki**, G. Orsi, S.A. Nagy, T. Lucza, A. Schwarcz, T. Koszegi, N. Kovacs, S. Komoly, J. Janszky, Z. Clemens, Alexithymia is associated with low level of vitamin D in young healthy adults, Nutr Neurosci (2014). [Epub ahead of print, PMID: 24593042] **IF : 2.114 (in 2013)**

G. Orsi, M. Aradi, S.A. Nagy, **G. Perlaki**, A. Trauninger, P. Bogner, J. Janszky, Z. Illes, T. Doczi, Z. Pfund, A. Schwarcz, Differentiating white matter lesions in multiple sclerosis and migraine using monoexponential and biexponential diffusion measurements, J Magn Reson Imaging (2014). [Epub ahead of print, PMID: 24677284] **IF : 2.788 (in 2013)**

E. Plozer, A. Altbacker, G. Darnai, **G. Perlaki**, G. Orsi, S.A. Nagy, A. Schwarcz, T. Koszegi, G.L. Woth, T. Lucza, N. Kovacs, S. Komoly, Z. Clemens, J. Janszky, Intracranial volume inversely correlates with serum 25(OH)D level in healthy young women, Nutr Neurosci (2014). [Epub ahead of print, PMID: 24524629] **IF : 2.114 (in 2013)**

C.R. von Jako, **G. Perlaki**, G. Orsi, A. Schwarcz, T. Doczi, A miniature optical neuronavigation system for CT-guided stereotaxy, Stereotact Funct Neurosurg 92 (2014) 1-7. **IF : 1.477 (in 2013)**

M. Aradi, E. Koszegi, G. Orsi, **G. Perlaki**, A. Trauninger, A. Toth, A. Schwarcz, Z. Illes, Quantitative MRI analysis of the brain after twenty-two years of neuromyelitis optica indicates focal tissue damage, Eur Neurol 69 (2013) 221-225. **IF : 1.362**

M. Aradi, A. Schwarcz, **G. Perlaki**, G. Orsi, N. Kovacs, A. Trauninger, D.O. Kamson, S. Erdelyi-Botor, F. Nagy, S.A. Nagy, T. Doczi, S. Komoly, Z. Pfund, Quantitative MRI studies of chronic brain white matter hyperintensities in migraine patients, Headache 53 (2013) 752-763. **IF : 3.189**

T. Bereczkei, A. Deak, P. Papp, **G. Perlaki**, G. Orsi, Neural correlates of Machiavellian strategies in a social dilemma task, Brain Cogn 82 (2013) 108-116. **IF : 2.683**

A. Horváth, M. Aradi, **G. Perlaki**, G. Orsi, C. Szalay, A. Schwarcz, A. Büki, F. Kövér, T. Dóczi, P. Bogner, A kómás agy strukturális és funkcionális vizsgálata multiparametrikus MR-technikával, Magyar Radiológia 87 (2013) 32-39. **IF: 0.0**

Z. Kalmar, N. Kovacs, I. Balas, **G. Perlaki**, E. Plozer, G. Orsi, A. Altbacker, A. Schwarcz, L. Hejjel, S. Komoly, J. Janszky, Effects of spinal cord stimulation on heart rate variability in patients with chronic pain, Ideggyogy Sz 66 (2013) 102-106. **IF : 0.343**

A. Mike, E. Strammer, M. Aradi, G. Orsi, **G. Perlaki**, A. Hajnal, J. Sandor, M. Banati, E. Illes, A. Zaitsev, R. Herold, C.R. Guttmann, Z. Illes, Disconnection mechanism and regional cortical atrophy contribute to impaired processing of facial expressions and theory of mind in multiple sclerosis: a structural MRI study, PLoS One 8 (2013) e82422. **IF : 3.534**

S.A. Nagy, M. Aradi, G. Orsi, **G. Perlaki**, D.O. Kamson, A. Mike, H. Komaromy, A. Schwarcz, A. Kovacs, J. Janszky, Z. Pfund, Z. Illes, P. Bogner, Bi-exponential diffusion signal decay in normal appearing white matter of multiple sclerosis, Magn Reson Imaging 31 (2013) 286-295. **IF : 2.022**

S.A. Nagy, I. Juhasz, H. Komaromy, K. Pozsar, I. Zsigmond, **G. Perlaki**, G. Orsi, A. Schwarcz, N. Walter, T. Doczi, P. Bogner, A Statistical Model for Intervertebral Disc Degeneration: Determination of the Optimal T2 Cut-Off

Values, Clin Neuroradiol (2013). [Epub ahead of print, PMID: 24218066] **IF : 1.615**

A. Toth, N. Kovacs, **G. Perlaki**, G. Orsi, M. Aradi, H. Komaromy, E. Ezer, P. Bukovics, O. Farkas, J. Janszky, T. Doczi, A. Buki, A. Schwarcz, Multi-modal magnetic resonance imaging in the acute and sub-acute phase of mild traumatic brain injury: can we see the difference?, J Neurotrauma 30 (2013) 2-10. **IF : 3.968**

G. File, G. Bajzik, T. Doczi, G. Orsi, **G. Perlaki**, Z. Lelovics, M. Aradi, A. Schwarcz, Brain tissue water content determination based on T1 relaxation time of water and quantitative cerebral 1H MRS at 3T using water as an internal reference, Ideggyogy Sz 65 (2012) 325-332. **IF : 0.348**

I. Gerlinger, **G. Perlaki**, G. Orsi, M. Aradi, É. Szabadi, H. Komáromy, L. Vitéz, F. Kövér, Az otitis media suppurativa chsonica cholesteatomatosa CT- és MRI-vizsgálata. A diffúzió súlyozott MRI-vizsgálat jelentősége, Otorhinolaringologia Hungarica 58 (2012) 19-24. **IF: 0.0**

D.O. Kamson, Z. Illes, M. Aradi, G. Orsi, **G. Perlaki**, E. Leel-Ossy, S. Erdelyi-Botor, L. Poto, A. Trauninger, Z. Pfund, Volumetric comparisons of supratentorial white matter hyperintensities on FLAIR MRI in patients with migraine and multiple sclerosis, J Clin Neurosci 19 (2012) 696-701. **IF : 1.253**

R. Steier, M. Aradi, J. Pal, **G. Perlaki**, G. Orsi, P. Bogner, F. Galyas, P. Bukovics, J. Janszky, T. Doczi, A. Schwarcz, A biexponential DWI study in rat brain intracellular oedema, Eur J Radiol 81 (2012) 1758-1765. **IF : 2.512**

C. Szalay, M. Aradi, A. Schwarcz, G. Orsi, **G. Perlaki**, L. Nemeth, S. Hanna, G. Takacs, I. Szabo, L. Bajnok, A. Vereczkei, T. Doczi, J. Janszky, S. Komoly, P. Ors Horvath, L. Lenard, Z. Karadi, Gustatory perception alterations in obesity: an fMRI study, Brain Res 1473 (2012) 131-140. **IF : 2.879**

R.A. Horvath, A. Schwarcz, M. Aradi, T. Auer, N. Feher, N. Kovacs, T. Tenyi, C. Szalay, **G. Perlaki**, G. Orsi, S. Komoly, T. Doczi, F.G. Woermann, C. Gyimesi, J. Janszky, Lateralisation of non-metric rhythm, Laterality 16 (2011) 620-635. **IF : 1.135**

Z. Kalmar, N. Kovacs, **G. Perlaki**, F. Nagy, Z. Aschermann, Z. Kerekes, B. Kaszas, I. Balas, G. Orsi, S. Komoly, A. Schwarcz, J. Janszky, Reorganization of motor system in Parkinson's disease, Eur Neurol 66 (2011) 220-226. **IF : 1.811**

G. Orsi, **G. Perlaki**, N. Kovacs, M. Aradi, Z. Papp, K. Karadi, C. Szalay, Z. Karadi, L. Lenard, T. Tenyi, E. Plozer, R. Gabriel, F. Nagy, T. Doczi, S. Komoly, H. Jokeit, A. Schwarcz, J. Janszky, Body weight and the reward system: the volume of the right amygdala may be associated with body mass index in young overweight men, Brain Imaging Behav 5 (2011) 149-157. **IF : 1.661**

G. Perlaki[*], G. Orsi[*], N. Kovacs, A. Schwarcz, Z. Pap, Z. Kalmar, E. Plozer, A. Csatho, R. Gabriel, S. Komoly, I. Janszky, J. Janszky, Coffee consumption may influence hippocampal volume in young women, Brain Imaging Behav 5 (2011) 274-284. **IF : 1.661**
[*]Equal contribution in first authorship

R. Steier, M. Aradi, J. Pal, P. Bukovics, **G. Perlaki**, G. Orsi, J. Janszky, A. Schwarcz, E. Sulyok, T. Doczi, The influence of benzamil hydrochloride on the evolution of hyponatremic brain edema as assessed by in vivo MRI study in rats, Acta Neurochir (Wien) 153 (2011) 2091-2097; discussion 2097. **IF : 1.520**

A. Vereczkei, C. Szalay, M. Aradi, A. Schwarcz, G. Orsi, **G. Perlaki**, Z. Karadi, L. Nemeth, S. Hanna, G. Takacs, I. Szabo, L. Bajnok, E. Mohos, L. Lenard, T. Doczi, J. Janszky, S. Komoly, O.P. Horvath, Functional MRI investigation of brain activity triggered by taste stimulation, Magy Seb 64 (2011) 289-293. **IF : 0.0**

M. Aradi, R. Steier, P. Bukovics, C. Szalay, **G. Perlaki**, G. Orsi, J. Pal, J. Janszky, T. Doczi, A. Schwarcz, Quantitative proton MRI and MRS of the rat brain with a 3T clinical MR scanner, J Neuroradiol (2010). **IF : 1.213**

S.A. Nagy, M. Aradi, Z. Pfund, G. Orsi, **G. Perlaki**, P. Bogner, Regionális látszólagos diffúziós koefficiens változások az életkor függvényében normál és sclerosis multiplex csoportokban, EGÉSZSÉG-AKADÉMIA 1 (2010) 239-247. **IF : 0.0**

T. Auer, S. Pinter, N. Kovacs, Z. Kalmar, F. Nagy, R.A. Horvath, B. Koszo, G. Kotek, **G. Perlaki**, M. Koves, B. Kalman, S. Komoly, A. Schwarcz, F.G.

Woermann, J. Janszky, Does obstetric brachial plexus injury influence speech dominance?, Ann Neurol 65 (2009) 57-66. **IF : 9.317**

R.A. Horvath, A. Fogarasi, R. Schulz, **G. Perlaki**, Z. Kalmar, V. Toth, N. Kovacs, A. Ebner, J. Janszky, Ictal vocalizations occur more often in temporal lobe epilepsy with dominant (left-sided) epileptogenic zone, Epilepsia 50 (2009) 1542-1546. **IF : 4.052**

7. Acknowledgements

All the work presented in this thesis could not have been carried out without the enormous help from numerous people, to whom I owe a great debt of gratitude.

First, I wish to thank my supervisors, Prof. József Janszky and Dr. Attila Schwarcz, for teaching me the basics of neuroscience research, their continuous support, efforts, guidance and irreplaceable help in summarizing my thesis. I would also like to emphasize my deep gratitude towards Béla Németh, Dr. Ferenc Kövér, Prof. Tamás Dóczi, Prof. Sámuel Komoly and Prof. Péter Bogner for the financial and technical support of my work. Each of them had an important role in completing my PhD work and thesis.

Special thanks must be paid to my friends, Dr. Mihály Aradi and Dr. Gergely Orsi, for working together as a team. I benefited greatly from invaluable discussions with them. They answered a series of my questions every day tirelessly and patiently, providing their knowledge and insight in the field of MRI.

I would like to thank all my colleagues at the Diagnostic Center of Pécs and the University of Pécs, in particular Dr. Réka Horváth, Szilvia Anett Nagy, Kristóf Biczó and Péter Bódi, for a fruitful common group effort that led us to achieve our goals. I am also grateful to my PhD

colleagues, first of all Anna Altbäcker, Dr. Enikő Plózer, Gergely Darnai, Dr. Arnold Tóth, and Dr. Andrea Horváth, for their daily help and advice.

My most special thanks go to my wife, Zsófia, for her continuous emotional support, encouragement and understanding. I express my gratitude to my parents for their love and providing me with every kind of support throughout my entire life.

The work presented in this thesis was supported by the grant SROP-4.2.2.A-11/1/KONV-2012-0017 „Identification of new biomarkers, especially, regarding the toxicity of free iron deposition in the nervous system, iron toxicity-induced oxidative stress and innate immune reactions with translational investigations”.