

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

*Ph.D. thesis*

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## TABLE OF CONTENTS

Abbreviations.....	5
1. General introduction .....	6
1.1. The role of Vitamin D in brain development, adult brain function, neropsychiatric diseases, and emotion regulation.....	9
1.2. Substance related and behavioral addictions: the rise of neuroimaging studies in problematic Internet use .....	11
1.2.1. Problematic Internet use.....	14
2. Technical background.....	16
2.1. Vitamin D synthesis, measurement, recommendations .....	16
2.2. Automated volumetric methods.....	18
2.2.1. Automated MRI volumetry.....	18
2.2.2. Voxel based morphometry (VBM) .....	19
2.2.3. Comparison of the two methods .....	20
3. Objectives .....	21
4. Materials and methods.....	22
4.1. Alexithymia and vitamin D level.....	22
4.1.1. Subjects .....	22
4.1.2. Questionnaires.....	22
4.1.3. Serum blood analysis .....	23
4.1.4. Statistical analysis .....	23
4.2. Problematic Internet use and the brain reward system .....	24
4.2.1. Subjects .....	24
4.2.2. Questionnaires.....	24
4.2.3. MRI examinations.....	26

4.2.4.	MRI data post processing evaluation .....	26
4.2.5.	Statistical analysis .....	27
5.	Results.....	29
5.1.	Alexithymia and vitamin D level.....	29
5.1.1.	Descriptive statistics .....	29
5.1.2.	Multiple linear regression .....	31
5.2.	Problematic Internet use and the brain reward system .....	32
5.2.1.	Descriptive statistics .....	32
5.2.2.	MR volumetry .....	34
5.2.3.	Voxel Based Morphometry (VBM) .....	35
6.	Discussion.....	37
6.1.	Alexithymia and vitamin D level.....	37
6.2.	Problematic Internet use and the brain reward system .....	40
7.	Summary.....	44
8.	References.....	46
9.	Publications.....	74
9.1.	Articles related to the thesis.....	74
9.2.	Oral and poster presentations related to the thesis.....	74
9.3.	Articles non-related to the thesis .....	75
9.4.	Oral and poster presentations non-related to the thesis .....	76
10.	Acknowledgements.....	78

*"Rabbit's clever," said Pooh thoughtfully.*

*"Yes," said Piglet, "Rabbit's clever." "And he has Brain."*

*"Yes," said Piglet, "Rabbit has Brain."*

*There was a long silence.*

*"I suppose," said Pooh, "that that's why he never understands anything."*

*A.A. Milne*

## Abbreviations

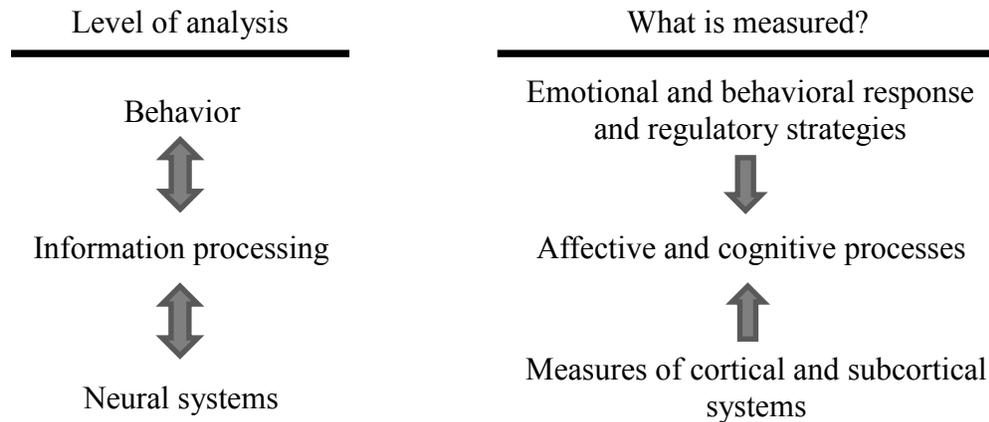
1, 25-OH D	1, 25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
BET	Brain Extraction Tool
BDI	Beck Depression Inventory
BMI	Body Mass Index
DSM-5	Diagnostic and Statistical Manual Version 5
EDI	Edinburgh Handedness Inventory
FA	Fractional Anisotropy
FoV	Field of View
GCA	Gaussian Classifier Array
GLM	General Linear Model
ICV	Intracranial Volume
MNI	Montreal Neurological Institute
MPRAGE	Magnetization Prepared Rapid Gradient-Echo
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
OFC	Orbitofrontal cortex
PIUQ	Problematic Internet Use Questionnaire
RPM	Rounds Per Minute
SD	Standard Deviation
STAIS	Spielberger State Anxiety Inventory
STAIT	Spielberger Trait Anxiety Inventory
TE	Echo Time
TI	Inversion Time
TFCE	Threshold-free Cluster Enhancement
TR	Repetition time
TAS-20	20-item Toronto Alexithymia Scale
UVB	Ultraviolet B
VBM	Voxel-Based Morphometry
VDR	Vitamin D receptor

## 1. General introduction

It is our brain that gives meaning to our thoughts and emotions and implements much of our behavior. On the other hand, our behavior and experiences may form brain structure and function through neuronal plasticity (Joseph 1999; Maguire, Woollet & Spiers 2006; Lövdén et al. 2013). Linking the human mind to behavior and to the brain stretches back over ancient times and has been an area of study of philosophy and biological sciences ever since (Davis et al. 1988; Wickens 2009).

The experimental study of mental processes and behavior had only begun with the inception of psychology in the 19<sup>th</sup> century. Psychology gave a central role to the mind – brain, and relatedly, to the behavior – brain relationship from the beginning (Wundt 1873; James 1890; Watson 1913; Davis et al. 1988; Barrett 2009; Wickens 2009), and several subdisciplines have emerged to understand behavior and mental processes from a variety of perspectives. Biological psychology, for example, was based on the assumption that all mental processes and actions have a neural basis in the brain and aimed to study the biology of the brain and how it produces behavior and mental processes (Davis et al. 1988; Wickens 2009). However, based on the qualitative difference between mental processes and neural mechanisms, some argue with the justification of reducing psychological to biological events (Miller 2010). Bandura (2001), for example, suggests that the latter are important but not exclusive components of psychological states, therefore “...*mapping the activation of neuronal circuitry subserving Martin Luther King’s “I Have a Dream” speech would tell us little about its powerful socially inspirational nature*” (Bandura 2001; Pervin 2009).

Taking their complex nature and qualitative differences into consideration, a multi-level approach drawing on areas within modern neuroscience and psychology might contribute to a better understanding of the relationship between behavior, psychological processes and neural systems (Ochsner et al. 2012) (check Figure 1. for a detailed description).



**Figure 1** A multi-level model of emotion and behavioral regulation that is based on three levels of analysis: behavior, process and neural systems (model proposed by Ochsner et al. 2012). We can only measure behavioral and neural levels and make conclusions about the affective or cognitive processes based on behavioral and neural observations. The bi-directional arrows between levels of analysis indicate bi-directional relationships while the arrows from behavioral and neural levels towards the process level indicate causal relationships.

Successful emotion and behavior regulation are both fundamental for mental health and adaptive behavior. These abilities are responsible for maintaining optimal homeostatic arousal, goal orientated functioning, impulse control, and adequate social behavior (Thompson 1994; Baumeister, Heatherton & Tice 1994; Gross 2001; Schore 2003; Hofmann, Friese, & Strack 2009; Wagner & Heatherton 2010; Heatherton 2011; Heatherton & Wagner 2011; O'Driscoll, Laing, & Mason 2014). 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 (Goodkind et al. 2010; Heatherton & Wagner 2011). 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 (Heatherton & Wagner 2011). 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 affectivity and emotion regulation (Good et al. 2001a; Good et al. 2001b; Ganzel et al. 2008; Welborn et al. 2009; Giorgio et al. 2010; Taki et al. 2011; Kühn, Gallinat, & Brass 2011; Hartley et al. 2011; May 2011; Ansell et al. 2012; Killgore, Olson, & Weber 2013; Ruigrok et al. 2014; Fox et al. 2014; Loh & Kanai 2014; Hermann et al. 2014, Vijayakumar et al. 2014; Deng et al. 2014).

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 (Dubrovsky 2005; Golubchik & Weizman 2008; Zorumski et al. 2013; Plózer et al. 2015, Annweiler et al. 2015). Inter-individual variability in neurosteroid concentrations have also been related to age, gender, habits, experiences, behavior regulation, and disturbances in emotional regulation (Orentreich et al. 1984; 1992; Brot, Jorgensen, & Sorensen 1999; Spivak et al. 2000; Mazat et al. 2001; Engel & Grant 2001; Pearson Murphy et al. 2001; Heydari & Le Melle'do 2002; Brambilla et al. 2003; van Broekhoven &Verkes 2003; Mithal et al. 2009; Wentz 2014).

These studies provide evidence for the presence of neuroanatomical and neurobiological variations in healthy population, which may carry functional and behavioral consequences that may serve to 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.

## **1.1. The role of Vitamin D in brain development, adult brain function, neuropsychiatric diseases, and emotion regulation**

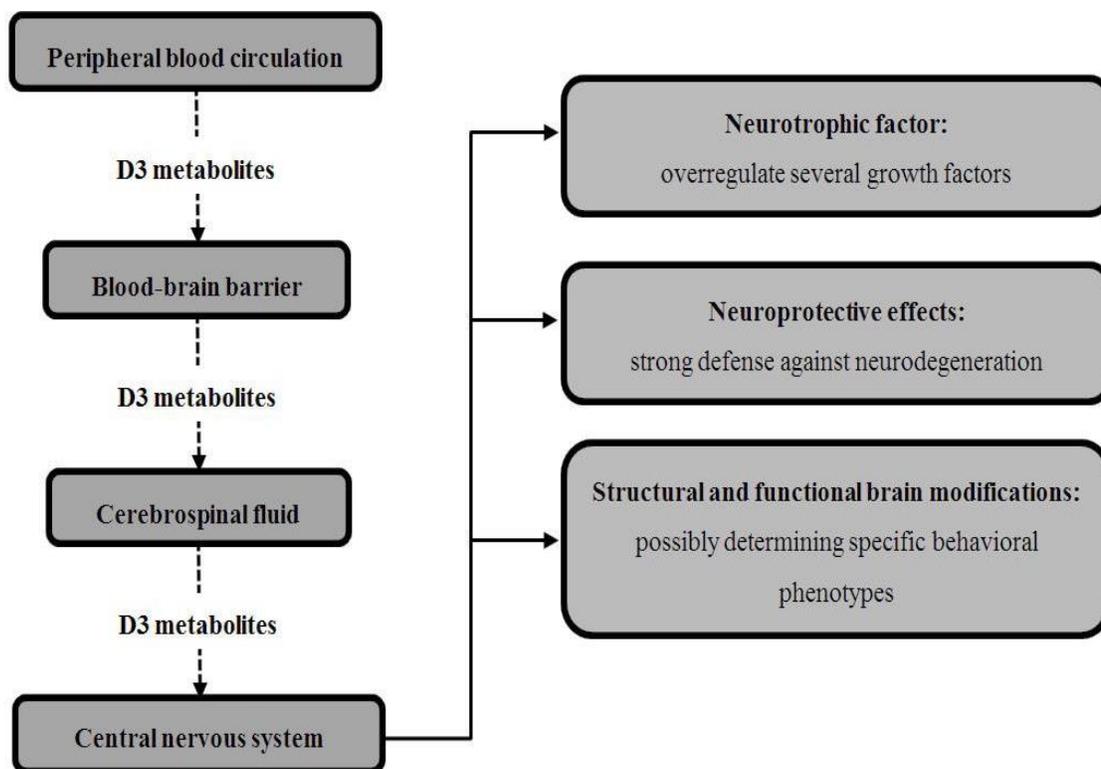
Vitamin D is a nuclear seco-steroid hormone that was primary known for its essential role in calcium homeostasis and being important for cardiovascular health and immune regulation (Holick 2007). The fact that vitamin D metabolites are able to cross the blood–brain barrier, and the presence of vitamin D metabolites, activating enzymes and vitamin D binding receptors (VDR) in the brain indicates that, like other neurosteroids, vitamin D may be important for normal brain development and brain function (Eyles et al. 2005; Smolders et al. 2011; Cui et al. 2013; McGrath et al. 2001a; Eyles, Burne, & McGrath 2011; Harms et al. 2011; Pioggia et al. 2014). (Figure 2).

The involvement of vitamin D in brain homeostasis, neurogenesis, and gene regulation (including the up-regulation of the nerve growth factor) suggests that it may serve as a neuroprotective factor against cognitive impairment and neurological conditions (Saporito et al. 1994; Cornet et al. 1998; McGrath et al. 2001a; Kalueff & Tuohimaa 2007; Holick 2007; Harms et al. 2012; Ramagopalan et al. 2010; Pioggia et al. 2014; Anastasiou et al. 2014; Annweiler et al. 2014). Indeed, low levels of vitamin D have been implicated in several neurological disorders including multiple sclerosis, Alzheimer’s, and Parkinson’s disorders as well as epilepsy (Mowry et al. 2012; Holló et al. 2012; Eyles, Burne & McGrath 2013; Holló, Clemens, & Lakatos 2014; Afzal, Bojesen, & Nordestgaard 2014).

Additionally, animal studies suggest that vitamin D deficiency during brain development leads to alterations in brain morphology (Eyles et al. 2003; Féron et al. 2005). Vitamin D related structural variations in the adult human brain were recently demonstrated by our research group, including enlarged intracranial volume, total cortical grey and cerebral white matter volumes in young healthy women with lower actual vitamin D levels (Plózer et al. 2015). The inverse association between intracranial volume and vitamin D status was also confirmed in elderly (Annweiler et al. 2015). These structural correlations may reflect a trait-like relationship between

vitamin D and brain size possibly determined by early development.

Vitamin D also seems to be involved in emotion regulation and mental health. Seasonal fluctuation in vitamin D has been suggested to play a role in seasonal affective disorder (Stumpf & Privette 1989). There is evidence supporting suboptimal vitamin D levels being associated with depression (Wilkins et al. 2006; Ganji et al. 2010). Prenatal and early childhood vitamin D deficiency has been associated with increased risk for autistic spectrum disorders (ASD) and schizophrenia (Cannell 2008; Grant & Soles 2009; McGrath et al. 2010; Kočovská et al. 2012). Neurological and psychiatric disorders with a vitamin D link are also known to be associated with higher prevalence of alexithymia, a personality trait characterized by impaired ability to experience, differentiate, and verbalize emotional experiences (Shipko et al. 1983; Linden et al. 1995; Bermond 1997; Honkalampi et al. 2001; Bewley et al. 2005; Bodini et al. 2008). 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.

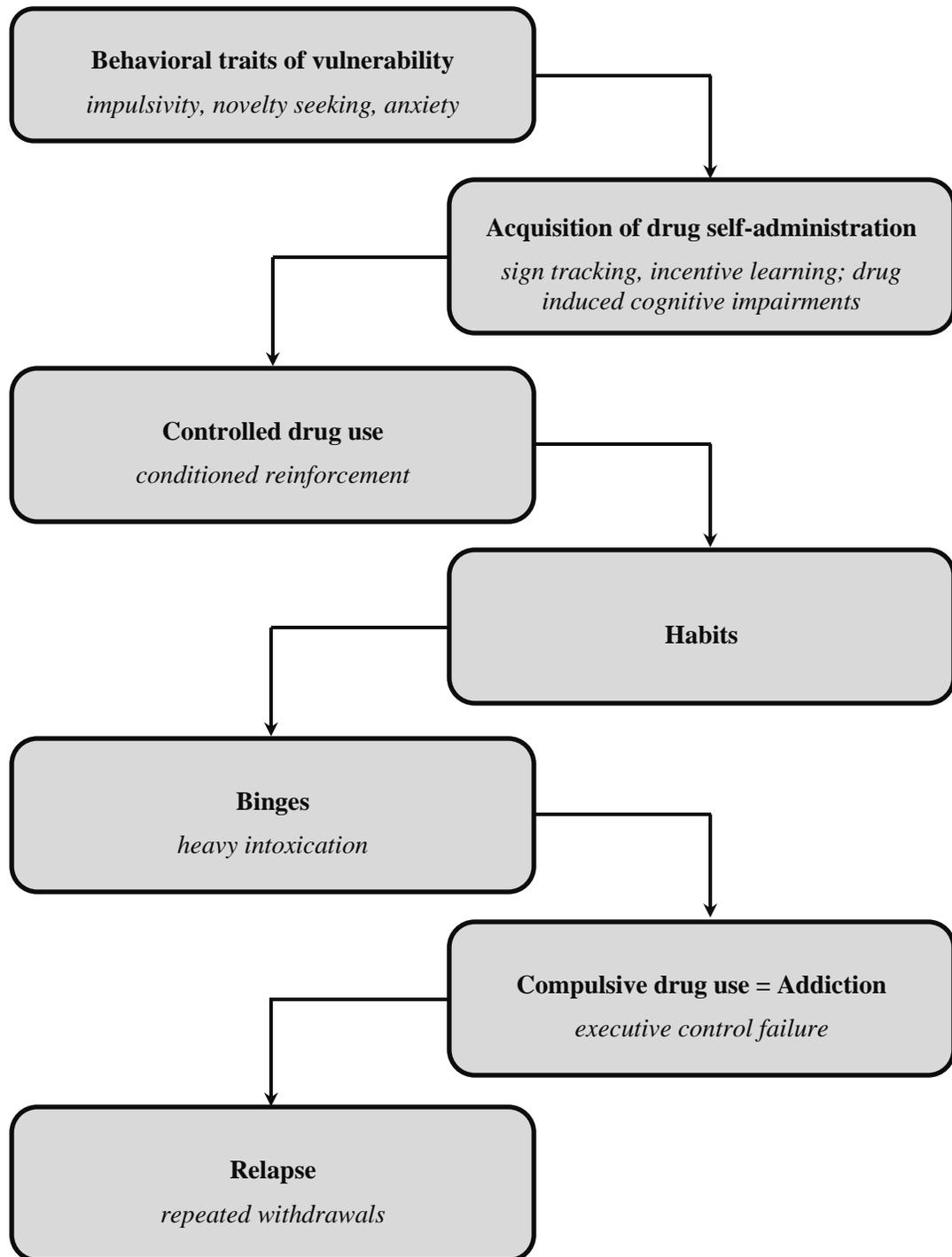


**Figure 2.** Vitamin D3 in the human brain (Pioggia et al. 2014)

## **1.2. Substance related and behavioral addictions: the rise of neuroimaging studies in problematic Internet use**

Addiction is a brain disease with critical biological, behavioral and social-context components (Leshner 1997; Levy 2013). It is characterized by a pathological pattern of automatic and compulsive behavior that develops from the initially voluntary behavior (e.g. psychoactive substance use) (Volkow & Baler 2014). According to the DSM-5 (Diagnostic and Statistical Manual Version 5, American Psychiatric Association 2013), core aspects of substance-related disorders (substance addiction) include a cluster of cognitive, behavioral and physiological symptoms (Figure 3):

- a. Impaired control (e.g. use larger amounts or use over a longer period against original intentions; failed attempts to decrease intake; spending a great deal of time revolving around the substance; craving)
- b. Social impairment (failure to fulfill major obligations; interpersonal problems related to substance; withdrawing social activities)
- c. Risky use (recurrent substance use in physically hazardous situations; failure to abstain from substance use despite awareness of psychological or physiological harm)
- d. Pharmacological criteria (*tolerance; withdrawal*).



**Figure 3.** A summary of psychological processes playing a role in turning voluntary drug seeking into compulsive drug use on a basis of vulnerability traits (based on a schematic model presented by Everitt 2014).

These core symptoms are sustained by modifications in the brain's neuronal circuits that mediate reward, motivation and behavioral flexibility. These changes include disturbed function and structural alterations of the fronto-striatal circuit (Volkow & Fowler 2000; Everitt & Robbins 2013; Volkow et al. 2013; Jentsch & Pennington 2014). Even though addiction was traditionally related solely to psychoactive substances, much of the core aspects of substance related disorders (i.e. impaired control; social impairment; engagement in the behavior despite negative consequences) are also present in non-substance related behavioral syndromes. Such behavioral syndromes arise from everyday activities (e.g. gambling disorder, compulsive buying, and problematic Internet use), and have been argued as behavioral addictions<sup>1</sup> that may share neuronal background with substance addictions (Albrecht, Kirschner, & Grüsser 2007; Chamberlain et al. 2015).

Investigating neural mechanisms related to behavioral addictions may contribute to the better understanding of the biological factors that prone some individuals to addiction, and neuronal patterns involved in sustaining addictive behavior (Grant, Brewer, & Potenza 2006; Chamberlain et al. 2015). In the next section, this thesis focuses on the conceptualization and neuroimaging findings about a possible behavioral addiction: problematic Internet use.

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<sup>1</sup> This perspective led to the inclusion of the category 'Substance Related and Addictive Disorders' in DSM-5. While only gambling disorder was classified as a behavioral addiction in DSM-5, 'Internet addiction' was listed as a condition requiring further study (Diagnostic and Statistical Manual Version 5, American Psychiatric Association, 2013).

### 1.2.1. Problematic Internet use

During the past decades, Internet has not only become our external memory and an essential media source for social life and entertainment, but such Internet-related activities<sup>2</sup> also have full potential to become addictive (Brenner 1997; Sparrow, Liu, & Wegner 2011). Various terms are available to describe maladaptive Internet use from “problematic Internet use” or “pathological Internet use” to “Internet addiction” or “Internet dependence” (Spada 2014). In this thesis, we adopt the term “problematic Internet use” is for general pathological use of the Internet (Davis 2001). It is still a matter of discussion whether problematic Internet use is an independent psychiatric disorder (Griffiths 2000; Mitchell 2000; Morahan-Martin 2005). However, it seems reasonable to interpret this phenomenon as a behavioral addiction that is a result of excessive use of certain activities available on the Internet. (Young 1999; Spada 2014; Laconi, Tricard, & Chabrol 2015).

Neuroimaging findings support the addiction theory frame as problematic Internet use has been related to changes in brain reward pathways usually associated with substance addiction (Dong, Huang, & Du 2011; Kuss & Griffith 2012). While the majority of the Magnetic Resonance Imaging (MRI) studies used functional paradigms, only few investigated possible structural correlates of excessive Internet use. However, structural and microstructural brain alterations have been already demonstrated in Internet addicted adolescents (relative to controls) in areas related to craving, motivation, and cognitive control (Yuan et al. 2011; Zhou et al. 2011). Furthermore, one study demonstrated negative associations between excessive Internet use with grey matter and altered functional connectivity in the fronto-striatal

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<sup>2</sup> It should be noted that online activities vary greatly on the role Internet play in them. For some offline activities, Internet is simply a new platform (such as online gambling and shopping). The Internet has also brought new dimensions to some offline activities (online gaming) while some activities can only take place online (such as information browsing and social networking) (Király et al. 2014). Related to such differentiation between Internet related activities, researchers started questioning whether there is a conceptual difference between generalized and specific maladaptive Internet use (Griffith et al. 2016).

circuitry in a large sample of healthy habitual user males (Kühn & Gallinat 2015).

A significant shortcoming of the previous brain imaging findings is related to the ongoing discussion whether gender differences are present in excessive Internet use. While clinical reports showed male predominance, others reported no significant gender difference or even female predominance (Shaw & Black 2008; Odaci & Çıkrıkçı 2014). Additionally, gender difference is present in the preferred activities online (Morahan-Martin & Schumacher 2000; Durkee et al. 2012). However, previous neuroimaging studies by-passed this question by focusing on males only or by using a gender matched approach (Yuan et al. 2011; Liu et al. 2010; Lin et al. 2012).

## 2. Technical background

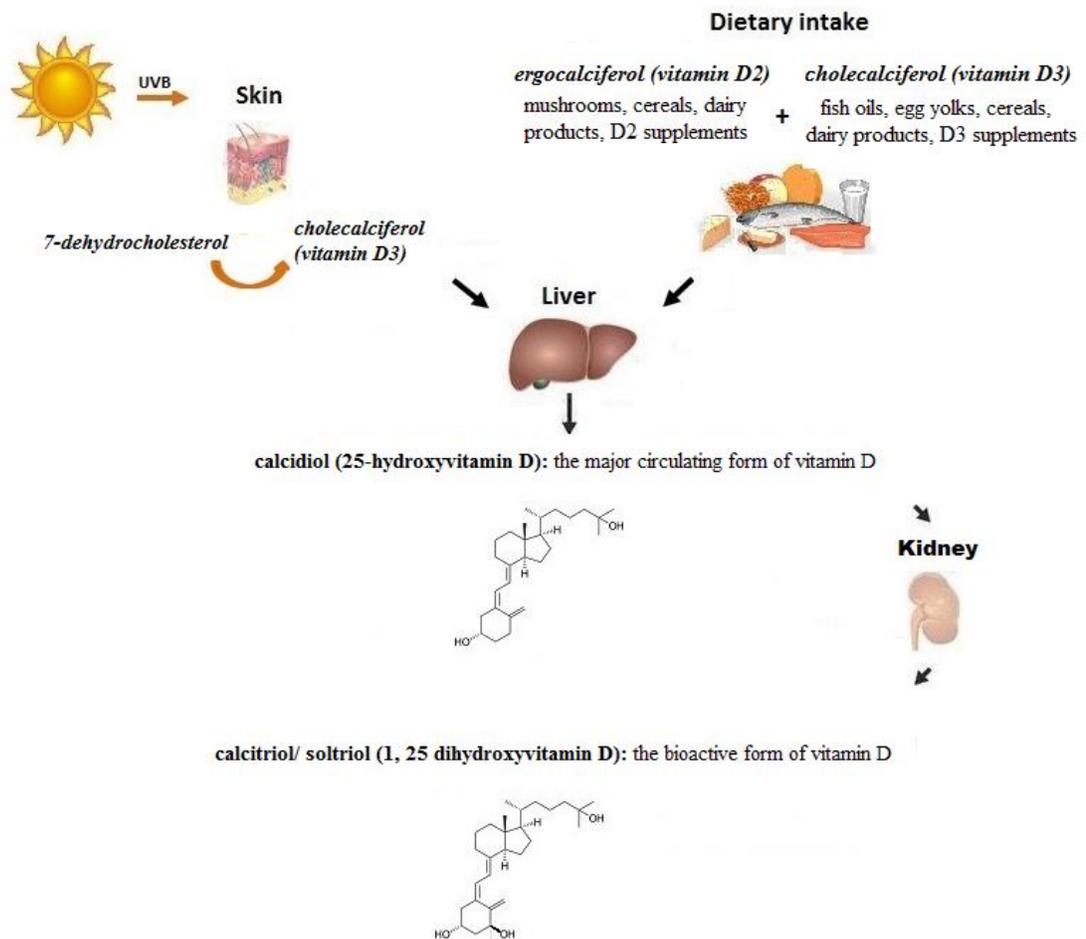
### 2.1. Vitamin D synthesis, measurement, recommendations

The main sources of vitamin D are sun exposure and vitamin D rich food (including fish oils, egg yolks, mushrooms, and dairy products) (Al Mheid et al. 2013). Vitamin D3 (cholecalciferol) is converted from vitamin D precursor 7-dehydrocholesterol as a photochemical reaction in the skin to ultraviolet B (UVB) irradiation. Additionally, dietary sources and supplementation for vitamin D3 are also available. Vitamin D2 (ergocalciferol) is produced by the irradiation of ergosterol, a membrane sterol found in Ergot fungus (available from dietary sources and D2 supplements).

To initiate the synthesis of the bioactive vitamin D hormone, calcitriol, one of the two biologically inactive forms of vitamin D is needed (D2 or D3). Whether vitamin D is synthesized in the skin or derived from diet, two hydroxylation steps are required to produce the active vitamin D hormone, calcitriol (or 1, 25-dihydroxyvitamin D (1, 25-OH D)). The first step occurs in the liver, where calciferol is hydroxylated to produce calcidol (25-hydroxyvitamin D (25(OH)D)), the major circulating form of vitamin D. 25(OH)D is then transported to the kidneys, where it is further hydroxylated by 1- $\alpha$ -hydroxylase, producing calcitriol. (DeLuca 1979; McGrath et al. 2001a; Kočovská et al. 2012; Al Mheid et al. 2013 (Figure 4).

Even though 1,25(OH)D is the biologically active form, its short half-life and narrow physiological range makes it unsuitable for clinical testing of actual vitamin D levels (Holick et al. 2011; Al Mheid et al. 2013). The only recommended vitamin D metabolite for evaluating vitamin D status is 25(OH)D, that is considered to be reliable measure of both vitamin D intake and vitamin D produced by sun exposure (Holick 2009). Since vitamin D levels are influenced by genetic factors, environmental factors (e.g. seasonal fluctuations of UVB levels, latitude), as well as individual behavior (e.g. dietary intake, outdoor activity, clothing) (McGrath et al. 2001b; Tangpricha et al. 2002; Karohl et al. 2010; Al Anouti et al. 2011), remarkable intra- and inter-individual differences may be present in serum 25(OH)D levels. There is no absolute consensus about normal range should be, however, latest

recommendations suggest 25(OH)D levels over 30 ng/ml to be sufficient, levels between 20–30 ng/ml to be insufficient and levels below 20 ng/ml to be deficient (Holick 2009).



**Figure 4.** Members of the vitamin D family, nomenclature and vitamin D synthesis (based on Al Mheid et al. 2013 and Kočovská et al. 2012)

## **2.2. Automated volumetric methods**

Manual tracing of brain regions by neuroanatomy experts used to be the golden standard. However, the increased need for investigating large MRI datasets also created the need for fast, automated user-independent approaches (Morey et al. 2009). Based on recent developments in MRI techniques, it became possible to investigate in vivo macroscopic structural variations of human neuroanatomy (such as volume, density, and connectivity) in an automated fashion (Galton & Hodges 2004; Kaufman & Nagrae-Poetscher 2004; Emerton et al. 2009). Compared to the manual tracing of brain structures, automated techniques do not require expert knowledge in neuroanatomy; making it less user independent are less time consuming. In general, these automated brain segmentation methods are based on 3D high-resolution T1 -weighted MR images with a good grey/white matter contrast, and segment those images into different tissue classes (grey matter, white matter, and cerebrospinal fluid) (Eggert et al. 2012). Based on this segmentation, various neuroanatomical measures can be calculated (such as cortical thickness, grey/white matter volume, and density) to investigate intra- and inter-individual differences in brain structure in clinical subpopulations and even within relatively homogeneous groups (e.g. healthy controls) (Hayano et al. 2009; Jansen et al. 2010; Orsi et al. 2011; Tavanti et al. 2012; Eggert et al. 2012; Heinzl et al. 2012; Borroni et al. 2015; Vriend et al. 2015; Sato et al. 2015; Darnai, et al. 2015; Yao et al.2016).

In the following subsections, two such automated volumetric methods are described and compared: automated MRI volumetry and voxel-based morphometry (VBM).

### **2.2.1. Automated MRI volumetry**

Here, automated MRI volumetry method is described as implemented in Freesurfer (Martinos Center for Biomedical Imaging, Harvard-MIT, Boston, USA), a free automated MRI brain segmentation software that is useful for both cortical and subcortical regions, and ideal for large datasets. During the automated segmentation protocol FreeSurfer (v4.0.5) “utilizes an affine rigid linear transformation and combines information about voxel intensity relative to a probability distribution for

tissue classes with information about the spatial relationship of the voxel to the location of neighboring structures obtained from a manually labeled atlas” (Morey et al. 2009). After several preprocessing steps, both cortical and subcortical segmentation are performed. The final automated neuroanatomical labeling of each voxel is based on both subject-specific measured values (i.e. intensity) and a subject-independent probabilistic atlas built from a training set (Gaussian classifier array (GCA) atlas). Once these labels are known, various anatomical measures can be calculated, including volumes of the pre-defined brain structures or cortical thickness (Fischl et al. 2002; 2004, Morey et al. 2009; Pardoe et al. 2009). A detailed description of the preprocessing steps and Freesurfer documentation can be assessed at <https://surfer.nmr.mgh.harvard.edu/fswiki/>.

### 2.2.2. Voxel based morphometry (VBM)

Voxel-based morphometry (VBM) is an alternative automated volumetric method that is particularly sensitive to region specific differences in a given tissue type while it also takes global morphological differences between subjects into account (Emerton et al. 2009).

An optimized VBM protocol can be performed with the freely available FMRIB's Software Library (FSL), for example (Good et al. 2001b). The image preprocessing process involves recurrent spatial normalization and tissue segmentation to increase the likelihood of any identified morphological findings to be tissue-related and not due to registration confounds. To identify within or between subject differences regarding tissue volume or relative tissue density VBM employs general linear model (GLM) framework (Emerton et al. 2009). VBM analysis with FSL involves the following steps: brain extraction (with FSL brain extraction tool (BET)), tissue-type segmentation (with FSL Automated Segmentation Tool (FAST)), study specific template creation, non-linear alignment of grey matter images to the study specific template space, smoothing, and statistical analysis. A detailed description of the FSL-VBM protocol can be found online at <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>.

### 2.2.3. Comparison of the two methods

In the interpretation of intra- or inter-individual structural brain differences it is very important to assure that the chosen volumetric method: (a) is able to precisely determine the exact amount of a given tissue in an MRI image (accuracy); and (b) that within-subject scan-rescan variability is minimal in volume measures (reliability) (Morey et al. 2009; Eggert et al. 2012). Both FreeSurfer and FSL show adequate accuracy and reliability comparable to manual segmentation (Fischl et al. 2002; Morey et al. 2009; Patenaude et al. 2011). As compared with other automated volumetric methods, FSL achieved the highest accuracy but demonstrated poor reliability while FreeSurfer showed the lowest accuracy, but high reliability (Eggert et al. 2012). For subcortical segmentation, FreeSurfer was found to be more accurate for hippocampus than FSL, while FSL was found to be superior to FreeSurfer in representing the shape of the amygdala (Morey et al. 2009).

Briefly, FreeSurfer and FSL are popular and free automated volumetric methods with various advantages and disadvantages. Despite some convergence, these two volumetric methods take different perspectives: while automated MRI volumetry (FreeSurfer) is based on the automatic segmentation of brain regions, VBM (FSL) follows a voxelwise approach (Good et al. 2001a; Morey et al. 2009; Keller & Roberts 2009; Perlaki et al. 2014). Accordingly, they enable different conclusions, cannot be taken as interchangeable and rather be conceptualized as complementary methods. The simultaneous use of these approaches can be particularly useful when investigating structural differences in regions characterized by greater degrees of anatomical variability (Testa et al. 2004; Giuliani et al. 2005; Kennedy et al. 2009; Emerton et al. 2009; Morey et al. 2009).

### 3. 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 VBM) 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 (Berthoz et al. 2014; van der Velde et al. 2015).** 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. To avoid possible influence of pathological factors, we examined young healthy adults with no history of chronic illness, neurological or psychiatric disorders.

**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 a large non-clinical sample of 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 the brain reward system in substance addictions, we hypothesized that regions of the fronto-striatal circuit (orbitofrontal cortex, caudate, putamen, nuclei accumbens) and amygdala -that provides important inputs to the striatum - would be associated with problematic Internet use (Volkow & Baler 2014).

## 4. Materials and methods

### 4.1. Alexithymia and vitamin D level

#### 4.1.1. Subjects

Healthy, right-handed Caucasian university students without history of substance abuse, chronic illnesses, neurological and psychiatric disorders, aged between 18 and 30 years were recruited via notice boards advertisement placed at the University of Pécs. Out of the 91 subjects contacted our recruitment team two subjects were excluded based on self-reported mental health problems identified by our life-style and health questionnaire (one subject with a known personality disorder and another one with symptoms of clinical depression). The final sample group thus comprised 89 subjects (59 females and 30 males). Mean age was 23.1 years ( $SD = 2.1$ ). No subject was taking vitamin D supplements. Blood sampling and administration of the self-reported questionnaires were carried out during the winter of 2011–2012. The study was approved by the Local Ethics Committee and all participants gave written informed consent prior to participating.

#### 4.1.2. Questionnaires

Alexithymia was measured by the Hungarian version of the 20-item Toronto Alexithymia Scale (TAS-20) (Cserjési, Luminet, & Lénárd 2007). TAS-20 items assess difficulties identifying and describing emotions, and tendencies for externally focused attention (e.g.: *“When I am upset I don’t know if I am sad, frightened, or angry.”*; *“I prefer to just let things happen rather than to understand why they turned out that way.”*; *“It is difficult for me to reveal my innermost feelings, even to close friends.”*).

Based on TAS-20 total scores (ranging between 0-100) the following subgroups were defined: non-alexithymia ( $\leq 51$ ), possible alexithymia (52-60) and alexithymia ( $\geq 61$ ) (Bagby & Taylor 1997). TAS-20 is considered to exhibit good internal

consistency and test-retest reliability (Bagby, Parker, & Taylor 1994). Cronbach's  $\alpha$  was .79 in our study indicating acceptable reliability.

Actual level of depression was measured by the Hungarian version of Beck Depression Inventory (BDI) (Beck, Steer, & Brown 1996; Kopp & Fóris 1993) while actual level of anxiety was measured by the Hungarian version of Spielberger State Anxiety Inventory (STAIS) (Spielberger et al. 1983; Sipos & Sipos 1983). Cronbach's  $\alpha$  was .80 for BDI and .92 for STAIS. To assess handedness, we used the Edinburgh Handedness Inventory (EDI) (Oldfield 1971). Additionally, subjects also completed an exploratory questionnaire on lifestyle factors, mental and physical health.

#### 4.1.3. Serum blood analysis

Fasting blood samples were analyzed for serum 25(OH)D with an automated electrochemiluminescence immunoassay measuring both vitamin D3 and D2. Five ml venous blood sample was collected from each subject using a Vacutainer plain tube which after complete blood coagulation was centrifuged at 3000 RPM (rounds per minute, approximately 1500g) for 10 minutes to separate serum from the clot. Vitamin D levels were measured on Elecsys 2010 analyzer with Elecsys Vitamin D Total kit (Roche Diagnostics) by the accredited diagnostic laboratory of Institute of Laboratory Medicine, University of Pécs, Faculty of Medicine.

#### 4.1.4. Statistical analysis

Statistical analyses were performed using IBM SPSS 20.0 software package (IBM Corp., Armonk, NY). As tests of normality showed that all psychological variables (TAS-20, BDI, and STAIS scores) significantly differ from normal distribution, non-parametric Spearman rank correlation tests were used for calculating correlations. First, correlation coefficient was calculated between TAS-20 scores and 25(OH)D levels. To control for possible confounders, a multiple linear regression analysis was performed where TAS-20 was defined as dependent while 25(OH)D level, age, and gender as independent variables. In a next step, BDI and STAS scores were also

entered as additional independent variables in the model. All assumptions of multiple linear regression were satisfied, as judged by testing for linearity, normality assumptions of the residues, outliers, independence of errors, homoscedasticity and multi-collinearity (Chan 2004).

## **4.2. Problematic Internet use and the brain reward system**

### 4.2.1. Subjects

Caucasian right-handed healthy female university students without history of substance abuse, chronic illnesses, neurological and psychiatric disorders, aged between 18 and 30 were recruited based on advertisements placed at the local university. Eighty-two females met the inclusion criteria and took part in our study. Mean age was 22.83 (SD = 2.3), and all participants use the Internet on a daily basis. The study was approved by the Local Ethics Committee and conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent prior to participating.

### 4.2.2. Questionnaires

Without clear diagnostic criteria, it is highly recommended to measure excessive Internet use with a multidimensional and continuous questionnaire without using unclear cut-off scores (Ko et al. 2005). Therefore, we used Problematic Internet Use Questionnaire (PIUQ), a validated self-report scale with good reliability and validity characteristics (Demetrovics, Szeredi, & Rózsa 2008). PIUQ was created based on the factor analysis and psychometric analysis of the original and modified items of Young's Internet Addiction Test (Young 1998). A confirmatory factor analysis verified the three factor model of the questionnaire (Koronczai et al. 2011). Each subscale contains six items and respondents answer each item using a 5-point scale, ranging from 1 to 5. Cronbach's  $\alpha$  was .89 in our study indicating good reliability.

1. **Obsession subscale** refers to obsessive thinking about the Internet (daydreaming, rumination, and fantasizing), and withdrawal symptoms caused by the lack of Internet use (anxiety, depression). (*“How often do you feel tense, irritated, or stressed if you cannot use the Internet for as long as you want to?”*)
2. **Neglect subscale** contains items about neglecting everyday activities, social life, and essential needs. (*“How often do you spend time online when you’d rather sleep”?*)
3. **Control disorder** subscale reflects difficulties in controlling time spent on the Internet. (*“How often do you realize saying when you are online, ‘just a couple of more minutes and I will stop’?”*)

Additional questions were administered to assess hours weekly spent on the Internet. To exclude possible neurological and psychiatric disorders, substance abuse and chronic illnesses, subjects also completed an exploratory questionnaire about lifestyle factors, mental and physical health. Similar to our previous study, we assessed alexithymia with the Hungarian version of the 20-item Toronto Alexithymia Scale (TAS-20) (Cserjési, Luminet, & Lénárd 2007), depression with the Hungarian version of Beck Depression Inventory (BDI) (Kopp & Fóris 1993), and trait anxiety with the Hungarian version of Spielberger Anxiety Inventory for trait anxiety (STAIT) (Sipos & Sipos 1983). Cronbach's  $\alpha$  was .82 for TAS, .85. for BDI, and .89 for STAIT respectively. Handedness was measured with Edinburgh Handedness Inventory (EDI) (Oldfield 1971).

### 4.2.3. MRI examinations

MRI measurements were performed on a whole-body 3 Tesla MR scanner (Siemens Magnetom Trio Tim System, Siemens AG, Erlangen, Germany) with a 12-channel head coil. For the volumetric analysis a T1 weighted axial reformation of the isotropic sagittal magnetization-prepared rapid acquisition with gradient echo (MPRAGE) images were used: FoV = 256x256<sup>2</sup> mm, TR = 2530 ms, TE = 3.37 ms, TI = 1100 ms, slice thickness = 1 mm, slice number = 176, FA = 7°, bandwidth = 200 Hz/pixel, 256x256 matrix.

### 4.2.4. MRI data post-processing evaluation

#### 4.2.4.1. Volumetric analysis

Freesurfer 4.5.0 was used for cortical reconstruction and volumetric segmentation of the images (<http://surfer.nmr.mgh.harvard.edu/>) to assess volumes of bilateral amygdala, nucleus accumbens, putamen, caudate and orbitofrontal cortex. Freesurfer's semi-automatic anatomical processing scripts (autorecon1, 2 and 3) were executed on all subjects' data. Manual verifications were performed in case of every subject after each script and error corrections were applied wherever it was indicated (<http://surfer.nmr.mgh.harvard.edu/fswiki/RecommendedReconstruction/>).

The volume-based stream is designed to preprocess MRI volumes and label subcortical tissue classes. All stages of the stream are fully described by Fischl et al. (2002). The final segmentation is based on a probabilistic atlas and the subject-specific measured values. Visual analysis of the images identified no brain abnormalities. Head correction was done using the statistical method: intracranial volume (ICV) was entered as additional independent variable (Perlaki et al. 2014).

#### 4.2.4.2. *Voxel-based morphometry*

VBM was performed with FSL-VBM (<http://www.fmrib.ox.ac.uk/fsl>) to assess grey matter volume of the above described regions. An ‘optimised’ VBM protocol (Good et al. 2001a) was carried out with FSL tools (Smith et al. 2004). First, structural images were brain-extracted using BET (Smith 2002). Next, tissue-type segmentation was carried out using FAST (Zhang, Brady, & Smith 2001). The resulting grey matter partial volume images were then aligned to MNI152 standard space using non-linear registration (Andersson, Jenkinson, & Smith 2007). The resulting images were averaged together with their respective mirror images to create a left–right symmetric study-specific grey matter template. The registered partial volume images were then modulated (to correct for local expansion or contraction owing to both affine and nonlinear components of the registration) by dividing by the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

#### 4.2.5. Statistical analysis

Statistical analyses for demographic data, questionnaires, and volumetric analyses were performed using IBM SPSS 20.0 software package (IBM Corp., Armonk, NY). Non-parametric Spearman rank correlation tests were used for calculating correlations. For reliability testing, Cronbach's alpha coefficients were also calculated for all questionnaires.

In the volumetric analysis, the following structures were investigated separately: bilateral amygdala, nuclei accumbens, putamen, caudate, and orbitofrontal cortex (OFC). To test whether problematic Internet use is associated with volumetric alterations in the reward system, multiple linear regression models were created for each structure as a dependent variable with all three subscales of PIUQ separately as an independent variable while controlling for age and intracranial volume (ICV). All assumptions of multiple linear regression were satisfied, as judged by testing for linearity, normality assumptions of the residues, outliers, independence of errors, homoscedasticity, and multicollinearity (Chan 2004).

VBM statistical analyses were conducted using FSL-VBM. To test association between above described regions and each subscale of PIUQ, voxelwise general linear models (GLM) were applied using permutation-based non-parametric testing (5000 permutations), correcting for multiple comparisons across space. Results were considered significant for  $p < .05$ , corrected for multiple comparisons using “threshold-free cluster enhancement” (TFCE), which avoids making an arbitrary choice of the cluster-forming threshold, while preserving the sensitivity benefits of clusterwise correction (Smith & Nichols 2009). Similar to volumetric analyses, head correction was done by entering ICV to GLM as an independent variable. Age was also included as a control variable for all comparisons.

## 5. Results

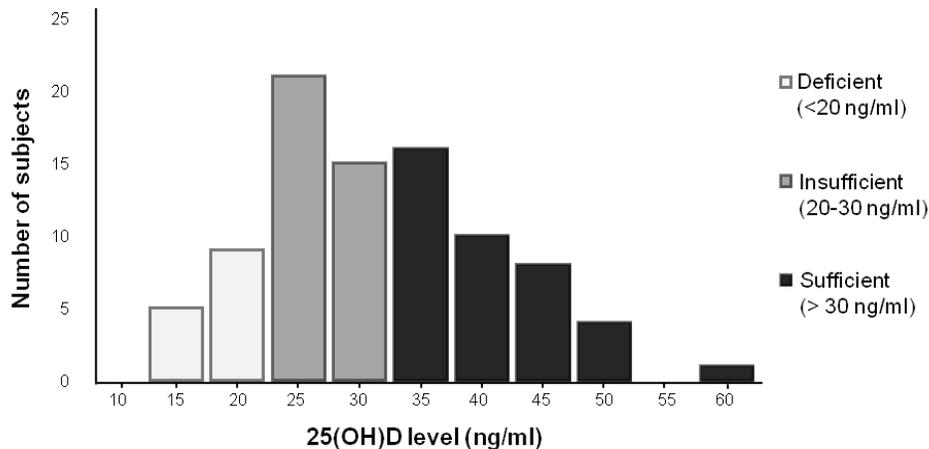
### 5.1. Alexithymia and vitamin D level

#### 5.1.1. Descriptive statistics

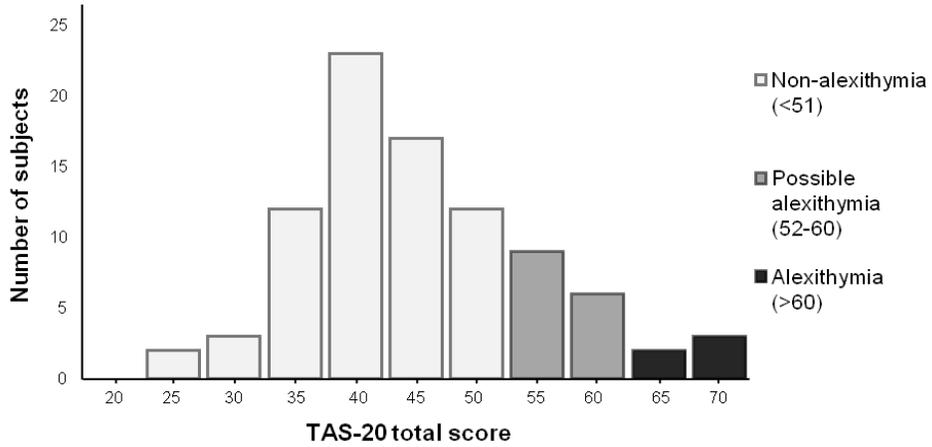
Mean 25(OH)D level was 28.9 ng/ml (SD = 9.4) (range: 13.2–59.2 ng/ml). Out of the 89 subjects, 14 (15.7%) had deficient (<20 ng/ml), 36 (40.4%) had insufficient (20–30 ng/ml), and 39 (43.8%) had sufficient (>30 ng/ml) 25(OH)D levels (Figure 5).

Mean TAS-20 score was 43.2 (SD = 9.7; range: 24–68). Based on TAS-20 scores 69 subjects (77.5%) were classified as non-alexithymic, 15 subjects (16.9%) as with possible alexithymia and five (5.1%) with alexithymia (Figure 6).

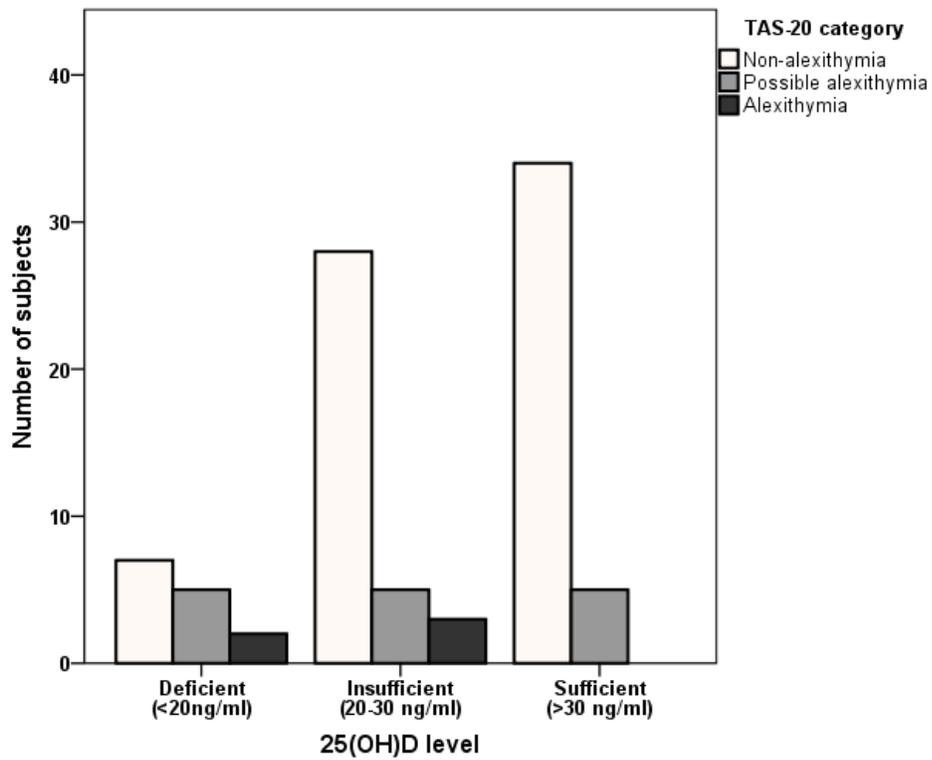
Spearman's rank correlation analysis revealed a marginally insignificant negative correlation between TAS-20 score and 25(OH)D levels ( $r_s = -.20$ ;  $p = .06$ ) (Figure 7 and 8).



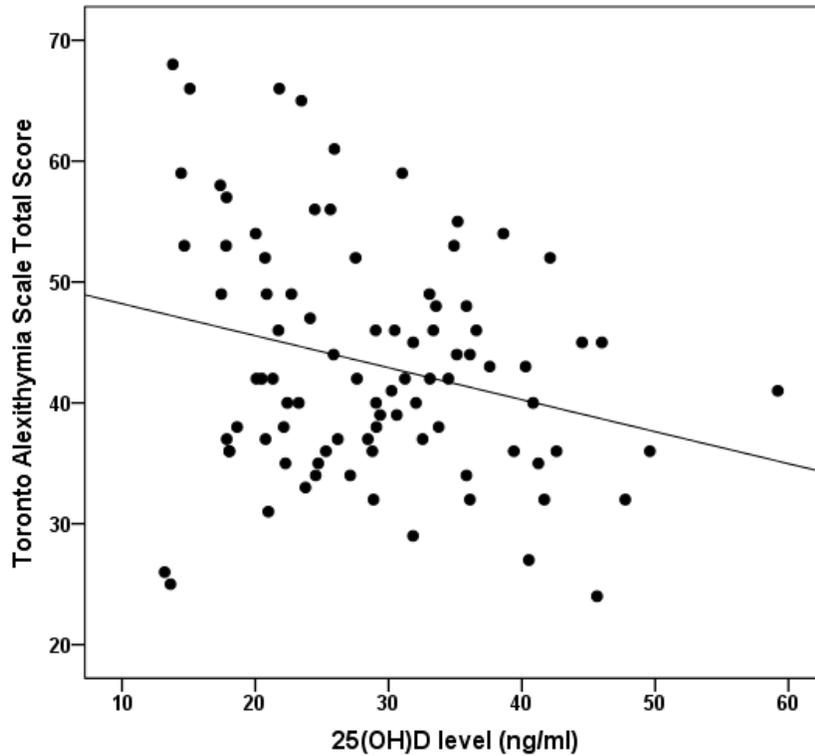
**Figure 5.** Distribution of 25(OH)D levels. Categories of deficient, insufficient, and sufficient vitamin D are indicated in light, medium, and dark grey, respectively.



**Figure 6.** Distribution of TAS-20 scores. Categories of non-alexithymia, possible alexithymia, and alexithymia are indicated in light, medium and dark grey, respectively.



**Figure 7.** Distribution of subjects according to the three TAS-20 and the three vitamin D categories.



**Figure 8.** Scatterplot representing the relationship between TAS-20 total score and 25(OH)D levels.

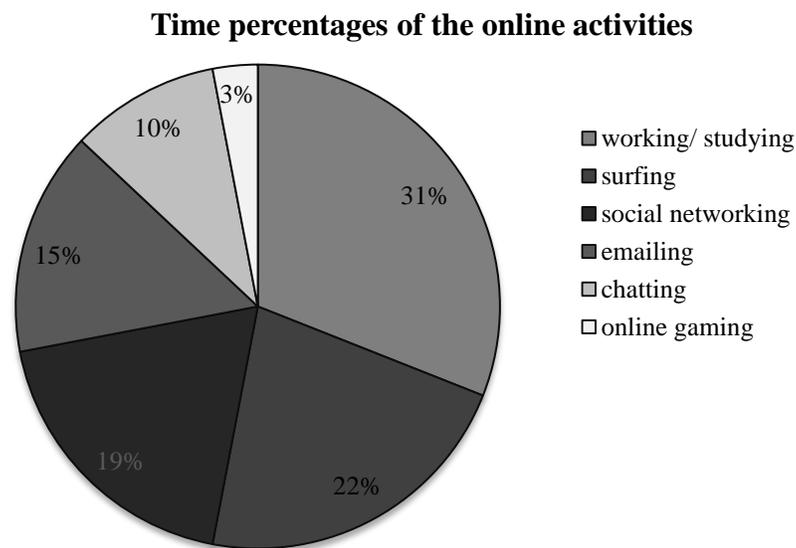
### 5.1.2. Multiple linear regression

A control for age and gender in the multiple linear regression model resulted in a significant 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 in this model. The inclusion of BDI and STAIS scores as additional independent variables in the model did not essentially change the relationship between 25(OH)D level and TAS-20 score ( $\beta = -.21$ ;  $p = .03$ ). In this model both BDI and STAIS scores showed a significant relation with TAS-20 ( $\beta = .26$ ;  $p = .01$  and  $\beta = .28$ ;  $p = .008$ , respectively). Both multiple linear regression models significantly predicted TAS-20 score ( $R^2 = .05$ ;  $p = .05$  and  $R^2 = .25$ ;  $p = .0001$ , respectively). Additional correlation analysis revealed the relation of 25(OH)D level with BDI, STAIS, and age to be non-significant.

## 5.2. Problematic Internet use and the brain reward system

### 5.2.1. Descriptive statistics

Participants spent 12.85 hours (SD = 9.33; range: .83-35) on the Internet per week on average. They used 31% of their time on the Internet on working/or studying, 22% on surfing, 19% on social networking, 15% on corresponding to emails, 10% on chatting and only 3% on online games (Figure 9).



**Figure 9.** Time percentages on the activities spent online on an average week.

Mean score for the PIUQ was 28.71 (SD = 7.76; range: 18-53). Mean score for the PIUQ subscales were 8.39 (SD = 2.28; range 6-16) for Obsession, 1.13 (SD = 2.28; range: 6-21) for Neglect and 1.18 (SD = 2.28; range 6-20) for Control Disorder. The total time spent with online activities was significantly correlated with Obsession ( $r_s = .291$ ;  $p < .01$ ), Neglect ( $r_s = .322$ ;  $p < .01$ ) and Control Disorder ( $r_s = .325$ ;  $p < .01$ ).

Spearman's rank correlation analysis revealed a significant positive association between PIUQ total score with STAIT total score, and between PIUQ Neglect subscale with BDI and STAIT total score. Age and TAS-20 showed no significant association with PIUQ total score and PIUQ subscales (Table 1).

	1	2	3	4	5	6	7	8
1 PIUQ Total score								
2 PIUQ Obsession	<b>.732**</b>							
3 PIUQ Neglect	<b>.874**</b>	<b>.496**</b>						
4 PIUQ Control Disorder	<b>.885**</b>	<b>.517**</b>	<b>.675**</b>					
5 Age	.081	.096	.025	.088				
6 TAS-20 Total Score	.182	.101	.191	.139	-.111			
7 BDI Total Score	.177	.102	<b>.300**</b>	.083	-.023	<b>.464**</b>		
8 STAIT Total Score	<b>.275*</b>	.159	<b>.364**</b>	.180	-.114	<b>.495**</b>	<b>.712**</b>	

**Table 1** Spearman rank-correlation coefficients between PIUQ Total Score, PIUQ subscales with TAS, BDI, and STAIT Total Scores; \* $p < .05$ ; \*\* $p < .01$

### 5.2.2. MR volumetry

Significant positive associations were found between Control disorder and both left and right putamen and between Obsession and right nucleus accumbens. Obsession also showed a significant negative association with both left and right OFC, while Neglect was negatively related to left OFC (see results for all investigated regions in Table 2).

Investigated brain regions		Predictor								
		Obsession			Neglect			Control Disorder		
		$\beta$	$R^2$	F	$\beta$	$R^2$	F	$\beta$	$R^2$	F
Left-sided structures	Amygdala	.188	.162	6.234	.050	.129	4.995	.082	.133	5.150
	Accumbens	.210	.085	3.516	.102	.051	2.453	.047	.043	2.199
	Caudatum	.118	.132	5.100	.067	.122	4.760	.178	.150	5.772
	Putamen	.160	.140	5.413	.093	.123	6.821	<b>.229*</b>	.169	6.486
	OFC	<b>-.226*</b>	.120	4.688	<b>-.232*</b>	.124	4.816	-.125	.084	3.491
Right-sided structures	Amygdala	.197	.144	5.544	.027	.105	4.171	.000	.104	4.146
	Accumbens	<b>.238*</b>	.105	4.165	.113	.061	2.739	.156	.072	3.101
	Caudatum	.065	.126	4.906	.023	.123	4.774	.108	.134	5.182
	Putamen	.194	.182	7.012	.124	.160	6.133	<b>.237*</b>	.202	7.835
	OFC	<b>-.297**</b>	.238	9.433	-.056	.151	5.809	-.072	.153	5.891

**Table 2.** Association of the investigated brain structures with Problematic Internet Use subscales controlled for ICV and age.  $df = 81$  in all models; \* $p < .05$ ; \*\* $p < .01$

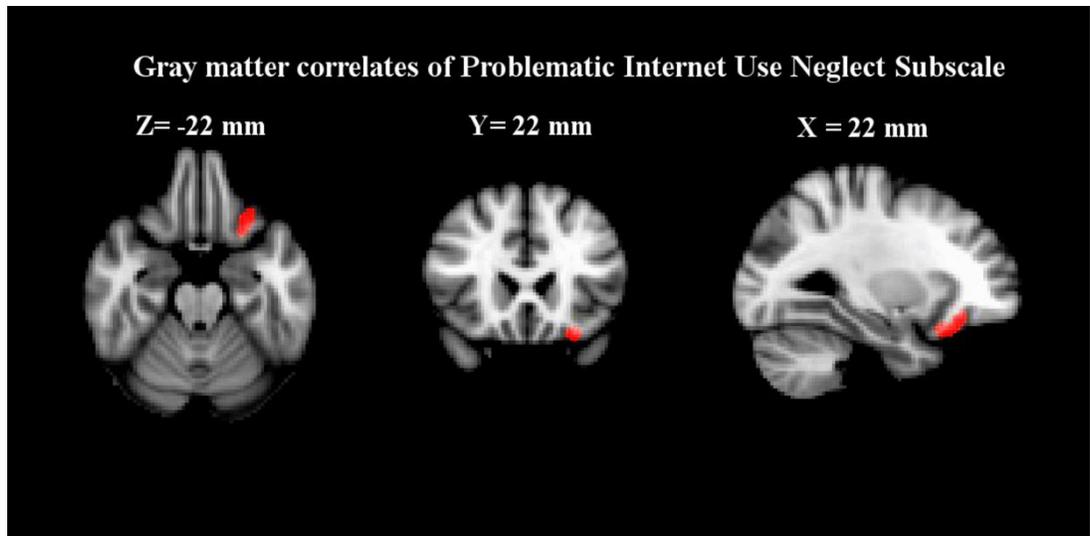
To test its possible confounding effect, average time spent online was also entered to each model as an additional independent variable. However, it did not essentially change the significant associations between PIUQ subscales and the volume of the investigated regions (Table 3).

		Predictor								
		Obsession			Neglect			Control Disorder		
Investigated brain regions		$\beta$	$R^2$	F	$\beta$	$R^2$	F	$\beta$	$R^2$	F
Left-sided structures	Amygdala	.181	.215	5.260	.031	.141	4.321	.060	.144	4.395
	Accumbens	.212	.075	2.641	.053	.032	1.659	<b>.242*</b>	.103	3.324
	Caudatum	.121	.126	3.922	.076	.117	3.680	.192	.149	4.533
	Putamen	.161	.130	4.027	.097	.113	3.580	<b>.238*</b>	.161	4.889
	OFC	<b>-.226*</b>	.109	3.471	<b>-.234*</b>	.113	3.575	-.127	.73	2.587
Right-sided structures	Amygdala	.196	.134	4.131	.022	.095	3.122	-.006	.094	3.111
	Accumbens	<b>.242*</b>	.103	3.324	.126	.059	2.264	.172	.073	2.588
	Caudatum	.064	.115	3.637	.022	.111	3.540	.108	.123	3.836
	Putamen	.196	.176	5.322	.133	.154	4.693	<b>.251*</b>	.201	6.080
	OFC	<b>-.297**</b>	.228	6.984	-.055	.140	4.301	-.072	.142	4.361

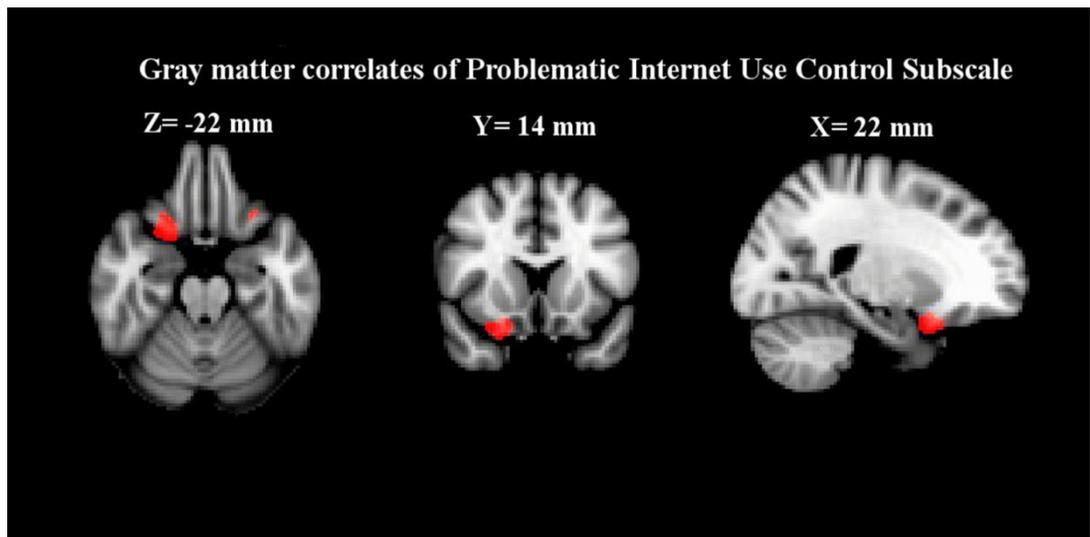
**Table 3.** Association of the investigated brain structures with Problematic Internet Use subscales controlled for ICV, age, and average hours spent online.  $df = 81$  in all models; \* $p < .05$ ; \*\* $p < .01$

### 5.2.3. Voxel Based Morphometry (VBM)

Subscales of PIUQ were used separately to predict the absolute amount of grey matter of the investigated brain regions in GLM while controlling for intracranial volume and age. A significant negative correlation was found between the absolute amount of grey matter in left OFC with Neglect (Figure 10.), and between the absolute amount of grey matter in right OFC and Control disorder (Figure 11.), while OFC showed no significant association with Obsession. Other regions of interest were not predicted significantly by any of PIUQ subscales.



**Figure 10.** Voxelwise analysis of the grey matter of the OFC using the data of 82 female including Neglect, age and ICV as independent variables in the statistical model. Red voxels are demonstrating a significant negative correlation between Neglect subscale and grey matter in left OFC (corrected  $p < .05$ ). The background image is the MNI152 standard space T1 template. *X*-, *Y*- and *Z*-values indicate the MNI slice coordinates in millimeter. Images are shown in radiological convention.



**Figure 11.** Voxelwise analysis of the grey matter of the OFC using the data of 82 female including Control subscale, age and ICV as independent variables in the statistical model. Red voxels are demonstrating a significant negative correlation between Control subscale and grey matter in right OFC (corrected  $p < .05$ ). The background image is the MNI152 standard space T1 template. *X*-, *Y*- and *Z*-values indicate the MNI slice coordinates in millimeter. Images are shown in radiological convention.

## **6. Discussion**

### **6.1. Alexithymia and vitamin D level**

To our knowledge, this is the first study exploring the relationship between vitamin D and alexithymia in healthy subjects. Previous studies on the relation between vitamin D and mental health mostly include patients with depression, autism, and schizophrenia (Eyles, Burne, & McGrath 2011; 2013). Prior to our study, only two studies have assessed the relation between vitamin D and psychological functions in a non-clinical sample. One found a weak association between childhood behavioral problems and low levels of vitamin D while the another study found 1,25(OH)D level to be associated with more extrovert and open behavior in adults (Ubberhorst et al. 2011; Tolppanen et al. 2012). Controlling for age and gender in this study we found a significant association between alexithymia and vitamin D level. Neither depression nor anxiety was associated with vitamin D in our sample, suggesting a more specific link with impaired emotional processing.

Vitamin D level is primarily determined by exposure to sunlight and secondarily by factors influencing vitamin D synthesis in the body. Wintertime vitamin D level was shown to be associated with genetic factors (Orton et al. 2008; Karohl et al. 2010). Our finding of a correlation between the actual level of vitamin D and alexithymia may be surprising given that previous studies generally did not find a gradual association between vitamin D level and psychological functions in cross-sectional studies (Parker & Brotchie 2011). However, longitudinal studies assessing maternal, perinatal, and early childhood vitamin D markers found a link between low vitamin D levels and an increased risk for psychiatric conditions manifesting in later life such as autism and schizophrenia (Cannell 2008; Grant & Soles 2009; McGrath et al. 2010; Grant & Cannell 2013; Cannell & Grant 2013). An acute effect of vitamin D on the level of alexithymia (or an opposite causal relationship) in this study cannot be entirely excluded but we deem it unlikely given that alexithymia is considered as a stable personality trait (Martínez-Sánchez et al. 2003). Instead, we suggest that the correlation between alexithymia and vitamin D to be regarded as a

trait-like relationship between two conditions which are rather stable longitudinally (i.e. alexithymia and wintertime vitamin D level) (Martínez-Sánchez et al. 1998; Orton & Ebers 2011). Such a correlation may be interpreted as a reflection of early life vitamin D deficiency determining life-long alexithymia. This seems to be plausible given that alexithymia appears to be highly comorbid with autism, a pervasive developmental spectrum disorder that is also thought to be related to low perinatal vitamin D levels (Hill, Berthoz & Frith 2004; Cannell 2008). Furthermore, higher incidence of alexithymia in ASD may be responsible for emotional impairments previously associated with autism itself (Bird et al. 2010; Bird, Press, & Richardson 2011; Cook et al. 2013).

Generally, a distinction is made between primary and secondary alexithymia. The former is regarded as a stable personality trait while the latter is more transient occurring in response to severe and chronic medical illness (Freyberger 1977). To minimize secondary alexithymia here, we included young adults free of neurologic, psychiatric, or other chronic disorders based on our questionnaires.

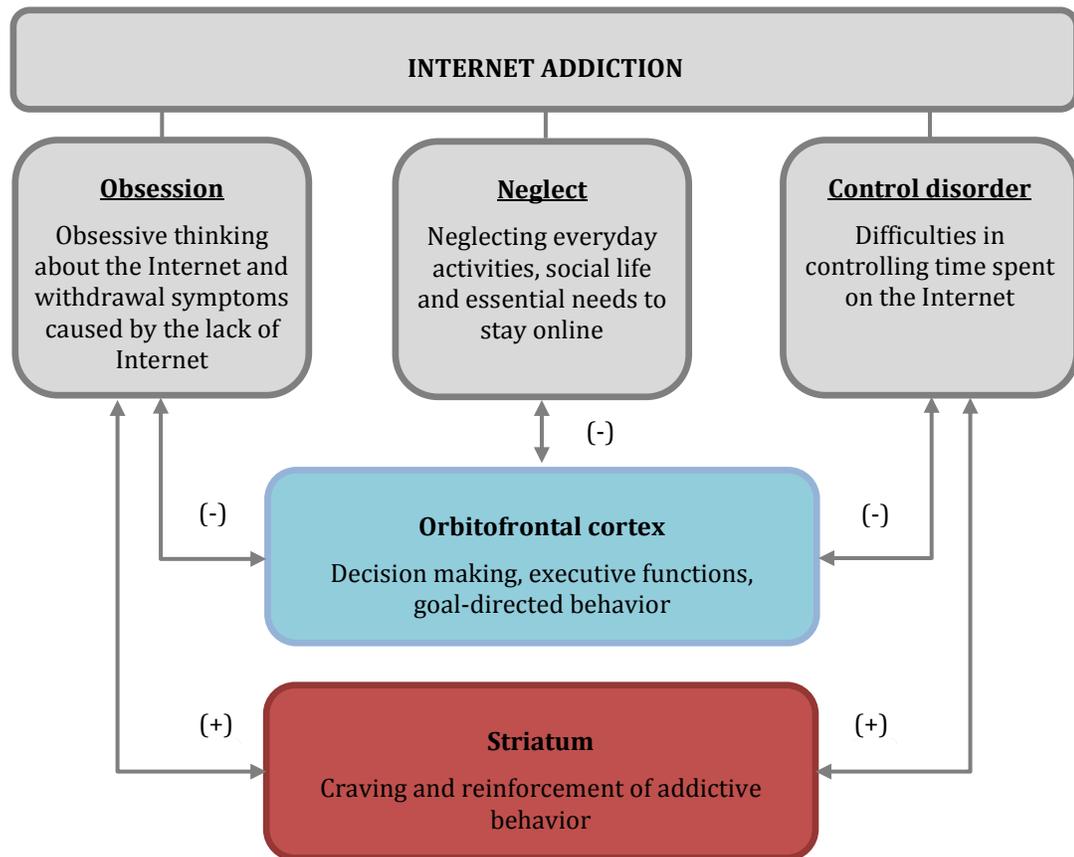
Studies in elderly indicate cognitive decline and depression to be associated with actual levels of vitamin D (Wilkins et al. 2006; Balion et al. 2012). Baseline vitamin D levels in elderly also predicted decline in cognition within a few years (Annweiler et al. 2012a; 2012b). Autism and schizophrenia, at the same time, are generally related to perinatal and early childhood vitamin D deficiency (Grant & Soles 2009; McGrath et al. 2010; Hossein-Nezhad & Holick 2013). There is substantial controversy as to whether middle-life depression is related to vitamin D (Parker & Brotchie 2011). Overall, the association between actual vitamin D levels and mental functions seems to be more pronounced with advancing age. Here we report a correlation between actual levels of vitamin D and alexithymia in young healthy university students indicating that an association between disturbed emotional processing and low vitamin D levels is already present in young healthy adults.

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 those patient groups, and whether it is affected by comorbidity factors (Pinard et al. 1996; Honkalampi et al. 2001; Bewley et al. 2005; Evren et al. 2008; Bordini et al. 2008; Craparo 2011; Mowry et al. 2012, Eyles, Burne & McGrath 2013; Eserian 2013; Scimeca et al. 2014; Holló, Clemens, & Lakatos 2014; Afzal, Bojesen & Nordestgaard 2014). A further step may explore whether the relationship between hypovitaminosis D and alexithymia is reflected in brain morphology and functional brain alterations. Related neuroimaging research may either focus on vitamin D related structural variations in overall brain volume or specific brain areas related to impaired emotion processing (Grabe et al. 2014; Berthoz et al. 2014; Plózer et al. 2015; Annweiler et al. 2015; Goerlich-Dobre et al. 2015). Investigations in this research field may contribute to more efficient therapy strategies in patient groups with difficulties in understanding affective experiences (Vanheule, Verhaeghe, & Desmet 2011).

## **6.2. Problematic Internet use and the brain reward system**

In this study, structural correlates of subclinical Internet addiction tendencies were demonstrated in the brain reward system in a large group of habitual Internet user females. We assessed a multidimensional continuous measure of problematic Internet use, PIUQ (Demetrovics, Szeredi, & Rózsa 2008). The three subscales of PIUQ capture different signs of addictive tendencies that are often present in behavioral and chemical addictions. Since PIUQ subscales represent different aspects of addictive symptoms that may have a distinguishable role in the brain reward system; we decided to investigate their potential effect separately.

To identify structural brain changes MRI volumetry and VBM were used. As highlighted earlier, these volumetric methods follow different approach and therefore enables different conclusions: while volumetry is based on automatic segmentation of brain regions, VBM provides “voxelwise overview of regional morphological effects” (Morey et al. 2009; Good et al. 2001a; Keller & Roberts 2009; Perlaki et al. 2014). Previous structural neuroimaging studies about Internet addiction used the VBM approach. For example, a VBM study in Internet addicted adolescents compared to normal controls found lower grey matter density in areas related to craving, motivation, emotional behavior regulation (left anterior cingulate cortex, left posterior cingulate cortex, left insula, and left lingual gyrus) (Zhou et al. 2011). Here, we demonstrated structural brain changes in the reward system 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 OFC to be associated with PIUQ subscales. The significant negative associations between the absolute amount of grey matter of bilateral OFC and PIUQ subscales were also present in the VBM analysis. These relationships remained significant even after controlling for average hours spent online, suggesting that the effect of addictive tendencies are not simply the result of the amount of time on the world wide web (Chou et al. 2005).



**Figure 12.** Summary of our findings. Figure shows how the three aspects of Problematic Internet use is related to the grey matter volume of the prefrontal (orbitofrontal) and subcortical regions (striatum) of the brain reward system in a large sample of habitual Internet user females

According to our results, structural brain changes in regions of the cortico-striatal network are present in healthy females (Figure 12). It is difficult to relate our findings to previous neuroimaging reports about Internet addiction since no study has been conducted in females in this specific field. However, craving and reinforcement of addictive behavior has already been related to functional changes in the nucleus accumbens in long term drug users and online gaming addict males (Kalivas & Volkow 2005; Ko et al. 2009). In our study, grey matter volume of right nucleus accumbens was positively related to Obsession, the preoccupation with Internet related thoughts. Accordingly, it may be hypothesized that our result is a structural correlate of Internet craving. Functional changes in the striatum have already been related to misuse of the Internet, as putamen is revealed to be the mostly involved subcortical region of the brain reward system with decreased

functional connectivity and reduced cortical thickness (Hong et al. 2013a; 2013b). At the cellular level, Internet addicts have reduced dopamine D2 receptor availability in the right putamen (Kim et al. 2011). In line with previous findings, structural changes in putamen related to Control disorder may reflect a deficit of the reward processing mediated by the cortico-striatal network related to compulsive Internet use (Jung et al. 2013).

The OFC plays an essential role in executive functions, emotional regulation and motivation, and has been linked to the compulsive aspect of addiction (Goldstein & Volkow 2002; Volkow, Fowler, & Wang 2003). Bilateral atrophy in OFC was already found in problematic Internet user teenager boys compared to controls (Yuan et al. 2011). In our study the negative association between grey matter of OFC and subscales of PIUQ was proved by both volumetry and VBM. Out of the PIUQ subscales, Neglect was related to both decreased volume and absolute amount of grey matter of the left OFC. This may be a result of decreased sensitivity for biological rewards and decreased control over Internet use. While previous studies with Internet addicted males suggested the right OFC to play a particularly important role in Internet addiction (Hong et al. 2013a), our results highlights the involvement of the left OFC in females. To find out whether there are hemisphere and gender-related differences in the role of OFC in Internet addiction, future studies are needed (Dom et al. 2005).

Taken together, our results suggest that problematic Internet use has structural brain correlates in the reward system in healthy habitual Internet user females. Since similar associations have been identified in the fronto-striatal circuit in habitual Internet user males (Kühn & Gallinat 2015), our findings can be interpreted as a proof for morphological brain alterations related to excessive Internet use in both genders. However, possible gender related associations between brain morphology and Internet habits should be further investigated as sexual dimorphism in the brain structure can contribute to behavioral differences (Mutlu et al. 2013; Sun et al. 2015).

One shortcoming of our finding is due to the cross-sectional nature of the study, therefore, the directionality of the relationship cannot be ascertained. The observed associations between Problematic Internet use and brain reward system may be explained two ways. Pre-existing structural alterations in the brain reward system may result in higher vulnerability to Internet addiction. Alternatively, problematic Internet use alone may lead to structural brain alterations as well (Kuss & Griffith 2012). Longitudinal studies are highly needed to test whether these structural correlates are the result of overall addictive tendencies or specific to problematic Internet use. Another challenge for future studies is to explore commonalities and discrepancies between generalized pathological Internet use (problematic Internet use) and specific pathological Internet use (Internet gaming addiction, social networking etc.) by comparing larger samples of problematic Internet use subtypes (Király et al. 2014; D'Hondt, Billieux & Maurage 2015; Griffith et al. 2016). Identifying the shared neuropsychobiological processes between problematic Internet use and other type of addictions could facilitate the development of more effective treatments for addictions (Grant, Brewer & Potenza 2006; Levy 2013; D'Hondt, Billieux, & Maurage 2015). On the general level, addiction should be treated as a brain disease for which biological, behavioral and social-context components are equally important (Levy 2013).

## 7. Summary

Successful emotion and behavior regulation are both fundamental for mental health and adaptive behavior while their dysregulation is present in a variety of psychiatric and neurological disorders. Modern neuroscience provides important insights into brain mechanisms related to emotional and behavioral regulation.

The presence of neuroanatomical and neurobiological variations in the healthy population may carry functional and behavioral consequences that may serve to mediate vulnerability to psychopathology. 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. 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 contribute to brain structural variations. 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 aimed to investigate 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. **Controlling for age, gender, depression, and anxiety, we found a significant inverse association 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.

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 a large non-clinical sample of habitual Internet user females using both automated MRI volumetry and voxel-based morphometry as complementary approaches. Based on previous neuroimaging findings and the known role of brain reward system in substance addictions, we hypothesized that regions of the fronto-striatal circuit (orbitofrontal cortex, caudate, putamen, nuclei accumbens) and amygdala - that provides important inputs to the striatum - would be associated with problematic Internet use. **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 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.

## 8. References

- Afzal, S., Bojesen, S. E., & Nordestgaard, B. G. (2014). Reduced 25-hydroxyvitamin D and risk of Alzheimer's disease and vascular dementia. *Alzheimer's & Dementia*, *10*(3), 296-302. [doi:10.1016/j.jalz.2013.05.1765](https://doi.org/10.1016/j.jalz.2013.05.1765)
- Al Anouti, F., Thomas, J., Abdel-Wareth, L., Rajah, J., Grant, W. B., & Haq, A. (2011). Vitamin D deficiency and sun avoidance among university students at Abu Dhabi, United Arab Emirates. *Dermato-Endocrinology*, *3*(4), 235-239. [doi:10.4161/derm.3.4.16881](https://doi.org/10.4161/derm.3.4.16881)
- Albrecht, U., Kirschner, N. E., & Grüsser, S. M. (2007). Diagnostic instruments for behavioural addiction: an overview. *GMS Psycho-Social Medicine*, *4*.
- Al Mheid, I., Patel, R. S., Tangpricha, V., & Quyyumi, A. A. (2013). Vitamin D and cardiovascular disease: is the evidence solid? *European Heart Journal*, *34*(48), 3691-3698. [doi:10.1093/eurheartj/eh166](https://doi.org/10.1093/eurheartj/eh166)
- American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (5<sup>th</sup> edition)*. Washington, DC: American Psychiatric Pub.
- Anastasiou, C. A., Yannakoulia, M., & Scarmeas, N. (2014). Vitamin D and cognition: an update of the current evidence. *Journal of Alzheimer's Disease: JAD*, *42*, S71-80.
- Andersson, J. L., Jenkinson, M., & Smith, S. (2007). *Non-linear registration, aka Spatial normalisation FMRIB technical report TR07JA2*. Retrieved from <https://www.fmrib.ox.ac.uk/analysis/techrep/tr07ja2/tr07ja2.pdf>
- Annweiler, C., Annweiler, T., Montero-Odasso, M., Bartha, R., & Beauchet, O. (2014). Vitamin D and brain volumetric changes: Systematic review and meta-analysis. *Maturitas*, *78*(1), 30-39. [doi:10.1016/j.maturitas.2014.02.013](https://doi.org/10.1016/j.maturitas.2014.02.013)

Annweiler, C., Bartha, R., Goncalves, S., Karras, S. N., Millet, P., Féron, F., & Beauchet, O. (2015). Vitamin D-related changes in intracranial volume in older adults: A quantitative neuroimaging study. *Maturitas*, *80*(3), 312-317.

[doi:10.1016/j.maturitas.2014.12.011](https://doi.org/10.1016/j.maturitas.2014.12.011)

Annweiler, C., Fantino, B., Schott, A. M., Krolak-Salmon, P., Allali, G., & Beauchet, O. (2012a). Vitamin D insufficiency and mild cognitive impairment: cross-sectional association. *European Journal of Neurology*, *19*(7), 1023-1029.

[doi:10.1111/j.1468-1331.2012.03675.x](https://doi.org/10.1111/j.1468-1331.2012.03675.x)

Annweiler, C., Montero-Odasso, M., Llewellyn, D. J., Richard-Devantoy, S., Duque, G., & Beauchet, O. (2012b). Meta-analysis of memory and executive dysfunctions in relation to vitamin D. *Journal of Alzheimer's disease: JAD*, *37*(1), 147-171.

Ansell, E. B., Rando, K., Tuit, K., Guarnaccia, J., & Sinha, R. (2012). Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. *Biological psychiatry*, *72*(1), 57-64.

[doi:10.1016/j.biopsych.2011.11.022](https://doi.org/10.1016/j.biopsych.2011.11.022)

Bagby, R. M., Parker, J. D., & Taylor, G. J. (1994). The twenty-item Toronto Alexithymia Scale—I. Item selection and cross-validation of the factor structure.

*Journal of Psychosomatic Research*, *38*(1), 23-32. [doi:10.1016/0022-3999\(94\)90005-1](https://doi.org/10.1016/0022-3999(94)90005-1)

Bagby, R. M., & Taylor, G. J. (1997). Measurement and validation of the alexithymia construct. In Taylor, G. J., Bagby, R. M., & Parker, J. D. (Eds.), *Disorders of affect regulation: Alexithymia in medical and psychiatric illness* (pp. 46-66). Cambridge, England: Cambridge University Press.

[doi:10.1017/CBO9780511526831.006](https://doi.org/10.1017/CBO9780511526831.006)

Balion, C., Griffith, L. E., Striffler, L., Henderson, M., Patterson, C., Heckman, G., ... & Raina, P. (2012). Vitamin D, cognition, and dementia. A systematic review

and meta-analysis. *Neurology*, 79(13), 1397-1405.

[doi:10.1212/WNL.0b013e31826c197f](https://doi.org/10.1212/WNL.0b013e31826c197f)

Bandura, A. (2001). Social cognitive theory: An agentic perspective. *Annual Review of Psychology*, 52(1), 1-26. [doi:10.1146/annurev.psych.52.1.1](https://doi.org/10.1146/annurev.psych.52.1.1)

Barrett, L. F. (2009). The future of psychology: Connecting mind to brain. *Perspectives on Psychological Science*, 4(4), 326-339. [doi:10.1111/j.1745-6924.2009.01134.x](https://doi.org/10.1111/j.1745-6924.2009.01134.x)

Baumeister, R. F., Heatherton, T. F., & Tice, D. M. (1994). *Losing control: How and why people fail at self-regulation*. San Diego, CA: Academic Press.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Beck Depression Inventory-II. *San Antonio, TX: Psychological Corporation*.

Bermond, B. (1997) Brain and alexithymia. In Vingerhoets, A., van Bussel, F. J., & Boelhouwer, A. J. (Eds.), *The (non)expression of emotions in health and disease* (pp. 115–129). Tilburg, Netherlands: Tilburg University Press.

Berthoz, S., Artiges, E., Van de Moortele, P. F., Poline, J. B., Rouquette, S., Consoli, S. M., & Martinot, J. L. (2014). Effect of impaired recognition and expression of emotions on frontocingulate cortices: an fMRI study of men with alexithymia. *American Journal of Psychiatry*. 159(6), 961-967.

Bewley, J., Murphy, P. N., Mallows, J., & Baker, G. A. (2005). Does alexithymia differentiate between patients with nonepileptic seizures, patients with epilepsy, and nonpatient controls? *Epilepsy & Behavior*, 7(3), 430-437. [doi:10.1016/j.yebeh.2005.06.006](https://doi.org/10.1016/j.yebeh.2005.06.006)

Bird, G., Press, C., & Richardson, D. C. (2011). The Role of Alexithymia in Reduced Eye-fixation in Autism Spectrum Conditions. *Journal of Autism and Developmental Disorders*, 41(11), 1556-1564. [doi:10.1007/s10803-011-1183-3](https://doi.org/10.1007/s10803-011-1183-3)

Bird, G., Silani, G., Brindley, R., White, S., Frith, U., & Singer, T. (2010). Empathic brain responses in insula are modulated by levels of alexithymia but not autism. *Brain*, *133*(5), 1515-1525. [doi:10.1093/brain/awq060](https://doi.org/10.1093/brain/awq060)

Bodini, B., Mandarelli, G., Tomassini, V., Tarsitani, L., Pestalozza, I., Gasperini, C., ... & Pozzilli, C. (2008). Alexithymia in multiple sclerosis: relationship with fatigue and depression. *Acta Neurologica Scandinavica*, *118*(1), 18-23. [doi:10.1111/j.1600-0404.2007.00969.x](https://doi.org/10.1111/j.1600-0404.2007.00969.x)

Borrioni, B., Premi, E., Formenti, A., Turrone, R., Alberici, A., Cottini, E., ... & Padovani, A. (2015). Structural and functional imaging study in dementia with Lewy bodies and Parkinson's disease dementia. *Parkinsonism & Related Disorders*, *21*(9), 1049-1055. [doi:10.1016/j.parkreldis.2015.06.013](https://doi.org/10.1016/j.parkreldis.2015.06.013)

Brambilla, F., Biggio, G., Pisu, M. G., Bellodi, L., Perna, G., Bogdanovich-Djukic, V., ... & Serra, M. (2003). Neurosteroid secretion in panic disorder. *Psychiatry Research*, *118*(2), 107-116. [doi:10.1016/S0165-1781\(03\)00077-5](https://doi.org/10.1016/S0165-1781(03)00077-5)

Brenner, V. (1997). Psychology of computer use: XLVII. Parameters of Internet use, abuse and addiction: The first 90 days of the Internet Usage Survey. *Psychological Reports*, *80*(3), 879-882. [doi:10.2466/pr0.1997.80.3.879](https://doi.org/10.2466/pr0.1997.80.3.879)

Brot, C., Jorgensen, N. R., & Sorensen, O. H. (1999). The influence of smoking on vitamin D status and calcium metabolism. *European Journal of Clinical Nutrition*, *53*(12), 920-926. [doi:10.1038/sj.ejcn.1600870](https://doi.org/10.1038/sj.ejcn.1600870)

Cannell, J. J. (2008). Autism and vitamin D. *Medical Hypotheses*, *70*(4), 750-759. [doi:10.1016/j.mehy.2007.08.016](https://doi.org/10.1016/j.mehy.2007.08.016)

Cannell, J. J., & Grant, W. B. (2013). What is the role of vitamin D in autism?. *Dermato-Endocrinology*, *5*(1), 199-204. [doi:10.4161/derm.24356](https://doi.org/10.4161/derm.24356)

Chamberlain, S. R., Lochner, C., Stein, D. J., Goudriaan, A. E., Holst, R. V. J., Zohar, J., & Grant, J. E. (In press). Behavioural addiction—A rising tide? *European Neuropsychopharmacology*. [doi:10.1016/j.euroneuro.2015.08.013](https://doi.org/10.1016/j.euroneuro.2015.08.013)

Chan, Y. H. (2004). Biostatistics 201: Linear regression analysis. *Singapore Medical Journal*, 45(2), 55-61.

Chou, C., Condrón, L., & Bell, J. C. (2005). A review of the research on Internet addiction. *Educational Psychology Review*, 17(4), 363-388. [doi:10.1007/s10648-005-8138-1](https://doi.org/10.1007/s10648-005-8138-1)

Cook, R., Brewer, R., Shah, P., & Bird, G. (2013). Alexithymia, not autism, predicts poor recognition of emotional facial expressions. *Psychological Science*, 24(5), 723-732. [doi:10.1177/0956797612463582](https://doi.org/10.1177/0956797612463582)

Cornet, A., Baudet, C., Neveu, I., Evercooren, B. V., Brachet, P., & Naveilhan, P. (1998). 1, 25-dihydroxyvitamin D3 regulates the expression of VDR and NGF gene in Schwann cells in vitro. *Journal of Neuroscience Research*, 53(6), 742-746.

Cserjési, R., Luminet, O., & Lénárd, L. (2007). A Torontói Alexitímia Skála (TAS-20) magyar változata: megbízhatósága és faktorvaliditása egyetemista mintán. *Magyar Pszichológiai Szemle*, 62(3), 355-368. [doi:10.1556/MPSzle.62.2007.3.4](https://doi.org/10.1556/MPSzle.62.2007.3.4)

Craparo, G. (2011). Internet addiction, dissociation, and alexithymia. *Procedia-Social and Behavioral Sciences*, 30, 1051-1056. [doi:10.1016/j.sbspro.2011.10.205](https://doi.org/10.1016/j.sbspro.2011.10.205)

Cui, X., Pelekanos, M., Liu, P. Y., Burne, T. H. J., McGrath, J. J., & Eyles, D. W. (2013). The vitamin D receptor in dopamine neurons; its presence in human substantia nigra and its ontogenesis in rat midbrain. *Neuroscience*, 236, 77-87. [doi:10.1016/j.neuroscience.2013.01.035](https://doi.org/10.1016/j.neuroscience.2013.01.035)

Darnai, G., Plózer, E., Perlaki, G., Orsi, G., Nagy, S. A., Horváth, R., ... & 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.

[doi:10.3109/09637486.2015.1093609](https://doi.org/10.3109/09637486.2015.1093609)

Davis, H. P., Rosenzweig, M. R., Becker, L. A., & Sather, K. J. (1988). Biological psychology's relationships to psychology and neuroscience. *American Psychologist*, 43(5), 359. [doi:10.1037/0003-066X.43.5.359](https://doi.org/10.1037/0003-066X.43.5.359)

Davis, R. A. (2001). A cognitive-behavioral model of pathological Internet use. *Computers in Human Behavior*, 17(2), 187-195. [doi:10.1016/S0747-5632\(00\)00041-8](https://doi.org/10.1016/S0747-5632(00)00041-8)

DeLuca, H. F. (1979). *Vitamin D. Metabolism and function*. Berlin, Germany: Springer. [doi:10.1007/978-3-642-81306-1](https://doi.org/10.1007/978-3-642-81306-1)

Deng, Z., Wei, D., Xue, S., Du, X., Hitchman, G., & Qiu, J. (2014). Regional gray matter density associated with emotional conflict resolution: Evidence from voxel-based morphometry. *Neuroscience*, 275, 500-507. [doi:10.1016/j.neuroscience.2014.06.040](https://doi.org/10.1016/j.neuroscience.2014.06.040)

Demetrovics, Zs., Szeredi, B., & Rózsa, S. (2008). The three-factor model of Internet addiction: the development of the Problematic Internet Use Questionnaire. *Behavior Research Methods*; 40(2), 563–574. [doi:10.3758/BRM.40.2.563](https://doi.org/10.3758/BRM.40.2.563)

D'Hondt, F., Billieux, J., & Maurage, P. (2015). Electrophysiological correlates of problematic Internet use: Critical review and perspectives for future research. *Neuroscience & Biobehavioral Reviews*, 59, 64-82. [doi:10.1016/j.neubiorev.2015.10.005](https://doi.org/10.1016/j.neubiorev.2015.10.005)

Dom, G., Sabbe, B. G. C. C., Hulstijn, W., & Van Den Brink, W. (2005). Substance use disorders and the orbitofrontal cortex. *The British Journal of Psychiatry*, 187(3), 209-220. [doi:10.1192/bjp.187.3.209](https://doi.org/10.1192/bjp.187.3.209)

Dong, G., Huang, J., & Du, X. (2011). Enhanced reward sensitivity and decreased loss sensitivity in Internet addicts: an fMRI study during a guessing task.

*Journal of Psychiatric Research*, 45(11), 1525-1529.

[doi:10.1016/j.jpsychires.2011.06.017](https://doi.org/10.1016/j.jpsychires.2011.06.017)

Dubrovsky, B. O. (2005). Steroids, neuroactive steroids and neurosteroids in psychopathology. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 29(2), 169-192. [doi:10.1016/j.pnpbp.2004.11.001](https://doi.org/10.1016/j.pnpbp.2004.11.001)

Durkee, T., Kaess, M., Carli, V., Parzer, P., Wasserman, C., Floderus, B., ... & Wasserman, D. (2012). Prevalence of pathological internet use among adolescents in Europe: demographic and social factors. *Addiction*, 107(12), 2210-2222. [doi:10.1111/j.1360-0443.2012.03946.x](https://doi.org/10.1111/j.1360-0443.2012.03946.x)

Eggert, L. D., Sommer, J., Jansen, A., Kircher, T., & Konrad, C. (2012). Accuracy and Reliability of Automated Gray Matter Segmentation Pathways on Real and Simulated Structural Magnetic Resonance Images of the Human Brain. *PLoS One*, 7(9). e45081. [doi:10.1371/journal.pone.0045081](https://doi.org/10.1371/journal.pone.0045081)

Emerton, B. C., Jerram, M., Deckersbach, T., Dougherty, D. D., Fulwiler, C., & Gansler, D. A. (2009). A comparison of voxel-based morphometry and volumetry methods in the context of the neural basis of aggression. *Brain Imaging and Behavior*, 3(4), 332-341. [doi:10.1007/s11682-009-9075-2](https://doi.org/10.1007/s11682-009-9075-2)

Engel, S. R., & Grant, K. A. (2001). Neurosteroids and behavior. *International Review of Neurobiology*, 46, 321-348. [doi:10.1016/S0074-7742\(01\)46067-3](https://doi.org/10.1016/S0074-7742(01)46067-3)

Eserian, J. K. (2013). Vitamin D as an effective treatment approach for drug abuse and addiction. *Journal of Medical Hypotheses and Ideas*, 7(2), 35-39. [doi:10.1016/j.jmhi.2013.02.001](https://doi.org/10.1016/j.jmhi.2013.02.001)

Eyles, D., Brown, J., Mackay-Sim, A., McGrath, J., & Feron, F. (2003). Vitamin D3 and brain development. *Neuroscience*, 118(3), 641-653. [doi:10.1016/S0306-4522\(03\)00040-X](https://doi.org/10.1016/S0306-4522(03)00040-X)

Eyles, D., Burne, T., & McGrath, J. (2011). Vitamin D: a neurosteroid affecting brain development and function; implications for neurological and psychiatric disorders. In: Feldman, D., Pike, J. W., & Adams, J. S. (Eds.), *Vitamin D. 3rd edition* (pp. 565–582). Amsterdam, Netherlands: Academic Press.

Eyles, D. W., Burne, T. H., & McGrath, J. J. (2013). Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Frontiers in Neuroendocrinology*, *34*(1), 47-64.

[doi:10.1016/j.yfrne.2012.07.001](https://doi.org/10.1016/j.yfrne.2012.07.001)

Eyles, D. W., Smith, S., Kinobe, R., Hewison, M., & McGrath, J. J. (2005). Distribution of the vitamin D receptor and 1 $\alpha$ -hydroxylase in human brain. *Journal of Chemical Neuroanatomy*, *29*(1), 21-30. [doi:10.1016/j.jchemneu.2004.08.006](https://doi.org/10.1016/j.jchemneu.2004.08.006)

Everitt, B. J., & Robbins, T. W. (2013). From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. *Neuroscience & Biobehavioral Reviews*, *37*(9), 1946-1954. [doi:10.1016/j.neubiorev.2013.02.010](https://doi.org/10.1016/j.neubiorev.2013.02.010)

Evren, C., Sar, V., Evren, B., Semiz, U., Dalbudak, E., & Cakmak, D. (2008). Dissociation and alexithymia among men with alcoholism. *Psychiatry and Clinical Neurosciences*, *62*(1), 40-47. [doi:10.1111/j.1440-1819.2007.01775.x](https://doi.org/10.1111/j.1440-1819.2007.01775.x)

Féron, F., Burne, T. H. J., Brown, J., Smith, E., McGrath, J. J., Mackay-Sim, A., & Eyles, D. W. (2005). Developmental Vitamin D3 deficiency alters the adult rat brain. *Brain Research Bulletin*, *65*(2), 141-148.

[doi:10.1016/j.brainresbull.2004.12.007](https://doi.org/10.1016/j.brainresbull.2004.12.007)

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., ... & Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–55.

[doi:10.1016/S0896-6273\(02\)00569-X](https://doi.org/10.1016/S0896-6273(02)00569-X)

Fischl, B., Salat, D. H., van der Kouwe, A. J., Makris, N., Ségonne, F., Quinn, B. T., & Dale, A. M. (2004). Sequence-independent segmentation of magnetic resonance images. *NeuroImage*, *23*, S69-S84. [doi:10.1016/j.neuroimage.2004.07.016](https://doi.org/10.1016/j.neuroimage.2004.07.016)

Fox, K. C., Nijeboer, S., Dixon, M. L., Floman, J. L., Ellamil, M., Rumak, S. P., ... & Christoff, K. (2014). Is meditation associated with altered brain structure? A systematic review and meta-analysis of morphometric neuroimaging in meditation practitioners. *Neuroscience & Biobehavioral Reviews*, *43*, 48-73. [doi:10.1016/j.neubiorev.2014.03.016](https://doi.org/10.1016/j.neubiorev.2014.03.016)

Freyberger, H. (1977). Supportive psychotherapeutic techniques in primary and secondary alexithymia/ Discussion. *Psychotherapy and Psychosomatics*, *28*(1-4), 337-345. [doi:10.1159/000287080](https://doi.org/10.1159/000287080)

Galton, C. J., & Hodges, J. R. (2004). Morphometric brain analysis in the dementias. In M. Rizzo & P. J. Eslinger (Eds.), *Principles and practice of behavioral neurology and neuropsychology* (pp. 81–89). Philadelphia, PA: W.B. Saunders Company.

Ganji, V., Milone, C., Cody, M. M., McCarty, F., & Wang, Y. T. (2010). Serum vitamin D concentrations are related to depression in young adult US population: the Third National Health and Nutrition Examination Survey. *International Archives of Medicine*, *3*(1), 1–8.

Ganzel, B. L., Kim, P., Glover, G. H., & Temple, E. (2008). Resilience after 9/11: multimodal neuroimaging evidence for stress-related change in the healthy adult brain. *NeuroImage*, *40*(2), 788-795. [doi:10.1016/j.neuroimage.2007.12.010](https://doi.org/10.1016/j.neuroimage.2007.12.010)

Giorgio, A., Santelli, L., Tomassini, V., Bosnell, R., Smith, S., De Stefano, N., & Johansen-Berg, H. (2010). Age-related changes in grey and white matter structure throughout adulthood. *NeuroImage*, *51*(3), 943-951. [doi:10.1016/j.neuroimage.2010.03.004](https://doi.org/10.1016/j.neuroimage.2010.03.004)

Giuliani, N. R., Calhoun, V. D., Pearlson, G. D., Francis, A., & Buchanan, R. W. (2005). Voxel-based morphometry versus region of interest: a comparison of two methods for analyzing gray matter differences in schizophrenia. *Schizophrenia Research*, 74(2), 135-147. [doi:10.1016/j.schres.2004.08.019](https://doi.org/10.1016/j.schres.2004.08.019)

Goerlich-Dobre, K. S., Votinov, M., Habel, U., Pripfl, J., & Lamm, C. (2015). Neuroanatomical profiles of alexithymia dimensions and subtypes. *Human Brain Mapping*, 36(10), 3805-3818. [doi:10.1002/hbm.22879](https://doi.org/10.1002/hbm.22879)

Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*, 159, 1642–1652. [doi:10.1176/appi.ajp.159.10.1642](https://doi.org/10.1176/appi.ajp.159.10.1642)

Golubchik, P., & Weizman, D. A. (2008). The Role of Neurosteroids in Development of Pediatric Psychopathology. In Weizman, A. (Ed.), *Neuroactive Steroids in Brain Function, Behavior and Neuropsychiatric Disorders. Novel Strategies for Research and Treatment* (pp. 539-553). Netherlands: Springer. [doi:10.1007/978-1-4020-6854-6\\_26](https://doi.org/10.1007/978-1-4020-6854-6_26)

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001a). A Voxel-Based Morphometric Study of Ageing in 465 Normal Adult Human Brains. *NeuroImage*, 14, 21-36. [doi:10.1006/nimg.2001.0786](https://doi.org/10.1006/nimg.2001.0786)

Good, C. D., Johnsrude, I., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001b). Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *NeuroImage*, 14(3), 685-700. [doi:10.1006/nimg.2001.0857](https://doi.org/10.1006/nimg.2001.0857)

Goodkind, M. S., Gyurak, A., McCarthy, M., Miller, B. L., & Levenson, R. W. (2010). Emotion regulation deficits in frontotemporal lobar degeneration and Alzheimer's disease. *Psychology and Aging*, 25(1), 30-37. [doi:10.1037/a0018519](https://doi.org/10.1037/a0018519)

Grabe, H. J., Wittfeld, K., Hegenscheid, K., Hosten, N., Lotze, M., Janowitz, D., ... & Freyberger, H. J. (2014). Alexithymia and brain gray matter volumes in a general population sample. *Human Brain Mapping, 35*(12), 5932-5945. [doi:10.1002/hbm.22595](https://doi.org/10.1002/hbm.22595)

Grant, J. E., Brewer, J. A., & Potenza, M. N. (2006). The neurobiology of substance and behavioral addictions. *CNS Spectrums, 11*(12), 924-930. [doi:10.1017/S109285290001511X](https://doi.org/10.1017/S109285290001511X)

Grant, W. B., & Cannell, J. J. (2013). Autism prevalence in the United States with respect to solar UV-B doses: an ecological study. *Dermato-Endocrinology, 5*(1), 159-164. [doi:10.4161/derm.22942](https://doi.org/10.4161/derm.22942)

Grant, W. B., & Soles, C. M. (2009). Epidemiologic evidence for supporting the role of maternal vitamin D deficiency as a risk factor for the development of infantile autism. *Dermato-Endocrinology, 1*(4), 223-228. [doi:10.4161/derm.1.4.9500](https://doi.org/10.4161/derm.1.4.9500)

Griffiths, M. (2000). Does Internet and computer “addiction” exist? Some case study evidence. *CyberPsychology and Behavior, 3*(2), 211-218. [doi:10.1089/109493100316067](https://doi.org/10.1089/109493100316067)

Griffiths, M. D., Kuss, D. J., Billieux, J., & Pontes, H. M. (2016). The evolution of Internet addiction: A global perspective. *Addictive Behaviors, 53*, 193-195. [doi:10.1016/j.addbeh.2015.11.001](https://doi.org/10.1016/j.addbeh.2015.11.001)

Gross, J. J. (2001). Emotion regulation in adulthood: Timing is everything. *Current Directions in Psychological Science, 10*(6), 214-219. [doi:10.1111/1467-8721.00152](https://doi.org/10.1111/1467-8721.00152)

Harms, L. R., Burne, T. H., Eyles, D. W., & McGrath, J. J. (2011). Vitamin D and the brain. *Best Practice & Research Clinical Endocrinology & Metabolism, 25*(4), 657-669. [doi:10.1016/j.beem.2011.05.009](https://doi.org/10.1016/j.beem.2011.05.009)

Harms, L. R., Cowin, G., Eyles, D. W., Kurniawan, N. D., McGrath, J. J., & Burne, T. H. (2012). Neuroanatomy and psychomimetic-induced locomotion in C57BL/6J and 129/X1SvJ mice exposed to developmental vitamin D deficiency. *Behavioural Brain Research*, 230(1), 125-131. [doi:10.1016/j.bbr.2012.02.007](https://doi.org/10.1016/j.bbr.2012.02.007)

Hartley, C. A., Fischl, B., & Phelps, E. A. (2011). Brain structure correlates of individual differences in the acquisition and inhibition of conditioned fear. *Cerebral Cortex*, 21(9), 1954-1962. [doi:10.1093/cercor/bhq253](https://doi.org/10.1093/cercor/bhq253)

Hayano, F., Nakamura, M., Asami, T., Uehara, K., Yoshida, T., Roppongi, T., ... & Hirayasu, Y. (2009). Smaller amygdala is associated with anxiety in patients with panic disorder. *Psychiatry and Clinical Neurosciences*, 63(3), 266-276. [doi:10.1111/j.1440-1819.2009.01960.x](https://doi.org/10.1111/j.1440-1819.2009.01960.x)

Heatherton, T. F. (2011). Neuroscience of self and self-regulation. *Annual Review of Psychology*, 62, 363-390. [doi:10.1146/annurev.psych.121208.131616](https://doi.org/10.1146/annurev.psych.121208.131616)

Heatherton, T. F., & Wagner, D. D. (2011). Cognitive neuroscience of self-regulation failure. *Trends in Cognitive Sciences*, 15(3), 132-139. [doi:10.1016/j.tics.2010.12.005](https://doi.org/10.1016/j.tics.2010.12.005)

Heinzel, A., Minnerop, M., Schäfer, R., Müller, H. W., Franz, M., & Hautzel, H. (2012). Alexithymia in healthy young men: A voxel-based morphometric study. *Journal of Affective Disorders*, 136(3), 1252-1256. [doi:10.1016/j.jad.2011.06.012](https://doi.org/10.1016/j.jad.2011.06.012)

Hermann, A., Bieber, A., Keck, T., Vaitl, D., & Stark, R. (2014). Brain structural basis of cognitive reappraisal and expressive suppression. *Social Cognitive and Affective Neuroscience*, 9(9), 1435-1442. [doi:10.1093/scan/nst130](https://doi.org/10.1093/scan/nst130)

Heydari, B., & Le Melledo, J. M. (2002). Low pregnenolone sulphate plasma concentrations in patients with generalized social phobia. *Psychological Medicine*, 32(5), 929-933. [doi:10.1017/S0033291702005238](https://doi.org/10.1017/S0033291702005238)

Hill, E., Berthoz, S., & Frith, U. (2004). Brief report: Cognitive processing of own emotions in individuals with autistic spectrum disorder and in their relatives. *Journal of Autism and Developmental Disorders*, 34(2), 229-235.  
[doi:10.1023/B:JADD.0000022613.41399.14](https://doi.org/10.1023/B:JADD.0000022613.41399.14)

Hofmann, W., Friese, M., & Strack, F. (2009). Impulse and self-control from a dual-systems perspective. *Perspectives on Psychological Science*, 4(2), 162-176.  
[doi:10.1111/j.1745-6924.2009.01116.x](https://doi.org/10.1111/j.1745-6924.2009.01116.x)

Holick, M. F. (2007). Vitamin D deficiency. *New England Journal of Medicine*, 357(3), 266-281. [doi:10.1056/NEJMra070553](https://doi.org/10.1056/NEJMra070553)

Holick, M. F. (2009). Vitamin D status: measurement, interpretation, and clinical application. *Annals of Epidemiology*, 19(2), 73-78.  
[doi:10.1016/j.annepidem.2007.12.001](https://doi.org/10.1016/j.annepidem.2007.12.001)

Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., ... & Weaver, C. M. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, 96(7), 1911-1930.  
[doi:10.1210/jc.2011-0385](https://doi.org/10.1210/jc.2011-0385)

Holló, A., Clemens, Z., Kamondi, A., Lakatos, P., & Szűcs, A. (2012). Correction of vitamin D deficiency improves seizure control in epilepsy: a pilot study. *Epilepsy & Behavior*, 24(1), 131-133. [doi:10.1016/j.yebeh.2012.03.011](https://doi.org/10.1016/j.yebeh.2012.03.011)

Holló, A., Clemens, Z., & Lakatos, P. (2014). Epilepsy and vitamin D. *International Journal of Neuroscience*, 124(6), 387-393.  
[doi:10.3109/00207454.2013.847836](https://doi.org/10.3109/00207454.2013.847836)

Hong, S. B., Kim, J. W., Choi, E. J., Kim, H. H., Suh, J. E., Kim, C. D., ... & Yi, S. H. (2013a). Reduced orbitofrontal cortical thickness in male adolescents with internet addiction. *Behavioral and Brain Functions*, 9(11), 9081-9089.  
[doi:10.1186/1744-9081-9-11](https://doi.org/10.1186/1744-9081-9-11)

Hong, S. B., Zalesky, A., Cocchi, L., Fornito, A., Choi, E. J., Kim, H. H., ... & Yi, S. H. (2013b). Decreased functional brain connectivity in adolescents with internet addiction. *PLoS One*, 8(2), e57831. [doi:10.1371/journal.pone.0057831](https://doi.org/10.1371/journal.pone.0057831)

Honkalampi, K., Hintikka, J., Laukkanen, E., & Viinamäki, J. L. H. (2001). Alexithymia and depression: a prospective study of patients with major depressive disorder. *Psychosomatics*, 42(3), 229-234. [doi:10.1176/appi.psy.42.3.229](https://doi.org/10.1176/appi.psy.42.3.229)

Hosseini-Nezhad, A., & Holick, M. F. (2013). Vitamin D for Health: A Global Perspective. *Mayo Clinic Proceedings*, 88(7), 720-755. [doi:10.1016/j.mayocp.2013.05.011](https://doi.org/10.1016/j.mayocp.2013.05.011)

James, W. (1890). *Principles of Psychology*. New York, NY: Henry Holt and Company.

Jansen, A., Liuzzi, G., Deppe, M., Kanowski, M., Ölschläger, C., Albers, J. M., ... & Knecht, S. (2010). Structural Correlates of Functional Language Dominance: A Voxel-Based Morphometry Study. *Journal of Neuroimaging*, 20(2), 148-156. [doi:10.1111/j.1552-6569.2009.00367.x](https://doi.org/10.1111/j.1552-6569.2009.00367.x)

Jentsch, J. D., & Pennington, Z. T. (2014). Reward, interrupted: inhibitory control and its relevance to addictions. *Neuropharmacology*, 76, 479-486 [doi:10.1016/j.neuropharm.2013.05.022](https://doi.org/10.1016/j.neuropharm.2013.05.022)

Joseph, R. (1999). Environmental influences on neural plasticity, the limbic system, emotional development and attachment: a review. *Child Psychiatry and Human Development*, 29(3), 189-208. [doi:10.1023/A:1022660923605](https://doi.org/10.1023/A:1022660923605)

Jung, W. H., Kang, D. H., Kim, E., Shin, K. S., Jang, J. H., & Kwon, J. S. (2013). Abnormal corticostriatal-limbic functional connectivity in obsessive-compulsive disorder during reward processing & resting-state. *NeuroImage: Clinical*, 3, 27-38. [doi:10.1016/j.nicl.2013.06.013](https://doi.org/10.1016/j.nicl.2013.06.013)

Kalivas, P. W., & Volkow, N. D. (2005). The neural basis of addiction: A pathology of motivation and choice. *American Journal of Psychiatry*, *162*, 1403–1413. [doi:10.1176/appi.ajp.162.8.1403](https://doi.org/10.1176/appi.ajp.162.8.1403)

Kalueff, A. V., & Tuohimaa, P. (2007). Neurosteroid hormone vitamin D and its utility in clinical nutrition. *Current Opinion in Clinical Nutrition & Metabolic Care*, *10*(1), 12-19. [doi:10.1097/MCO.0b013e328010ca18](https://doi.org/10.1097/MCO.0b013e328010ca18)

Karohl, C., Su, S., Kumari, M., Tangpricha, V., Veledar, E., Vaccarino, V., & Raggi, P. (2010). Heritability and seasonal variability of vitamin D concentrations in male twins. *The American Journal of Clinical Nutrition*, *92*(6), 1393-1398. [doi:10.3945/ajcn.2010.30176](https://doi.org/10.3945/ajcn.2010.30176)

Kaufman, W. E., & Nagae-Poetscher, L. M. (2004). Structural brain imaging in neurodevelopmental disorders. In M. Rizzo & P. J. Eslinger (Eds.), *Principles and practice of behavioral neurology and neuropsychology* (pp. 91–114). Philadelphia, PA: W.B. Saunders Company.

Keller, S. S., & Roberts, N. (2009). Measurement of brain volume using MRI: software, techniques, choices and prerequisites. *Journal of Anthropological Sciences*, *87*, 127-151.

Kennedy, K. M., Erickson, K. I., Rodrigue, K. M., Voss, M. W., Colcombe, S. J., Kramer, A. F., ... & Raz, N. (2009). Age-related differences in regional brain volumes: a comparison of optimized voxel-based morphometry to manual volumetry. *Neurobiology of Aging*, *30*(10), 1657-1676. [doi:10.1016/j.neurobiolaging.2007.12.020](https://doi.org/10.1016/j.neurobiolaging.2007.12.020)

Killgore, W. D., Olson, E. A., & Weber, M. (2013). Physical exercise habits correlate with gray matter volume of the hippocampus in healthy adult humans. *Scientific Reports*, *3*, 3457-3457. [doi:10.1038/srep03457](https://doi.org/10.1038/srep03457)

Kim, S. H., Baik, S. H., Park, C. S., Kim, S. J., Choi, S. W., & Kim, S. E. (2011). Reduced striatal dopamine D2 receptors in people with Internet addiction. *Neuroreport*, 22(8), 407-411. [doi:10.1097/WNR.0b013e328346e16e](https://doi.org/10.1097/WNR.0b013e328346e16e)

Király, O., Griffiths, M. D., Urbán, R., Farkas, J., Kökönyei, G., Elekes, Z., ... & Demetrovics, Z. (2014). Problematic internet use and problematic online gaming are not the same: Findings from a large nationally representative adolescent sample. *Cyberpsychology, Behavior, and Social Networking*, 17(12), 749-754. [doi:10.1089/cyber.2014.0475](https://doi.org/10.1089/cyber.2014.0475)

Ko, C. H., Yen, J. Y., Chen, C. C., Chen, S. H., & Yen, C. F. (2005). Gender differences and related factors affecting online gaming addiction among Taiwanese adolescents. *The Journal of Nervous and Mental Disease*, 193(4), 273-277. [doi:10.1097/01.nmd.0000158373.85150.57](https://doi.org/10.1097/01.nmd.0000158373.85150.57)

Ko, C. H., Liu, G. C., Hsiao, S., Yen, J. Y., Yang, M. J., Lin, W. C., ... & Chen, C. S. (2009). Brain activities associated with gaming urge of online gaming addiction. *Journal of Psychiatric Research*, 43(7), 739-747. [doi:10.1016/j.jpsychires.2008.09.012](https://doi.org/10.1016/j.jpsychires.2008.09.012)

Kočovská, E., Fernell, E., Billstedt, E., Minnis, H., & Gillberg, C. (2012). Vitamin D and autism: Clinical review. *Research in Developmental Disabilities*, 33(5), 1541-1550. [doi:10.1016/j.ridd.2012.02.015](https://doi.org/10.1016/j.ridd.2012.02.015)

Kopp, M., Fóris, N. (1995). *A szorongás kognitív viselkedésterápiája*. Budapest, Hungary: Végeken.

Koronczai, B., Urbán, R., Kökönyei, G., Paksi, B., Papp, K., Kun, B. Arnold, P., Kállai, J., & Demetrovics, Z. (2011). Confirmation of the three-factor model of problematic internet use on off-line adolescent and adult samples. *Cyberpsychology, Behavior and Social Networking*, 14(11), 657-664. [doi:10.1089/cyber.2010.0345](https://doi.org/10.1089/cyber.2010.0345)

Kühn, S. & Gallinat, J. (2015). Brains online: structural & functional correlates of habitual Internet use. *Addiction Biology*, 20(2), 415-422. [doi:10.1111/adb.12128](https://doi.org/10.1111/adb.12128)

Kühn, S., Gallinat, J., & Brass, M. (2011). Keep calm and carry on?': Structural correlates of expressive suppression of emotions. *PloS One*, 6(1), e16569.

[doi:10.1371/journal.pone.0016569](https://doi.org/10.1371/journal.pone.0016569)

Kuss, D. J., & Griffiths, M. D. (2012). Internet and gaming addiction: a systematic literature review of neuroimaging studies. *Brain Sciences*, 2(3), 347-374.

[doi:10.3390/brainsci2030347](https://doi.org/10.3390/brainsci2030347)

Laconi, S., Tricard, N., & Chabrol, H. (2015). Differences between specific and generalized problematic Internet uses according to gender, age, time spent online and psychopathological symptoms. *Computers in Human Behavior*, 48, 236-244.

[doi:10.1016/j.chb.2015.02.006](https://doi.org/10.1016/j.chb.2015.02.006)

Leshner, A. I. (1997). Addiction is a brain disease, and it matters. *Science*, 278(5335), 45-47. [doi:10.1016/j.chb.2015.02.006](https://doi.org/10.1016/j.chb.2015.02.006)

Levy, N. (2013). Addiction is not a brain disease (and it matters). *Frontiers in Psychiatry*, 4, 24. [doi:10.3389/fpsyt.2013.00024](https://doi.org/10.3389/fpsyt.2013.00024)

Linden, W., Wen, F., & Paulhus, D. L. (1995). Measuring alexithymia: reliability, validity, and prevalence. *Advances in Personality Assessment*, 10, 51-95.

Lin, F., Zhou, Y., Du, Y., Qin, L., Zhao, Z., Xu, J., & Lei, H. (2012). Abnormal white matter integrity in adolescents with internet addiction disorder: a tract-based spatial statistics study. *PloS One*, 7(1), e30253. [doi:10.1371/journal.pone.0030253](https://doi.org/10.1371/journal.pone.0030253)

Liu, J., Gao, X. P., Osunde, I., Li, X., Zhou, S. K., Zheng, H. R., & Li, L. J. (2010). Increased regional homogeneity in Internet addiction disorder a resting state functional magnetic resonance imaging study (2009). *Chinese Medical Journal (Engl)*, 123(14), 1904-1908.

Loh, K. K., & Kanai, R. (2014). Higher media multi-tasking activity is associated with smaller gray-matter density in the anterior cingulate cortex. *PloS One*, 9(9), e106698.

Lövdén, M., Wenger, E., Mårtensson, J., Lindenberger, U., & Bäckman, L. (2013). Structural brain plasticity in adult learning and development. *Neuroscience & Biobehavioral Reviews*, 37(9), 2296-2310. [doi:10.1016/j.neubiorev.2013.02.014](https://doi.org/10.1016/j.neubiorev.2013.02.014)

Maguire, E. A., Woollett, K., & Spiers, H. J. (2006). London taxi drivers and bus drivers: a structural MRI and neuropsychological analysis. *Hippocampus*, 16(12), 1091-1101. [doi:10.1002/hipo.20233](https://doi.org/10.1002/hipo.20233)

Martínez-Sánchez, F., Ato-García, M., Adam, E. C., Medina, T. B. H., & España, J. J. S. (1998). Stability in alexithymia levels: a longitudinal analysis on various emotional answers. *Personality and Individual Differences*, 24(6), 767-772. [doi:10.1016/S0191-8869\(97\)00239-0](https://doi.org/10.1016/S0191-8869(97)00239-0)

Martínez-Sánchez, F., Ato-García, M., & Ortiz-Soria, B. (2003). Alexithymia—State or Trait? *The Spanish Journal of Psychology*, 6(01), 51-59. [doi:10.1017/S1138741600005205](https://doi.org/10.1017/S1138741600005205)

May, A. (2011). Experience-dependent structural plasticity in the adult human brain. *Trends in Cognitive Sciences*, 15(10), 475-482. [doi:10.1016/j.tics.2011.08.002](https://doi.org/10.1016/j.tics.2011.08.002)

Mazat, L., Lafont, S., Berr, C., Debuire, B., Tessier, J. F., Dartigues, J. F., & Baulieu, E. E. (2001). Prospective measurements of dehydroepiandrosterone sulfate in a cohort of elderly subjects: relationship to gender, subjective health, smoking habits, and 10-year mortality. *Proceedings of the National Academy of Sciences*, 98(14), 8145-8150. [doi:10.1073/pnas.121177998](https://doi.org/10.1073/pnas.121177998)

McGrath, J. J., Eyles, D. W., Pedersen, C. B., Anderson, C., Ko, P., Burne, T. H., ... & Mortensen, P. B. (2010). Neonatal vitamin D status and risk of schizophrenia: a population-based case-control study. *Archives of General Psychiatry*, 67(9), 889-894. [doi:10.1001/archgenpsychiatry.2010.110](https://doi.org/10.1001/archgenpsychiatry.2010.110)

McGrath, J., Feron, F., Eyles, D., & Mackay-Sim, A. (2001a). Vitamin D: the neglected neurosteroid? *Trends in Neurosciences*, 24(10), 570-572. [doi:10.1016/S0166-2236\(00\)01949-4](https://doi.org/10.1016/S0166-2236(00)01949-4)

McGrath, J. J., Kimlin, M. G., Saha, S., Eyles, D. W., & Parisi, A. V. (2001b). Vitamin D insufficiency in South-East Queensland. *Medical Journal of Australia*, *174*(3), 150-150.

Miller, G. A. (2010). Mistreating Psychology in the Decades of the Brain. *Perspectives on Psychological Science*, *5*(6), 716-743.  
[doi:10.1177/1745691610388774](https://doi.org/10.1177/1745691610388774)

Mitchell, P. (2000). Internet addiction: Genuine diagnosis or not? *Lancet*, *355*, 632. [doi:10.1016/S0140-6736\(05\)72500-9](https://doi.org/10.1016/S0140-6736(05)72500-9)

Mithal, A., Wahl, D. A., Bonjour, J. P., Burckhardt, P., Dawson-Hughes, B., Eisman, J. A., ... & IOF Committee of Scientific Advisors (CSA) Nutrition Working Group. (2009). Global vitamin D status and determinants of hypovitaminosis D. *Osteoporosis International*, *20*(11), 1807-1820. [doi:10.1007/s00198-009-0954-6](https://doi.org/10.1007/s00198-009-0954-6)

Morahan-Martin, J. (2005). Internet abuse: Addiction? Disorder? Symptom? Alternative explanations? *Social Science Computer Review*, *23*, 39-48.  
[doi:10.1177/0894439304271533](https://doi.org/10.1177/0894439304271533)

Morahan-Martin, J., & Schumacher, P. (2000). Incidence and correlates of pathological Internet use among college students. *Computers in Human Behavior*, *16*(1), 13-29. [doi:10.1016/S0747-5632\(99\)00049-7](https://doi.org/10.1016/S0747-5632(99)00049-7)

Morey, R. A., Petty, C. M., Xu, Y., Hayes, J. P., Wagner, H. R., Lewis, D. V., ... & McCarthy, G. (2009). A comparison of automated segmentation and manual tracing for quantifying hippocampal and amygdala volumes. *NeuroImage*, *45*(3), 855-866. [doi:10.1016/j.neuroimage.2008.12.033](https://doi.org/10.1016/j.neuroimage.2008.12.033)

Mowry, E. M., Waubant, E., McCulloch, C. E., Okuda, D. T., Evangelista, A. A., Lincoln, R. R., ... & Pelletier, D. (2012). Vitamin D status predicts new brain magnetic resonance imaging activity in multiple sclerosis. *Annals of Neurology*, *72*(2), 234-240. [doi:10.1002/ana.23591](https://doi.org/10.1002/ana.23591)

Mutlu, A. K., Schneider, M., Debbané, M., Badoud, D., Eliez, S., & Schaer, M. (2013). Sex differences in thickness, and folding developments throughout the cortex. *NeuroImage*, 82, 200-207. [doi:10.1016/j.neuroimage.2013.05.076](https://doi.org/10.1016/j.neuroimage.2013.05.076)

Ochsner, K. N., Silvers, J. A., & Buhle, J. T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences*, 1251(1), E1-E24. [doi:10.1111/j.1749-6632.2012.06751.x](https://doi.org/10.1111/j.1749-6632.2012.06751.x)

Odacı, H., & Çıkrıkçı, Ö. (2014). Problematic internet use in terms of gender, attachment styles and subjective well-being in university students. *Computers in Human Behavior*, 32, 61-66. [doi:10.1016/j.chb.2013.11.019](https://doi.org/10.1016/j.chb.2013.11.019)

O'Driscoll, C., Laing, J., & Mason, O. (2014). Cognitive emotion regulation strategies, alexithymia and dissociation in schizophrenia, a review and meta-analysis. *Clinical Psychology Review*, 34(6), 482-495. [doi:10.1016/j.cpr.2014.07.002](https://doi.org/10.1016/j.cpr.2014.07.002)

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 9(1), 97-113. [doi:10.1016/0028-3932\(71\)90067-4](https://doi.org/10.1016/0028-3932(71)90067-4)

Orentreich, N., Brind, J. L., Rizer, R. L., & Vogelman, J. H. (1984). Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *The Journal of Clinical Endocrinology and Metabolism*, 59(3), 551-555. [doi:10.1210/jcem-59-3-551](https://doi.org/10.1210/jcem-59-3-551)

Orentreich, N., Brind, J. L., Vogelman, J. H., Andres, R., & Baldwin, H. (1992). Long-term longitudinal measurements of plasma dehydroepiandrosterone sulfate in normal men. *The Journal of Clinical Endocrinology and Metabolism*, 75(4), 1002–1004.

Orsi, G., Perlaki, G., Kovacs, N., Aradi, M., Papp, Z., Karadi, K., ... & Janszky, J. (2011). 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 and Behavior*, 5(2), 149-157. [doi:10.1007/s11682-011-9119-2](https://doi.org/10.1007/s11682-011-9119-2)

Orton, S. M., & Ebers, G. C. (2011). Heritability of serum vitamin D concentrations: twin studies. *The American Journal of Clinical Nutrition*, 93(3), 667-668. [doi:10.3945/ajcn.110.009423](https://doi.org/10.3945/ajcn.110.009423)

Orton, S. M., Morris, A. P., Herrera, B. M., Ramagopalan, S. V., Lincoln, M. R., Chao, M. J., ... & Ebers, G. C. (2008). Evidence for genetic regulation of vitamin D status in twins with multiple sclerosis *The American Journal of Clinical Nutrition*, 88(2), 441-447.

Pardoe, H. R., Pell, G. S., Abbott, D. F., & Jackson, G. D. (2009). Hippocampal volume assessment in temporal lobe epilepsy: how good is automated segmentation? *Epilepsia*, 50(12), 2586-2592. [doi:10.1111/j.1528-1167.2009.02243.x](https://doi.org/10.1111/j.1528-1167.2009.02243.x)

Parker, G., & Brotchie, H. (2011). 'D' for depression: any role for vitamin D? *Acta Psychiatrica Scandinavica*, 124(4), 243-249. [doi:10.1111/j.1600-0447.2011.01705.x](https://doi.org/10.1111/j.1600-0447.2011.01705.x)

Patenaude, B., Smith, S. M., Kennedy, D. N., & Jenkinson, M. (2011). A Bayesian model of shape and appearance for subcortical brain segmentation. *NeuroImage*, 56(3), 907-922. [doi:10.1016/j.neuroimage.2011.02.046](https://doi.org/10.1016/j.neuroimage.2011.02.046)

Pearson Murphy, B. E., Steinberg, S. I., Hu, F. Y., & Allison, C. M. (2001). Neuroactive ring A-reduced metabolites of progesterone in human plasma during pregnancy: elevated levels of 5 $\alpha$ -dihydroprogesterone in depressed patients during the latter half of pregnancy. *The Journal of Clinical Endocrinology & Metabolism*, 86(12), 5981-5987. [doi:10.1210/jcem.86.12.8122](https://doi.org/10.1210/jcem.86.12.8122)

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. [doi:10.1016/j.neulet.2014.04.013](https://doi.org/10.1016/j.neulet.2014.04.013)

Pervin, L. A. (2009). The relationship between biology and psychology. *Roczniki Psychologiczne*, 12(1), 7-21.

Pioggia, G., Tonacci, A., Tartarisco, G., Billeci, L., Muratori, F., Ruta, L., & Gangemi, S. (2014). Autism and lack of D3 vitamin: A systematic review. *Research in Autism Spectrum Disorders*, 8(12), 1685-1698. [doi:10.1016/j.rasd.2014.09.003](https://doi.org/10.1016/j.rasd.2014.09.003)

Pinard, L., Negrete, J. C., Annable, L., & Audet, N. (1996). Alexithymia in substance abusers. *The American Journal on Addictions*, 5(1), 32-39. [doi:10.1111/j.1521-0391.1996.tb00281.x](https://doi.org/10.1111/j.1521-0391.1996.tb00281.x)

Plózer, E., Altbäcker, 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. [doi:10.1179/1476830514Y.0000000109](https://doi.org/10.1179/1476830514Y.0000000109)

Ramagopalan, S. V., Heger, A., Berlanga, A. J., Mauger, N. J., Lincoln, M. R., Burrell, A., ... & Knight, J. C. (2010). A ChIP-seq defined genome-wide map of vitamin D receptor binding: associations with disease and evolution. *Genome Research*, 20(10), 1352-1360. [doi:10.1101/gr.107920.110](https://doi.org/10.1101/gr.107920.110)

Ruigrok, A. N., Salimi-Khorshidi, G., Lai, M. C., Baron-Cohen, S., Lombardo, M. V., Tait, R. J., & Suckling, J. (2014). A meta-analysis of sex differences in human brain structure. *Neuroscience & Biobehavioral Reviews*, 39, 34-50. [doi:10.1016/j.neubiorev.2013.12.004](https://doi.org/10.1016/j.neubiorev.2013.12.004)

Saporito, M. S., Brown, E. R., Hartpence, K. C., Wilcox, H. M., Vaught, J. L., & Carswell, S. (1994). Chronic 1, 25-dihydroxyvitamin D 3-mediated induction of nerve growth factor mRNA and protein in L929 fibroblasts and in adult rat brain. *Brain Research*, 633(1), 189-196. [doi:10.1016/0006-8993\(94\)91539-3](https://doi.org/10.1016/0006-8993(94)91539-3)

Sato, K., Kirino, E., & Tanaka, S. (2015). A Voxel-Based Morphometry Study of the Brain of University Students Majoring in Music and Nonmusic Disciplines. *Behavioural Neurology*, 501, 274919. [doi:10.1155/2015/274919](https://doi.org/10.1155/2015/274919)

Schore, A. N. (2003). *Affect Dysregulation and Disorders of the Self*. Norton Series on Interpersonal Neurobiology (Vol. 1). New York, NY: WW Norton & Company.

Scimeca, G., Bruno, A., Cava, L., Pandolfo, G., Muscatello, M. R. A., & Zoccali, R. (2014). The relationship between alexithymia, anxiety, depression, and internet addiction severity in a sample of Italian high school students. *The Scientific World Journal*, 2014. 504376. [doi:10.1155/2014/504376](https://doi.org/10.1155/2014/504376)

Shaw, M., & Black, D. W. (2008). Internet addiction. definition, assessment, epidemiology and clinical management. *CNS Drugs*, 22(5), 353-365. [doi:10.2165/00023210-200822050-00001](https://doi.org/10.2165/00023210-200822050-00001)

Shipko, S., Alvarez, W. A., & Noviello, N. (1983). Towards a teleological model of alexithymia: Alexithymia and post-traumatic stress disorder. *Psychotherapy and Psychosomatics*, 39(2), 122-126. [doi:10.1159/000287730](https://doi.org/10.1159/000287730)

Sipos, K., & Sipos, M. (1983). The development and validation of the Hungarian Form of the State-Trait Anxiety Inventory. *Series in Clinical & Community Psychology: Stress & Anxiety*, 51-61.

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, 17(3), 143-155. [doi:10.1002/hbm.10062](https://doi.org/10.1002/hbm.10062)

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., ... & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, 23, S208-S219. [doi:10.1016/j.neuroimage.2004.07.051](https://doi.org/10.1016/j.neuroimage.2004.07.051)

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence & localisation in cluster inference. *NeuroImage*, 44(1), 83-98. [doi:10.1016/j.neuroimage.2008.03.061](https://doi.org/10.1016/j.neuroimage.2008.03.061)

Smolders, J., Moen, S. M., Damoiseaux, J., Huitinga, I., & Holmøy, T. (2011). Vitamin D in the healthy and inflamed central nervous system: access and function. *Journal of the Neurological Sciences*, *311*(1), 37-43. [doi:10.1016/j.jns.2011.07.033](https://doi.org/10.1016/j.jns.2011.07.033)

Spada, M. M. (2014). An overview of problematic Internet use. *Addictive Behaviors*, *39*(1), 3-6. [doi:10.1016/j.addbeh.2013.09.007](https://doi.org/10.1016/j.addbeh.2013.09.007)

Sparrow, B., Liu, J., & Wegner, D. M. (2011). Google effects on memory: Cognitive consequences of having information at our fingertips. *Science*, *333*(6043), 776-778. [doi:10.1126/science.1207745](https://doi.org/10.1126/science.1207745)

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Spivak, B., Maayan, R., Kotler, M., Mester, R., Gil-Ad, I., Shtauf, B., & Weizman, A. (2000). Elevated circulatory level of GABAA-antagonistic neurosteroids in patients with combat-related post-traumatic stress disorder. *Psychological Medicine*, *30*(05), 1227-1231. [doi:10.1017/S0033291799002731](https://doi.org/10.1017/S0033291799002731)

Stumpf, W. E., & Privette, T. H. (1988). Light, vitamin D and psychiatry. Role of 1, 25 dihydroxyvitamin D<sub>3</sub> (solatriol) in etiology and therapy of seasonal affective disorder and other mental processes. *Psychopharmacology*, *97*(3), 285-294. [doi:10.1007/BF00439440](https://doi.org/10.1007/BF00439440)

Sun, Y., Lee, R., Chen, Y., Collinson, S., Thakor, N., Bezerianos, A., & Sim, K. (2015). Progressive Gender Differences of Structural Brain Networks in Healthy Adults: A Longitudinal, Diffusion Tensor Imaging Study. *PLoS One*, *10*(3), e0118857. [doi:10.1371/journal.pone.0118857](https://doi.org/10.1371/journal.pone.0118857)

Taki, Y., Thyreau, B., Kinomura, S., Sato, K., Goto, R., Kawashima, R., & Fukuda, H. (2011). Correlations among brain gray matter volumes, age, gender, and hemisphere in healthy individuals. *PLoS One*, *6*(7), e22734. [doi:10.1371/journal.pone.0022734](https://doi.org/10.1371/journal.pone.0022734)

Tangpricha, V., Pearce, E. N., Chen, T. C., & Holick, M. F. (2002). Vitamin D insufficiency among free-living healthy young adults. *The American Journal of Medicine*, *112*(8), 659-662. [doi:10.1016/S0002-9343\(02\)01091-4](https://doi.org/10.1016/S0002-9343(02)01091-4)

Tavanti, M., Battaglini, M., Borgogni, F., Bossini, L., Calossi, S., Marino, D., ... & De Stefano, N. (2012). Evidence of diffuse damage in frontal and occipital cortex in the brain of patients with post-traumatic stress disorder. *Neurological Sciences*, *33*(1), 59-68. [doi:10.1007/s10072-011-0659-4](https://doi.org/10.1007/s10072-011-0659-4)

Testa, C., Laakso, M. P., Sabbatoli, F., Rossi, R., Beltramello, A., Soininen, H., & Frisoni, G. B. (2004). A comparison between the accuracy of voxel-based morphometry and hippocampal volumetry in Alzheimer's disease. *Journal of Magnetic Resonance Imaging*, *19*(3), 274-282. [doi:10.1002/jmri.20001](https://doi.org/10.1002/jmri.20001)

Thompson, R. A. (1994). Emotion regulation: A theme in search of definition. *Monographs of the Society for Research in Child Development*, *59*(2-3), 25-52. [doi:10.2307/1166137](https://doi.org/10.2307/1166137)

Tolppanen, A. M., Sayers, A., Fraser, W. D., Lewis, G., Zammit, S., & Lawlor, D. A. (2012). The association of serum 25-hydroxyvitamin D3 and D2 with depressive symptoms in childhood—a prospective cohort study. *Journal of Child Psychology and Psychiatry*, *53*(7), 757-766. [doi:10.1111/j.1469-7610.2011.02518.x](https://doi.org/10.1111/j.1469-7610.2011.02518.x)

Ubbenhorst, A., Striebich, S., Lang, F., & Lang, U. E. (2011). Exploring the relationship between vitamin D and basic personality traits. *Psychopharmacology*, *215*(4), 733-737. [doi:10.1007/s00213-011-2175-x](https://doi.org/10.1007/s00213-011-2175-x)

van Broekhoven, F., & Verkes, R. J. (2003). Neurosteroids in depression: a review. *Psychopharmacology*, *165*(2), 97-110.

van der Velde, J., Gromann, P. M., Swart, M., Wiersma, D., de Haan, L., Bruggeman, R., ... & Aleman, A. (2015). Alexithymia influences brain activation during emotion perception but not regulation. *Social Cognitive and Affective Neuroscience*, *10*(2), 285-293. [doi:10.1093/scan/nsu056](https://doi.org/10.1093/scan/nsu056)

Vanheule, S., Verhaeghe, P., & Desmet, M. (2011). In search of a framework for the treatment of alexithymia. *Psychology and Psychotherapy: Theory, Research and Practice*, 84(1), 84-97.

Vijayakumar, N., Whittle, S., Yücel, M., Dennison, M., Simmons, J., & Allen, N. B. (2014). Thinning of the lateral prefrontal cortex during adolescence predicts emotion regulation in females. *Social Cognitive and Affective Neuroscience*, 9(11), 1845-1854. [doi:10.1093/scan/nst183](https://doi.org/10.1093/scan/nst183)

Volkow, N. D., & Baler, R. D. (2014). Addiction science: Uncovering neurobiological complexity. *Neuropharmacology* 76, 235-249. [doi:10.1016/j.neuropharm.2013.05.007](https://doi.org/10.1016/j.neuropharm.2013.05.007)

Volkow, N. D., & Fowler, J. S. (2000). Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cerebral Cortex*, 10(3), 318-325. [doi:10.1093/cercor/10.3.318](https://doi.org/10.1093/cercor/10.3.318)

Volkow, N. D., Fowler, J. S., & Wang, G. J. (2003). The addicted human brain: insights from imaging studies. *Journal of Clinical Investigation*, 111(10), 1444–1451. [doi:10.1172/JCI200318533](https://doi.org/10.1172/JCI200318533)

Volkow, N. D., Wang, G. J., Tomasi, D., & Baler, R. D. (2013). Unbalanced neuronal circuits in addiction. *Current Opinion in Neurobiology*, 23(4), 639-648. [doi:10.1016/j.conb.2013.01.002](https://doi.org/10.1016/j.conb.2013.01.002)

Vriend, C., Boedhoe, P. S., Rutten, S., Berendse, H. W., van der Werf, Y. D., & van den Heuvel, O. A. (2015). A smaller amygdala is associated with anxiety in Parkinson's disease: a combined FreeSurfer—VBM study. *Journal of Neurology, Neurosurgery & Psychiatry*, 310383. [doi:10.1136/jnnp-2015-310383](https://doi.org/10.1136/jnnp-2015-310383)

Wagner, D. D., & Heatherton, T. F. (2010). Giving in to temptation: the emerging cognitive neuroscience of self-regulatory failure. Vohs, K. D., & Baumeister, R. F. (Eds.), *Handbook of Self-regulation: Research, Theory and Applications* (pp. 41-63). New York, NY: The Guilford Press.

Watson, J. B. (1913). Psychology as the behaviorist views it. *Psychological Review*, 20(2), 158-177. [doi:10.1037/h0074428](https://doi.org/10.1037/h0074428)

Welborn, B. L., Papademetris, X., Reis, D. L., Rajeevan, N., Bloise, S. M., & Gray, J. R. (2009). Variation in orbitofrontal cortex volume: relation to sex, emotion regulation and affect. *Social Cognitive and Affective Neuroscience*, 4(4), 328-339. [doi:10.1093/scan/nsp028](https://doi.org/10.1093/scan/nsp028)

Wentz, L. M. (2014). Vitamin D Status May Affect Resilience and Recovery from Mild Traumatic Brain Injury in Military Personnel. *Austin Journal of Nutrition and Food Sciences*, 2(5), 1030.

Wickens, A. (2009). Introduction to Biopsychology. *An introduction to neurons, brains and biological psychology (3<sup>rd</sup> Edition)* (pp. 2-53). Pearson Education.

Wilkins, C. H., Sheline, Y. I., Roe, C. M., Birge, S. J., & Morris, J. C. (2006). Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *The American Journal of Geriatric Psychiatry*, 14(12), 1032-1040. [doi:10.1097/01.JGP.0000240986.74642.7c](https://doi.org/10.1097/01.JGP.0000240986.74642.7c)

Wundt, W. (1873-1874). *Grundzfige der Physiologischen Psychologie* [Principles of physiological psychology]. Leipzig, Germany: Engelmann.

Yao, L., Li, W., Dai, Z., & Dong, C. (2016). Eating behavior associated with gray matter volume alternations: A voxel based morphometry study. *Appetite*, 96, 572-579. [doi:10.1016/j.appet.2015.10.017](https://doi.org/10.1016/j.appet.2015.10.017)

Young, K. S. (1998). *Caught in the net: How to recognize the signs of internet addiction and a winning strategy for recovery*. New York, NY: John Wiley & Sons.

Young, K. S. (1999). *A therapist's guide to assess and treat internet addiction: An exclusive guide for practitioners*. Retrieved from <http://www.netaddiction.com/articles/practitioners.pdf>

Yuan, K., Qin, W., Wang, G., Zeng, F., Zhao, L., Yang, X., ... & Tian, J. (2011). Microstructure abnormalities in adolescents with Internet addiction disorder. *PloS One*, 6(6), e20708. [doi:10.1371/journal.pone.0020708](https://doi.org/10.1371/journal.pone.0020708)

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model & the expectation-maximization algorithm. *Medical Imaging, IEEE Transactions on*, 20(1), 45-57. [doi:10.1109/42.906424](https://doi.org/10.1109/42.906424)

Zhou, Y., Lin, F. C., Du, Y. S., Zhao, Z. M., Xu, J. R., & Lei, H. (2011). Gray matter abnormalities in Internet addiction: a voxel-based morphometry study. *European Journal of Radiology*, 79(1), 92-95. [doi:10.1016/j.ejrad.2009.10.025](https://doi.org/10.1016/j.ejrad.2009.10.025)

Zorumski, C. F., Paul, S. M., Izumi, Y., Covey, D. F., & Mennerick, S. (2013). Neurosteroids, stress and depression: potential therapeutic opportunities. *Neuroscience & Biobehavioral Reviews*, 37(1), 109-122. [doi:10.1016/j.neubiorev.2012.10.005](https://doi.org/10.1016/j.neubiorev.2012.10.005)

## 9. Publications

### 9.1. 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.

[doi:10.1179/1476830514Y.0000000114](https://doi.org/10.1179/1476830514Y.0000000114) **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. [doi:10.1007/s11682-015-9454-9](https://doi.org/10.1007/s11682-015-9454-9) **IF: 3.667 (in 2015)**

### 9.2. 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

### 9.3. Articles non-related to the thesis

Kalmár, Z., Kovács, N., Balás, I., Perlaki, G., Plózer, E., Orsi, G., **Altbacker, 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., **Altbacker, 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.  
[doi:10.1016/j.bandc.2013.05.005](https://doi.org/10.1016/j.bandc.2013.05.005) **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. [doi:10.1016/j.neulet.2014.04.013](https://doi.org/10.1016/j.neulet.2014.04.013) **IF: 2.030**

Darnai, G., Plózer, E., Perlaki, G., Orsi, G., Nagy, S. A., Horváth, R., Schwarcz, A., Kovács, N., **Altbäcker, 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. [doi:/10.3109/09637486.2015.1093609](https://doi.org/10.3109/09637486.2015.1093609) **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.  
[doi:10.1111/sbr.12077](https://doi.org/10.1111/sbr.12077) **IF: 0.628**

Plózer, E., **Altbäcker, 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.  
[doi:10.1179/1476830514Y.0000000109](https://doi.org/10.1179/1476830514Y.0000000109) **IF: 2.616**

Darnai, G., **Altbäcker, 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. [doi:10.1016/j.neulet.2015.12.056](https://doi.org/10.1016/j.neulet.2015.12.056) **IF: 2.107**

Darnai, G., Plózer, E., **Altbäcker, 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: 0.386**

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

Lucza, T., Darnai, G., Plózer, E., **Altbäcker, 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., **Altbäcker, 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., Schwarcz, 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., Dóczi T., Komoly S., Bogner P., Schwarcz 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, Hungary

**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

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