

# **Disturbances in emotion processing and behavioral regulation: neuroanatomical and neurobiological factors**

Ph.D. Thesis

**Anna Altbäcker**

University of Pécs

Doctoral School of Clinical Neuroscience

Supervisor:

**Prof. József Janszky, M.D, D.Sc.**

Leader of Doctoral Program:

**Prof. József Janszky, M.D., D.Sc.**

Leader of Doctoral School:

**Prof. Sámuel Komoly, M.D., D.Sc.**



Pécs, 2016

## **Table of contents**

1. Introduction .....	3
2. Objectives.....	4
3. Materials and Methods .....	5
3.1 Alexithymia and vitamin D level .....	5
3.2 Problematic Internet use and the brain reward system .....	5
4. Results .....	6
4.1 Alexithymia and vitamin D .....	6
4.2 Problematic Internet use and the brain reward system .....	7
5. Conclusions .....	8
5.1 Alexithymia and vitamin D .....	8
5.2 Problematic Internet use and the brain reward system .....	9
6. Publications .....	10
6.1 Articles related to the thesis .....	10
6.2 Oral and poster presentations related to the thesis .....	10
6.3 Articles non-related to the thesis .....	10
6.4 Oral and poster presentations non-related to the thesis .....	11
7. Acknowledgment .....	13

## **1. Introduction**

Successful emotion and behavior regulation are both fundamental for mental health. These abilities are responsible for maintaining goal orientated functioning, impulse control, and adequate social behavior. On the other hand, emotion and behavior dysregulation are present in a variety of psychiatric and neurological disorders enhancing symptom severity and impairments in everyday life rather than being disorder specific aspects. For the better understanding of how people regulate and control their behaviors and emotions, modern neuroscience provides important insights into brain mechanisms related to (both adaptive and disturbed) emotional and behavioral regulation. This thesis is focused on neuroanatomical and neurobiological findings related to this topic.

While our knowledge about structural bases of individual differences was primarily based on group of patients with well-defined, circumscribed lesions and postmortem studies, recent developments in structural magnetic resonance imaging (MRI) techniques (e.g. MRI volumetry, voxel-based morphometry, and diffusion tensor imaging) made it possible to investigate the macro- and microstructural bases of inter-individual differences in healthy subjects. Both macro- and microstructural variability have been found to be related to a wide range of factors that can possibly contribute to disturbed psychological processes. These factors include age, gender, habits, experiences, behavior regulation, and variations in emotion regulation.

On the neurobiological level, neurosteroids play a significant role in the neurodevelopment and maintenance of a variety of psychopathological processes primary through neurotransmitter modulation, and may also be related to brain structural variations. Evidence shows that inter-individual

variability in neurosteroid concentrations is also related to gender, age, habits, experiences, behavior regulation, and disturbances in emotional regulation.

Such neuroanatomical and neurobiological variations in healthy population may carry functional and behavioral consequences that possibly mediate vulnerability to psychopathology. Investigating such variations in healthy subjects may extend our knowledge about normal patterns, which in turn contribute to the better understanding of abnormalities in clinical groups.

## 2. Objectives

This thesis aimed to investigate psychological correlates of neuroanatomical and neurobiological variability in a large set of healthy normal volunteers using self-reported measures of emotion and behavior regulation with the latest neuroimaging methods (such as automated MRI volumetry and voxel-based morphometry) and serum blood analysis.

Our first study investigated **whether there is a direct link between a neurosteroid hormone, vitamin D, and alexithymia, a personality trait defined by impaired emotion regulation processes**. Although both vitamin D deficiency and alexithymia were described as a correlate of a variety of pathological conditions, their specific interrelation has not yet been studied.

In our second study, we aimed to investigate **the structural brain correlates of a newly identified condition defined by poor behavior regulation, problematic Internet use, in habitual Internet user females using both automated MRI volumetry and voxel-based morphometry (VBM) as complementary approaches**. Based on previous neuroimaging findings and the known role of brain reward system in addictions, we

hypothesized that regions of the fronto-striatal circuit (orbitofrontal cortex, caudate, putamen, nucleus accumbens) and amygdala -that provides important inputs to the striatum -would be associated with problematic Internet use.

### **3. Materials and Methods**

#### **3.1 Alexithymia and vitamin D level**

Eighty-nine healthy, right-handed Caucasian university students without history of substance abuse, chronic illnesses, neurological and psychiatric disorders, aged between 18 and 30 years were included in this study (59 females and 30 males; mean age: 23.1 years, SD= 2.1).

To assess vitamin D level, fasting blood samples were analyzed for serum 25(OH)D. Alexithymia was measured by the Hungarian version of the 20-item Toronto Alexithymia Scale (TAS-20). Actual level of depression was measured by the Hungarian version of Beck Depression Inventory (BDI), while actual level of anxiety was measured by the Hungarian version of Spielberger State Anxiety Inventory (STAI-S). Handedness was measured with Edinburgh Handedness Inventory (EHI). Subjects also completed an exploratory questionnaire on lifestyle factors, mental and physical health.

#### **3.2 Problematic Internet use and the brain reward system**

Eighty-two healthy, right-handed Caucasian female university students without history of substance abuse, chronic illnesses, neurological and psychiatric disorders, aged between 18 and 30 took part in this study. Mean age was 22.83 (SD = 2.3) and all participants used the internet on a daily basis.

T1-weighted Magnetic Resonance (MR) images were collected from all subjects. Structural brain measures were investigated using both automated MR volumetry and voxel based morphometry (VBM).

Excessive internet use was measured with Problematic Internet Use Questionnaire (PIUQ), which consists of three subscales: (1) Obsession (obsessive thinking about the Internet and withdrawal symptoms caused by the lack of Internet use), (2) Neglect (neglecting everyday activities, social life and essential needs), and (3) Control disorder (difficulties in controlling time spent on the Internet). Additional questions were administered to assess hours weekly spent on the Internet. Similar to our previous study, TAS-20, BDI, STAIT and EHI were also administered.

## **4. Results**

### **4.1 Alexithymia and vitamin D**

Spearman's rank correlation analysis revealed a marginally insignificant negative correlation between TAS-20 score and 25(OH)D levels ( $r_s = -.20$ ;  $p = .06$ )

A control for age and gender in a multiple linear regression model resulted in a significant inverse relation between 25(OH)D level and TAS-20 score ( $\beta = -.29$ ;  $p = .03$ ). Neither age ( $\beta = -.06$ ;  $p = .6$ ) nor gender ( $\beta = -.16$ ;  $p = .17$ ) contributed significantly to TAS-20 score. The inclusion of BDI and STAIS scores as additional independent variables in a second linear regression model did not essentially change the significant relationship between 25(OH)D level and TAS-20 score ( $\beta = -.21$ ;  $p = .03$ ), while BDI and STAIS scores also showed a significant relation with TAS-20 ( $\beta = .26$ ;  $p = .01$  and  $\beta = .28$ ;  $p = .008$ , respectively).

## 4.2 Problematic Internet use and the brain reward system

### MR volumetry

Significant positive associations were found between Control disorder and both left and right putamen ( $\beta = .229$ ;  $p < .05$  and  $\beta = .237$ ;  $p < .05$ , respectively) and between Obsession and right nucleus accumbens ( $\beta = .238$ ;  $p < .05$ ). Obsession also showed a significant negative association with both left and right OFC ( $\beta = -.226$ ;  $p < .05$  and  $\beta = -.297$ ;  $p < .01$ , respectively) while Neglect was negatively related to left OFC ( $\beta = -.232$ ;  $p < .05$ ). To test its possible confounding effect, average time spent online was also entered to each model as an additional independent variable. However, it did not essentially change the significant associations between PIUQ subscales and the volume of the investigated regions.

### Voxel Based Morphometry (VBM)

Subscales of PIUQ were used separately to predict the absolute amount of grey matter of the investigated brain regions in separate general linear models while controlling for intracranial volume and age. A significant negative correlation was found between Neglect with the absolute amount of grey matter in left OFC, and between Control disorder and the absolute amount of grey matter in right OFC, while showed no significant association with Obsession OFC. Other regions of interest were not predicted significantly by any of the PIUQ subscales.

## 5. Conclusions

### 5.1 Alexithymia and vitamin D

Our first experiment aimed to investigate whether there is a direct link between vitamin D and alexithymia. Although both vitamin D deficiency and alexithymia were described as a correlate of a variety of pathological conditions, their specific interrelation has not yet been studied. **Controlling for age, gender, depression, and anxiety, we found a significant inverse correlation between actual levels of vitamin D and alexithymia in young healthy volunteers.** We suggest that the association between alexithymia and vitamin D reflects a trait-like relationship between two conditions that is rather stable longitudinally. Such a correlation may be interpreted as a reflection of early life vitamin D deficiency determining life-long alexithymia. Since alexithymia and vitamin D deficiency are highly prevalent in a range of psychiatric and neurological disorders, future cross-sectional and longitudinal studies should investigate whether the direct link revealed by our study in healthy controls are also present in certain patient groups and whether comorbidity factors play a significant role. Our results may contribute to the development of more efficient therapy strategies in patient groups with difficulties in understanding affective experiences.



## 5.2 Problematic Internet use and the brain reward system

Our second experiment investigated the structural brain correlates of problematic Internet use in a large non-clinical sample of habitual Internet user females using both automated MRI volumetry and voxel-based morphometry as complementary approaches. **We demonstrated structural brain correlates of problematic Internet use in regions of the fronto-striatal circuit in females with both techniques.** MRI based volumetry revealed increased grey matter volume of bilateral putamen and right nucleus accumbens and decreased grey matter volume of orbitofrontal cortex to be associated with Problematic Internet Use questionnaire's subscales. The significant negative associations between the absolute amount of grey matter of the bilateral orbitofrontal cortex and Problematic Internet Use questionnaire's subscales were also present in the voxel based morphometry analysis. Taken together, our results suggest that problematic Internet use has structural brain correlates in the fronto-striatal circuit in healthy habitual Internet user females. Since similar associations have been identified in the fronto-striatal circuit in habitual Internet user males, our findings can be interpreted as a proof for morphological brain alterations related to excessive Internet use in both genders. Our results may offer new insights into neuroanatomy of problematic Internet use.

## 6. Publications

### 6.1 Articles related to the thesis

**Altbäcker, A.**, Plózer, E., Darnai, G., Perlaki, G., Orsi, G., Nagy, S. A., ... & Clemens, Z. (2014). Alexithymia is associated with low level of vitamin D in young healthy adults. *Nutritional Neuroscience*, 17(6), 284-288. **IF: 2.274**

**Altbäcker, A.**, Plózer, E., Darnai, G., Perlaki, G., Horváth, R., Orsi, G., Nagy, S. A., Bogner, P., Schwarcz, A., Kovács, N., Komoly, S., Clemens, Z., Janszky, J. (2015, September 23). Problematic Internet use is associated with structural alterations in the brain reward system in females. *Brain Imaging and Behavior*. Advance online publication. **IF: 3.667 (in 2015)**

### 6.2 Oral and poster presentations related to the thesis

**Altbäcker, A.**, Plózer, E., Darnai, G., Janszky, J., Clemens, Zs. (2012, November). Az alexitímia és a D-vitamin kapcsolata. Poster session presented at Magyar Ideg- és Elmeorvosok Társaságának XXXV. Vándorgyűlése, Debrecen, Hungary

**Altbäcker, A.**, Janszky, J., Clemens, Zs. (2013, March). *Problematic Internet Use and the brain reward system: A pilot study*. Oral presentation at 1<sup>st</sup> International Conference on Behavioral Addictions, Budapest, Hungary

**Altbäcker, A.**, Plózer, E., Darnai, G., Perlaki, G., Orsi, G., Nagy, Sz. A., Schwarcz, A., Clemens, Zs., Janszky, J. (2013, April). *Strukturális agyi elváltozások internetfüggőségben (előtanulmány)*. Oral presentation at Neuroimaging Workshop, Pécs, Hungary

### 6.3 Articles non-related to the thesis

Kalmár, Z., Kovács, N., Balás, I., Perlaki, G., Plózer, E., Orsi, G., **Altbäcker, A.**, Schwarcz, A., Hejmel, L., Komoly, S., Janszky, J. (2013). Effects of spinal cord stimulation on heart rate variability in patients with chronic pain. *Ideggyógyászati Szemle/Clinical Neuroscience* 66(3-4), 102-106. **IF: 0.343**

Perlaki, G., Horvath, R., Orsi, G., Aradi, M., Auer, T., Varga, E., Kantor, Gy., **Altbäcker, A.**, John, F.; Doczi, T., Komoly, S., Kovacs, N., Schwarcz, A., Janszky, J. (2013). White-matter microstructure and language

lateralization in left-handers: a whole-brain MRI analysis. *Brain and Cognition*, 82(3), 319-328. **IF: 2.683**

Perlaki, G., Orsi, G., Plozer, E., **Altbacker, A.**, Darnai, G., Nagy, S. A., ... & Janszky, J. (2014). Are there any gender differences in the hippocampus volume after head-size correction? A volumetric and voxel-based morphometric study. *Neuroscience Letters*, 570, 119-123. **IF: 2.030**

Darnai, G., Plózer, E., Perlaki, G., Orsi, G., Nagy, S. A., Horváth, R., Schwarcz, A., Kovács, N., **Altbacker, A.**, Janszky, J., Clemens, Z. (2015). Milk and dairy consumption correlates with cerebral cortical as well as cerebral white matter volume in healthy young adults. *International Journal of Food Sciences and Nutrition*, 66(7), 826-829. **IF: 1.451**

Kuperczkó, D., Perlaki, G., Faludi, B., Orsi, G., **Altbacker, A.**, Kovács, N., ... & Janszky, J. (2015). Late bedtime is associated with decreased hippocampal volume in young healthy subjects. *Sleep and Biological Rhythms*, 13(1), 68-75. **IF: 0.588**

Plózer, E., **Altbacker, A.**, Darnai, G., Perlaki, G., Orsi, G., Nagy, S. A., ... & Janszky, J. (2015). Intracranial volume inversely correlates with serum 25 (OH) D level in healthy young women. *Nutritional Neuroscience*, 18(1), 37-40. **IF: 2.616**

Darnai, G., **Altbacker, A.**, Plózer, E., Perlaki, G., Orsi, G., Nagy, Sz. A., Horváth, R., Schwarcz, A., Kovács, N., Janszky, J., Clemens, Zs. (2016). 2D:4D finger ratio positively correlates with total cerebral cortex in males. *Neuroscience Letters*, 615, 33-36. **IF: 2.107**

Darnai, G., Plózer, E., **Altbacker, A.**, Perlaki, G., Orsi, G., Kőszegi, T., Nagy, Sz. A., Lucza, T., Kovács, N., Janszky, J., Clemens, Zs. (In press). The relationship between serum cholesterol and verbal memory may be influenced by body mass index (BMI) in young healthy women. *Ideggyógyászati Szemle/Clinical Neuroscience*. **IF: 0.376**

#### **6.4 Oral and poster presentations non-related to the thesis**

Lucza, T., Darnai, G., Plózer, E., **Altbacker, A.**, Janszky, J., Orsi, G., Perlaki, G., Karádi, K. (2012, June). *Mentális forgatási képesség és agytérfogat összefüggésének nemi összehasonlító vizsgálata*. Poster session presented at Magatartástudományi napok, Szeged, Hungary

Darnai, G., Plózer, E., **Altbacker, A.**, Lucza, T., Karádi, K., Kovács, N., Clemens, Zs., Janszky, J. (2012, November). *D-vitamin hatása a kognitív*

*funkciókra*. Poster session presented at Magyar Ideg- és Elmeorvosok Társaságának XXXV. Vándorgyűlése, Debrecen, Hungary

Perlaki, G., Horváth, R., Orsi, G., Aradi, M., Auer, T., Varga, E., Kántor, Gy., **Altbäcker, A.**, Dóczy, T., Komoly, S. Kovács, N., Schwarcz, A., Janszky, J. (2012, November). *A fehérállomány microszerkezete és a nyelvi lateralizáció balkezeseiben*. Oral presentation at Magyar Neuroradiológiai Társaság XX. Kongresszusa, Eger, Hungary

Plózer, E., **Altbäcker, A.**, Darnai, G., Orsi, G., Perlaki, G., Nagy, Sz. A., Schwarz, A., Clemens, Zs., Janszky, J. (2012, November). *D-vitamin és az egészséges agyszerkezet: Kvantitatív MR vizsgálatok*. Poster session presented at Magyar Ideg- és Elmeorvosok Társaságának XXXV. Vándorgyűlése, Debrecen, Hungary

Darnai, G., Perlaki, G., Szolcsányi, T., Hegedűs, G., Kincses, P., Plózer, E., **Altbäcker, A.**, Janszky, J. (2013, April). *A gumikéz illúzió és a kérgi aktivitás (előtanulmány)*. Oral presentation at Neuroimaging Workshop, Pécs, Hungary

Perlaki G., Orsi G., Nagy Sz. A., Plózer E., **Altbäcker A.**, Darnai, G., Tóth A., Dóczy T., Komoly S., Bogner P., Schwarz A., Janszky, J. (2013, April). *Is there sexual dimorphism in hippocampal volume?* Oral presentation at Neuroimaging workshop, Pécs, Hungary

Plózer, E., **Altbäcker, A.**, Darnai, G., Perlaki, G., Orsi, G., Nagy Sz. A., Kőszegi, T., Schwarcz, A., Komoly, S., Janszky, J., Clemens, Zs. (2013, April). *Az intrakraniális térfogat és a 25(OH)D szint közötti összefüggés vizsgálata fiatal nőkben*. Oral presentation at Neuroimaging Workshop, Pécs, Hungary

Darnai, G., **Altbäcker, A.**, Plózer, E., Perlaki, G., Horváth, R., Orsi, G., Nagy, Sz. A., Clemens, Zs., Janszky, J. (2014, October). *Iron deposition in subcortical nuclei and Intelligence in young adults*. Poster session presented at 2nd Joint WPA-INA-HSRPS International Psychiatric Congress, Athens, Greece

**Altbäcker, A.**, Takács, E., Czigler, I., Balázs, L. (2015, July). *Effects of microgravity on blinking rate during cognitive tasks: preliminary results*. Poster session presented at 20th Humans in Space Symposium, Prague, Czech Republic

### **Scientometric data**

Cumulative impact factor: 18,135

Number of independent citations: 28

## **7. Acknowledgment**

I would like to express my sincere thanks to all of those who made my Ph.D thesis possible. First of all, I want to express gratitude towards my supervisor, Prof. József Janszky for introducing me to this exciting field of neuroscience, his continuous support, efforts and guidance, his help is irreplaceable. I am also thankful for Dr. Zsófia Clemens for her ideas and continuous help with the articles related to this Ph.D. I would also like to emphasize my gratitude to Prof. Sámuel Komoly for his encouragement and support of my work. I am thankful for all of them for providing me the opportunity for my work.

I want to express my sincere appreciation to my colleagues and friends, Dr. Enikő Plózer and Dr. Gergely Darnai, for such a fruitful collaboration throughout these years. I am also grateful to my Ph.D colleagues, Dr. Gábor Perlaki, Dr. Gergely Orsi, Dr. Réka Horváth, Dr. Tivadar Luca, Dr. Arnold Tóth, Dr. Diána Kuperckó, and Dr. Emese Lovadi for their continuous help and advice. My words of thanks should also go to all of my colleagues at the Diagnostic Center of Pécs, in particular, Szilvia Anett Nagy, Kristóf Biczó and Péter Bódi; and to my current colleagues at the Institute of Cognitive Neuroscience and Psychology in the Research Centre for Natural Sciences.

My most special thanks go to my husband, Gyuri, my closest friends and most importantly, to my family, for their continuous emotional support, patience and understanding. This dissertation is dedicated to all of them.

The work presented in this thesis was supported by grants of the Hungarian Brain Research Program (KTIA-NAP-13-a-II/9), SROP-4.2.1.B-10/2/KONV-2010-0002, SROP-4.2.2/A-11/1/KONV-2012-0017 and the PTE ÁOK-KA-2013/34039.