DOI:10.14753/SE.2021.2379

THE EFFECT OF L-DOPA THERAPY ON HIPPOCAMPUS AND NON-MOTOR SYMPTOMS IN NEWLY DIAGNOSTIZED PARKINSON'S DISEASE

PhD thesis

Orsolya Györfi

János Szentágothai Doctoral School of Neurosciences

Semmelweis University

Supervisor: Szabolcs Kéri, MD, D.Sc

Official reviewers: Norbert Kovács, MD, D.Sc
Gábor Csukly, MD, Ph.D

Head of the comprehensive exam committee: János Réthelyi, MD, D.Sc

Members of the comprehensive exam committee: Péter Klivényi, MD, D.Sc
Xénia Gonda, MD, Ph.D

Budapest

2019

DOI:10.14753/SE.2021.2379

TABLE OF CONTEST

DOI:10.14753/SE.2021.2379

DOI:10.14753/SE.2021.2379

LIST OF ABREVIATIONS

AD: Alzheimer's disease

ANOVA: Analysis of variance

CA: Cornu Ammonis

CAPE: Community Assessment of Psychic Experiences

CEARD: Consortium to Establish a Registry to Alzheimer's disease

D1/D5 receptor: dopamine1/ dopamine 5 receptors

D2/D3 receptors: dopamine 2/dopamine 3 receptors

DDS: dopamine dysregulation syndrome

DG: dentate gyrus

DS: dorsal striatum

EC: entorhinal cortex

FDR: false discovery rate

fMRI: functional magnetic resonance imaging

GDNF: glial cell – line derived neurotrophic factor

HAM-A: Hamilton Anxiety Rating Scale

HAM-D: Hamilton Depression Rating Scale

HSD: Honestly Significant Difference

ICC: intraclass correlation coefficients

ICD: impulse control disorders

l-DOPA: levo-dopa

LED: levodopa equivalent dose

LI: latent inhibition

LTP: long-term potentiation

MCI: mild cognitive impairment

MDD: major depressive disorder

MPTP: 1- methyl-4-phenyl-1,2,3,6-tetrahydropyridine

MRI: magnetic resonance imaging

N.acc: nucleus accumbens

NGF: nerve growth factor

NMDA: N-methyl-D-aspartate

NR2A/2B: N-methyl D-aspartate receptor subtype 2A/2B

O-LIFE: Oxford-Liverpool Inventory of Feeling and Experiences

ODHA: 6- hydroxydopamine

PD: Parkinson's disease

PERG: pattern electroretinogram

PET: positron emission tomography

PFC: prefrontal cortex

PVEP: pattern visual evoked potentials

RAVLT: Rey's Auditory Verbal Learning Test

SGZ: subgranular zone

SN pc: substantia nigra pars compacta

SPECT: Single-photon emission computed tomography

SPM: statistical parametric mapping

SVZ: subventricular zone

UK: United-Kingdom

UPDRS: Unified Parkinson's Disease Rating Scale

VBM: voxel-based morphometry

VTA: ventral tegmental area

DOI:10.14753/SE.2021.2379

LIST OF TABLES AND FIGURES

TABLES

FIGURES

DOI:10.14753/SE.2021.2379

1. INTRODUCTION

1.1. Cognitive and affective functions in PD

Traditional theories of hippocampal formation emphasize its pivotal role in spatial and episodic memory. As an important part of the limbic system, it prominently regulates flexible cognition and social behavior. Histological studies suggested that it is affected in early stages of neurodegenerative disease where the cardinal symptom is a progressive cognitive decline, such as mild cognitive impairment (MCI), Alzheimer's disease (AD), and advanced stages of PD when the cognitive and affective non-motor symptoms reach a significative level. This classical view has recently been challenged. It has been highlighted that the hippocampal structural and consequent functional alterations characterize several neuropsychiatric disorders, not necessarily at an advanced disease stage. In PD the literature highlights a possible association between altered hippocampal function and early non-motor symptoms. These hippocampal impairments pertain to neuropsychiatric symptoms such as subtle depression, anxiety, apathy, and behavioral disorders even at an early phase (Calabresi et al., 2003).

In PD the characteristic dopaminergic loss results in impaired functions in basal ganglia motor circuit, clinically characterized by bradykinesia, rigidity, postural instability, and resting tremor. Within the basal-ganglia network, resting-state fMRI in non-medicated PD patients showed an attenuated connectivity between posterior putamen and globus pallidus internus, in contrast to enhanced connections of the subthalamic nucleus. In cortical motors areas these abnormalities might result in an exaggerated inhibitory output contributing to bradykinesia. The increased activity between the subthalamic nucleus and cortex lags behind the appearance of resting tremor. L-DOPA administration is able to reestablish the striato-thalamo-cortical motor circuit (Gao et al., 2016).

Dopamine deficiency is a key aspect in PD pathophysiology. The discovery of dopamine in basal ganglia is one of the most important landmarks in PD's therapeutic development. Firstly, in 1959 animal models suggested a possible central, 'extrapyramidal effect' of l-DOPA, a precursor of dopamine synthesis. In the following years post-mortem studies performed on PD patients confirmed the striatal dopamine

deficiency, setting the scientific proof of a benefic effect of l-DOPA replacement therapy. Clinical trials with l-DOPA administration defined the dopamine substitution therapy as a gold standard in PD (Hornykiewicz, 2010).

The substitution therapy in the early disease stage assures an equilibrated daily dopamine level, but later, due to the progressive neurodegeneration, there is an increased necessity of the replacement therapy. The consequent fluctuating dopamine levels might result in motor complications, including wearing-off phenomenon, freezing of gait, and levodopa-induced dyskinesia. Epidemiological data indicates that within 2-5 years form the onset, 50% of PD patients might experience treatment related motor fluctuations. The prevalence of these complications might rich 80-100% within 10 years (Freitas et al., 2017).

Due to its disabling effect on patient's quality of life, the non-motor symptoms also received widespread attention. The broad spectrum of non-motor symptoms includes mood disorders (anxiety, depression), cognitive changes (memory, attention, and learning deficits), and impulsive-compulsive symptoms.

DOI:10.14753/SE.2021.2379

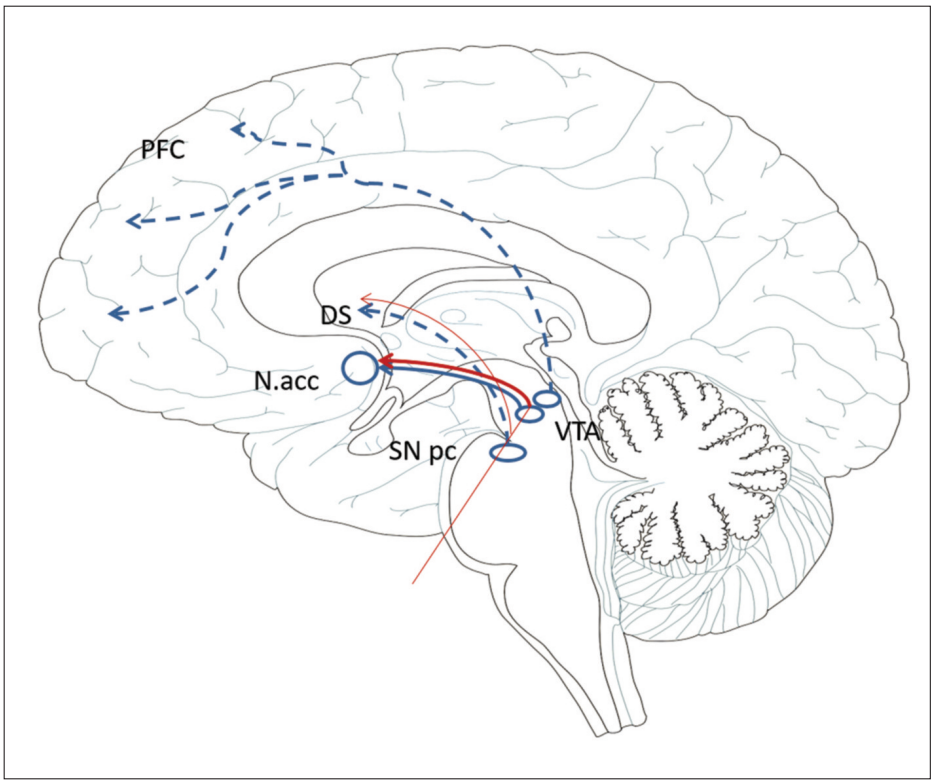

Figure 1. *Dopaminergic pathways in newly diagnosed PD*

The blue dashed lines show the deficient mesocortical (from ventral tegmental area to the prefrontal cortex) and nigrostriatal pathway (from substantia nigra pars compacta to dorsal striatum composed of nucleus caudatus and putamen) inducing the classical motor symptoms and impaired executive functions. The red line shows the effect of dopaminergic treatment that reestablish the deficient dopamine levels in nigrostriatal pathway but overdose the relatively intact mesolimbic projections responsible for psychiatric complications (impulsivity and psychotic symptoms).

The long-term cumulative prevalence of psychotic symptoms might reach 60%, typically in the form of visual hallucinations. A possible explanation might be that the chronic l-DOPA therapy excessively stimulates the mesocorticolimbic D2/D3 receptors (Wolters et al., 1999). However, there is not a clear correlation between dopamine dosage or treatment duration and the severity of psychotic symptoms (Aarsland et al., 1999).

At a closer perspective it seems that there is a clinical difference between PD associated depression and primary mood disorders. Depression in PD might be associated more frequently with anxiety, suicide ideation, less guilt and self-reproach compared to major depression. Impulse control disorders (ICD) including compulsive gambling, buying, hypersexuality, and binge eating are recognized as a side effect of D2/D3 receptor agonist therapy. At least one of the above-mentioned ICD appears in 14% during the therapy, while 4% of patients have more than one such disorders. Dopamine dysregulation syndrome (DDS), another manifestation of ICD, appears at a similar incidence (14%) (Weintraub et al., 2011).

Imaging studies confirmed the mesocortical and mesolimbic dopaminergic pathway's involvement is ICD. PET studies revealed that PD patients with ICD showed higher dopamine release in the ventral striatum for reward-related cues overwhelming the brain's reward circuit in the limbic system (Jimenez-Urbieta et al., 2015).

In several cases psychotic symptoms in PD remain subclinical manifestations that do not require antipsychotic treatment, but it might affect the patient's goal-oriented learning strategies. Our group conducted a study in newly diagnosed PD patients in order to examine in more details the reinforcement learning methods. Specifically, the incentive (adaptive) salience is attributed to phasic dopaminergic signals in response to reward predicting cues appearing in a well-predictable manner. A disorganized, unsettled stimulus-reward association related to dopaminergic treatment might lead to the emergence of aberrant salience linked to psychiatric disorders (schizophrenia-psychotic-like experiences spectrum). By implementing a computer based salience attribution task, we examined the conditioning effect of dopaminergic medication in PD patients, and in parallel we assessed psychosis-related feelings and experiences. According to our results, the dopamine agonist therapy facilitated not only adaptive, but aberrant salience as well, and mood elevation correlated with increased (but clinically irrelevant) Oxford-Liverpool Inventory of Feeling and Experiences (O-LIFE) unusual experiences (Nagy et al., 2012).

Subclinical psychosis-like experiences might be explained by low latent inhibition (LI) related to dopaminergic medication. LI in classical conditioning refers to an individual's ability to recognize and update the changed value (positive or negative) of a previously exposed irrelevant stimulus. According to the LI paradigm, the previously experienced irrelevant stimulus needs longer time to acquire value and relevance in a new context relative to novel stimuli that were not acquired as irrelevant. Patients with schizophrenia show low LI, which may reflect altered associations between a conditioned and an unconditioned stimulus when the conditioned stimulus was previously experienced in a different context. In other worlds the patients have difficulty to detach from past experiences (Swerdlow et al., 2003). LI can be facilitated by dopamine antagonists: animal experiments demonstrated that rats injected with 0.1 mg/kg haloperidol in a behavioral paradigm showed a more pronounced LI effect (Weiner and Feldon, 1987). Remarkably, amphetamine and other D2 dopamine agonists attenuated visual LI in healthy subjects in a within-subject, placebo controlled study design (Swerdlow et al., 2003).

Animal experiments described the phenomenon of LI in amphetamine induced schizophrenia models. The experiment reported that 15 daily injections of 1.5 mg/kg dl amphetamine significantly reduced LI, which was interpreted as an attentional deficit that might be similar to human subjects' inability to ignore irrelevant stimuli (i.e. to correctly direct their attention).

Weiner et al., suggested that amphetamine might modulate the dopaminergic system and the LI in a dose dependent manner. Low doses (1 mg/kg) of amphetamine enhance the mesolimbic pathway, while high doses (5 mg/kg) boost the nigrostriatal dopaminergic pathway. They reported enhanced locomotor effect and abolished LI after low doses of amphetamine injected into the nucleus accumbens (n. acc). In contrast, high doses of amphetamine boosted the stereotyped behavior, mediated by nigrostriatal system, but did not affect LI. These finding suggesting that the LI disruption might be modulated by the mesolimbic dopaminergic system (Weiner et al., 1988).

The dopaminerg dysfunction represents a reciprocal association between PD and schizophrenia: in schizophrenia, phasic dopaminergic activity is exaggerated in the associative striatum, whereas in PD the pathological hallmark is the loss of dopamine.

The memory impairments may also present a reversed pattern that can be demonstrated by the LI effect (Lubow et al., 1999).

Given the above-mentioned evidences, it is possible that non-medicated PD patients (decreased dopaminergic activity) show an increased LI, which may be reversed by dopaminergic medications (Lubow 1999).

Our research group aimed to evaluate the modulating effect of the dopaminergic therapy on LI and schizotypal traits in PD patients compared to a healthy control group. We assessed LI with a visual search task. In the pre-exposure phase, the subjects learned to identify a target stimulus among distracters. During the next step, the targets varied (in first condition the target was the same stimuli as the distracter in the pre-exposure phase, and in the second condition the target was a new stimulus). The dependent variable was the reaction time of the target identification. Schizotypal traits were assessed with the O-LIFE questionnaire, measuring four dimensions of schizotypy: unusual experiences, introvertive anhedonia, cognitive disorganization, and impulsive nonconformity. Compared to healthy controls, the PD patients on dopaminergic therapy scored higher on all four subscales of schizotypal traits, but the cognitive disorganization seemed the most relevant trait. PD subjects compared to controls presented significantly lower reaction time to recognize the targets on the task assessing LI. The correlation analysis revealed that the daily levodopa equivalent dose (LED) positively predicted the scores measuring unusual experiences and cognitive disorganization. These results could be explained by the fact that in PD the replacement therapy might direct the cortico-hippocampal network into exploratory behavior without contextual relevance. The finding that LI was negatively predicted by LED suggests a dose-dependent disrupting effect of dopaminergic drugs (Polner et al., 2016).

1.2. Hippocampal subregional organization

The hippocampal formation is a relatively small structure in order of a few millimeters. Cytoarchitecturally it is divided into Cornu Ammonis fields (CA1-CA4), dentate gyrus, and subiculum (Strange et al., 2014). The main function of the hippocampal formation is memory acquisition, which is structurally linked to a trisynaptic circuit. The trisynaptic wiring starts at entorhinal cortex (EC) sending the

major polymodal sensory input to the dentate gyrus (DG) via the perforant pathway. The axons of DG granule cells (mossy fibers) project to CA3 pyramidal cells, which then project through Schaffer collaterals to CA1 pyramidal cells. The CA1 subregion receives preprocessed information from the subnetworks of the DG and CA3, but also receives direct projections from the EC. The axon collaterals of CA3 pyramidal neurons form a recurrent autoassociative network. The CA1 pyramidal neurons are the major output relay neurons, projecting via the subicular complex back to the EC and to various subcortical and cortical areas (**Figure 2**) (Neves et al., 2008).

Considering the complexity of the hippocampal network, it has been suggested that these subregions perform complementary operations in different cognitive tasks. The CA1 subregion has a main role in detecting the contrasts between the unprocessed sensory data arriving from EC and familiar information transferred from the CA3. The CA1 is also involved in autobiographical memory retrieval and in learning the map-like representations. The DG differentiates the similar and dissimilar patterns. The operation is termed pattern separation, which is a prerequisite tool in novelty detection. The autoassociative CA3 region is able to reconstruct the whole memory trace through pattern completion by using a just a fragment from a previous experience (Bartsch et al., 2015).

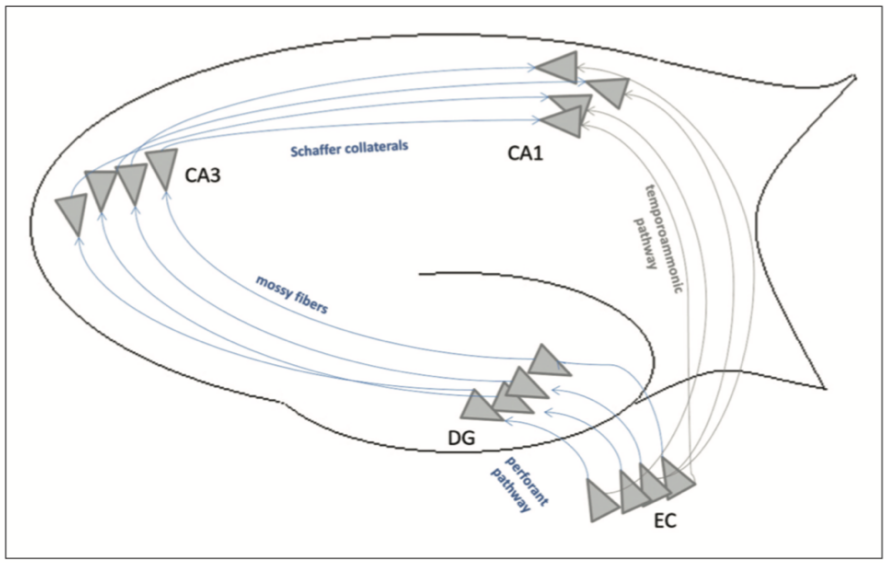

Figure 2. *Connectivity within the hippocampus*

The trisynaptic pathway from the EC via the DG, CA3 and CA1 subregions represents the main direction of the information flow. The CA1 subregion represents the anatomical junction between the novel and already known sensory data.

1.3.Dopamine dependent hippocampal operations

The hippocampus can be considered a hub in the center of a functional loop, connecting the medial temporal lobe, basal ganglia, midbrain, and frontal lobe. The meso-corticolimbic dopaminergic projection connects the ventral tegmental area (VTA) to medial temporal lobe, including the hippocampus, where long-term potentiation takes place as a substrate of memory formation **(Figure 1)**. The neurobiological model of learning discloses that the information storage implies a durable strengthening of the neural connections in order to enhance synaptic transmission (O'Keefe et al., 1971; Strange et al., 2104).

The classical views of hippocampal long-term potentiation (LTP) (Nicoll et al., 2013) does not emphasis dopaminerg modulation during the prototypical cellular LTP cascade. However, in-vivo animal experiments highlighted the dopaminergic boosting effect on the LTP. In freely moving rats, electrical stimulation of the Schaffer collaterals and recording the resultant excitatory postsynaptic potentials (an indirect measure of synaptic transmission) in CA1 hippocampal regions showed that the LTP can be induced

by spatial exploration. D1/D5 receptor agonist administration lowered the electric threshold needed to induce LTP. The novelty related dopaminergic signal is able to activate the CA1 region necessary to LTP related denovo protein synthesis, which is crucial for the maintenance of subsequent synaptic changes (Lemon et al., 2006).

In-vitro experiments in human and rat hippocampal slices, stimulating the perforant path and recording the DG, found that D1 receptor agonists increase the synaptic response in DG, suggesting an indirect proof that the dopamine signal elicited from the VTA into DG amplifies dendritic excitability (Hamilton et al., 2010).

Based on these finding it can be summarized that in early phase of PD mood disorders and cognitive impairments might be a consequence of dysfunctional hippocampal synaptic plasticity influenced by altered dopaminergic neurotransmission (Calabresi et al., 2013).

In PD the accumulation of pathologic alpha-synuclein in hippocampal cells might impede the physiological response to VTA originated dopaminerg input. In experimental PD models, electrophysiological studies showed a reduced synaptic transmission in CA1 hippocampal area. The altered synaptic transmission was restored after l-DOPA administration. Another alteration in PD that contributes to diminished LTP is the decreased ratio of NR2A/NR2B subunits of the NMDA receptors, as observed in 6-hydroxydopamine (6-ODHA) lesioned animals (Costa el al., 2012).

The functional connection between the hippocampus and n.acc is considered a limbic integrator network responsible to direct the motor executive control toward salient (reward-oriented) decisions (Sesack et al., 2010). It has been hypothesized that the striatum has different functional roles in learning along the longitudinal axis. The ventral striatum (n.acc) is implicated in similar cue association (optimal stimuli-stimuli choices) by recognizing a sequential pattern, whereas the dorsal striatum is in charge for pattern formation among discrepant, irregular stimuli. The n.acc nucleus receives dopaminerg input from the VTA, while the substantia nigra supplies the dorsal striatum. The replacement therapy might overdose the unaffected ventral striatum, resulting in impairments in learning ordinary stimuli-stimuli associations. This hypothesis has been demonstrated in a cue selection task during which PD patients on dopaminergic medications showed a decreased performance in analogous stimuli recognition, even

without an immediate feedback. The medicated patients selected better the cues under ambiguous influences (MacDonald et al., 2011).

1.4. Hippocampal subregional volume changes in psychiatric and neurodegenerative disease

Researchers aiming to describe the profile of the hippocampal subregions applied manual segmentation for many years. However, manual segmentation is time consuming, the amount of processed data is limited, moreover, the subjectiveness of intra- and interrater variability also could influence the statistical results. Neuroimaging developments implemented automated segmentation from ultrahigh resolution MR images. The FreeSurfer software (Laboratory for Computational Neuroimaging, Boston, United States) that works with commonly available T1-weighted MRI sequences enables automated segmentation of the hippocampal subfields, using information obtained from manual segmentation. In brief, the technique was developed by Van Leemput et al. (2009). Initially, in ten healthy subjects they divided manually the right hippocampus into seven subfields including the presubiculum, subiculum, CA2-3, CA4-DG, fimbria, from T1-weighted coronal 3 Tesla MR images. The segmented data were used to create a probabilistic atlas mesh. The automatically segmented images were correlated with the manual segmentation. The software computations predict how the voxels on the labeled image are related to a specific hippocampal subfields (Van Leemput et al., 2009).

By implementing the FreeSurfer software, several associations have been discovered between different psychiatric and neurological conditions and hippocampal structural alterations.

An extensive research compared the hippocampal subregional volumes of 702 psychiatric patients (diagnosed with schizophrenia or bipolar disorder) to age-matched healthy controls. The patient group showed bilaterally smaller CA2-3, CA4-DG, subiculum, and right CA1 volumes compared to control subject. Examination of the patient group revealed that schizophrenic patients had bilaterally smaller subiculum and a more severe, right sided presubicular volume loss than the depressed subjects. The subicular atrophy positively correlated with negative symptoms. These outcomes support the presence of hippocampal structural abnormalities in psychiatric diseases, particularly

the involvement of the hippocampal outflow region (subiculum and presubiculum) (Haukvik et al., 2014).

Another study investigating schizophrenic patients reported a negative correlation between positive symptoms (hallucinations and delusions) and CA1 and CA2-3 hippocampal subregional volumes. The results strengthen the CA1 and CA3 hippocampal subfields' role in the generation of positive psychotic symptoms (Kuhn et al., 2012).

Van Mierlo et al. (2015) published a negative correlation between bilateral hippocampal and right amygdala volume in depressed PD patients. However, their patients were not de novo diagnosed, they had a mean disease duration of 2.95 years and they received already l-DOPA therapy (Van Mierlo et al., 2015).

Apostolova et al. (2010) aimed to describe the pattern of hippocampal volume changes in PD patients and its correlation with memory performance. The study population consisted of non-demented PD patients with and without visual hallucinations and a control group. Using automated volumetry, they differentiated seven hippocampal subfields, including the CA sectors, subiculum, presubiculum, and the DG. Comparing the hippocampal subfields, the patient group presented CA2-3 and CA4-DG volume loss versus controls, while PD patients with visual hallucinations presented an additional subicular atrophy. Examining the whole patient group, the learning scores correlated with CA2-3 and CA4-DG volumes, while the authors did not find any association regarding recall performance and recognition memory. The association of regional atrophy pertaining to DG-CA3 volume (the hippocampal input regions) with learning deficits confirmed the functional specialization of hippocampal subfields in memory processing (Apostolova et al., 2010).

A study conducted in 31 drug-naïve patients with AD found that the hippocampal presubicular and subicular volume positively correlated with CEARD verbal delayed recall scores, confirming these subregional involvement in episodic memory (Lim et al., 2013). Similarly, patients with MCI with vascular etiology shower reduced hippocampal volume in left subiculum, presubiculum, and right CA4-DG compared to controls. This is in line with the assumed hippocampal ischemic vulnerability (Li et al., 2016).

Investigating in more details the volumetric changes in the limbic system of PD patients, Junqué et al. (2005) found that PD patients without dementia showed 10% higher reduction in amygdala and hippocampal volume compared to age-matched controls. The

difference in percentage was doubled to 20% when comparing demented PD subjects to healthy controls (Junqué et al., 2005).

Researching the hippocampal subregion's role in memory performances by implementing the automated segmentation method, Pereria et al. (2013) found smaller CA2-3, CA4-DG in non-demented PD patient group compared to elderly controls. The correlation analysis found a significant association between CA2-3, CA4-DG and verbal learning and long-term recall scores. This outcome highlights the hippocampal input regions role in learning performances (Pereria et al., 2013).

In newly diagnosed, drug-naïve cognitively intact and PD patients with MCI Beyer et al. (2013) studied the pattern of verbal memory processing. They found that in PD subjects delayed free recall scores correlates with CA1, CA3 and subicular volume, whereas impaired recognition was associated with CA1 atrophy. The involvement of the posterior hippocampal region in verbal memory recall and retrieval assumes that in early stages of PD the memory consolidation pattern is affected (Beyer et al., 2013).

It can be concluded that in the past two decades several studies demonstrated the hippocampal involvement in non-demented PD patients. Even early neuropathological studies emphasized the link between the medial temporal lobe pathology and PD (Double et al., 1996). Early neuroimaging studies intending to detect a biological marker of early AD reported that hippocampal volume loss is not a unique finding in AD, because hippocampal atrophy also occurred in non-demented PD patients (Laakso et al., 1996). Consistent with neuropathological and neuroimaging studies, early clinical trials also showed that visual and verbal memory deficits correlated with hippocampal atrophy in cognitively intact PD patients (Riekkinen et al., 1998).

However, although most of the studies agree on hippocampal atrophy in non-demented PD patients, some results are still inconclusive.

Researchers created 3D statistical maps to get a better insight into the structural changes of the hippocampus and nucleus caudatus in PD patients with and without dementia. The cognitively impaired PD patients showed atrophy at the head of the caudate nucleus and enlargement of the posterior part of the lateral ventricles. This study group did not detect statistically significant hippocampal atrophy (Apostolova et al., 2010).

DOI:10.14753/SE.2021.2379

Voxel based morphometric studies intended to characterize the pattern of cerebral atrophy in neurodegenerative diseases. One study compared patients with neurodegenerative diseases to elderly controls: frontal lobe atrophy was evident in PD without dementia, extending into medial temporal, occipital and parietal areas in PD cases with dementia. In AD the same areas seemed to be affected with a more severe medial temporal lobe engagement (Burton et al., 2004).

DOI:10.14753/SE.2021.2379

2. AIMS

Our thesis aimed to verify the following hypothesis:

1. In the first part of our study (Study 1), we evaluated the potential psychomimetic-like effect of a single dose of l-DOPA in patients with PD. We hypothesized that a single dose of l-DOPA might induce subclinical psychosis-like symptoms through decreasing LI.

2. In the second part of our study (Study 2), we measured the hippocampal subfield volumes of drug-naïve, cognitively intact PD patients to healthy controls. We hypothesized that the newly diagnosed PD patients might show decreased CA2-3, CA4-DG hippocampal volumes compared to controls.

3. We investigated the link between the extent of hippocampal volume reductions and clinical symptoms with a special attention to depression. We hypothesized that the volumetric changes are associated with the depressive symptoms.

4. We followed-up the hippocampal volumetric changes after l-DOPA treatment. We hypothesized that l-DOPA treatment might have a benefic effect on hippocampal subfield.

DOI:10.14753/SE.2021.2379

3. METHODS

3.1. STUDY 1: The effect of l-DOPA on LI and its psychoactive effect

3.1.1. Participants

We recruited 28 newly diagnosed, drug-naïve patients with PD and 25 healthy individuals matched for age gender and education at the National Institute of Psychiatry and Addiction, Budapest, Hungary. All participants signed a written consent, the study was conducted in accordance with the Declaration of Helsinki. The study was approved by ETT-TUKEB (18/2015).

To establish the diagnosis of PD, we used the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Hughes et al., 1992). In order to rate the disabilities and impairments, we used the Hoehn–Yahr Scale (Hoehn and Yahr, 1967) and the Unified Parkinson's Disease Rating Scale (UPDRS) (Lang and Fahn, 1989) (Table 1).

Table 1. Study 1. *Demographic and clinical characteristics of PD patients and healthy controls*

Data are mean (standard deviation) with the exception of gender, side of motor symptom onset, and Hoehn–Yahr stages. Two-tailed t tests and Chi-square tests indicated no significant differences between the patients with PD and healthy control individuals in demographic parameters
off l-DOPA: patients before l-DOPA intake, on l-DOPA: the same patients after l- DOPA intake

	Parkinson's disease (N=28)	Healthy controls (N=25)
Age (years)	50.6 (6.3)	51.2 (6.8)
Gender (male/female)	19/9	17/8
Education (years)	14.0 (3.5)	13.8 (3.8)
Time since onset of first symptoms (months)	19.5 (7.7)	
Hoehn–Yahr stages (stage: number of patients)	1: 4; 1.5: 2; 2: 20; 2.5: 2	
UPDRS total	38.9 (5.3)	
UPDRS motor off l-DOPA	25.7 (4.0)	
UPDRS motor on l-DOPA	19.3 (4.1)	
Side of motor symptom onset	Left: 20 Right: 8	

3.1.2. Screening for psychosis-like experiences and psychomimetic effect

To detect the possible subclinical psychotic symptoms, we implemented the (Community Assessment of Psychic Experiences) CAPE scale, a 42-item self-report questionnaire. The participants were screened for positive symptoms (ideas of reference, suspiciousness, and paranoid tendencies), negative symptoms (social withdrawal, decreased experience of pleasure, and blunted affect), and depression (Konings et al., 2006). The potential psychoactive effect of l-DOPA was evaluated with the visual

analogue scale (VAS). The VAS scale is a 100 mm long horizontal line with a description at each end expressing the two extremes of the corresponding feeling. This assessment pertained to perception (changes in experiences of thinking, passing of time, and mental 'highness'), relaxation (experiences of mental slowness, drowsiness, and muzziness), and dysphoria (suspiciousness, feeling of special meaning, and experiencing voices that are not real) (Kleinloog et al., 2014).

3.1.3. Evaluation of LI

LI was assessed with a computer-based visual search task. Twenty figures were displayed on a computer screen. Nineteen had similar shape and size (distractor stimuli), one was different (target stimuli). The participants had to press the left arrow key as quickly as possible if they observed the target stimulus on the left side of the screen or the right arrow key if the target was on the right side of the screen. To acquire the target-distractor rule, the participant in the pre-exposure phase completed 96 trials. The following test phase consisted of a 'pre-exposure' conditions: the distractor became the target, and the target stimuli were the distractors. The participants had to switch the target-stimulus rule to complete the task. In the 'non-pre-exposure' condition, the target was a completely new figure. The extent of LI was measured by the mean reaction time difference between the pre-exposure and non-pre-exposure conditions. The slower 'switch' in pre-exposure conditions resulted in a larger difference, indicating higher LI **(Figure 3),** (Lubow et al., 2000; Kéri 2011).

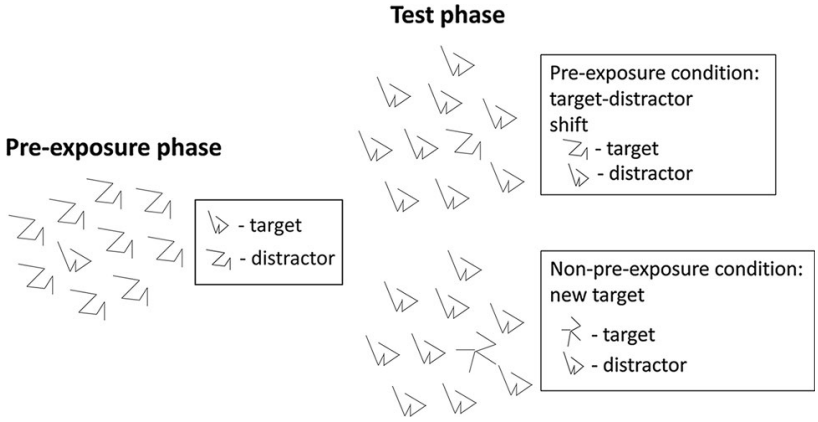

Figure 3. *Latent inhibition testing paradigm*

In the pre-exposure phase, participants completed a visual search task (the detection of the right-left location of a target). In the subsequent test phase, there were two critical conditions. In the pre- exposure condition, the target of the previous pre-exposure phase became the distractor, and the distractor became the target (target- distractor shift). In this condition, the previously salient target became non-salient, and the previously non-salient (latently inhibited) distractor became salient. In the non-pre-exposure condition, the target was new. In this condition, the salient stimulus (target) was not exposed before as a non-salient stimulus, and it was not latently inhibited

3.1.4. Experimental procedure

At the baseline the PD patients were enrolled into a ’placebo group’ or a ’treatment group’ receiving 250 mg l-DOPA/62.5 mg benserazide (8–11 a.m., before meal). The LI test, CAPE, and VASs were performed 60 minutes after the l-DOPA administration (Geffe et al., 2016) (Table 4). The follow-up testing took place after 2-3 days. The healthy controls received placebo, and they completed one testing session.

DOI:10.14753/SE.2021.2379

3.2. STUDY 2.: The effect of l-DOPA on hippocampal structure and clinical symptoms

3.2.1. Participants

In the second part of our study, we included 35 PD patients and 30 healthy controls matched for age, gender, and education. The patients were recruited through eight outpatients center specialized for movement disorders. The diagnosis of PD was made according to UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria. (Hughes et al., 1992).

We recorded the participant's demographic characteristics, socioeconomic status with Hollingshead Four-Factor Index (Cirino et al., 2002), and the general intelligence with the Wechsler Adult Intelligence Scale (WAIS-R) (Wisse et al., 2014) **(Table 2)**. To assess the stage of PD the patients received the Hoehn–Yahr scale (Hoehn and Yahr, 1967), number of patients in each stage: 1:7, 1.5:5, 2:20, 2.5:3, and the UPDRS (Table 3) (Lang et al., 1989). Further neuropsychological batteries included the Montreal Cognitive Assessment, Rey's Auditory Verbal Learning Test (RAVLT), semantic/phonological fluency, Visual Form Discrimination Test, and the Benton Facial Recognition Test (Pereira et al., 2013; Chou et al., 2010). The exclusion criteria included the presence of MCI, assessed with Movement Disorder Society Task Force guideline (Litvan et al., 2010), impulsive-compulsive spectrum behavior evaluated according to the criteria of Voon et al. (Voon et al., 2007), history of neurological and psychiatric disorders, diabetes mellitus, hypertension, and smoking. The participants were asked not to change their body weight with more than 2%.

3.3.2. Evaluation of mood disorders

The affective status was evaluated with the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A) (Table 3) (Mountjoy et al., 1982).

DOI:10.14753/SE.2021.2379

Table 2. Study 2. *Demographical characteristics of the participants*

Data are mean (SD) except gender distribution. There were no significant differences between Parkinson's patients and healthy control participants (ps > 0.5). RAVLT, Rey's Auditory Verbal Learning Test; BMI, body mass index.

	Parkinson's patients	*Control subjects*
	(n = 35)	*(n = 30)*
Age (years)	51.9 (7.2)	51.3 (6.4)
Gender (male/female)	21/14	20/10
Education (years)	14.5 (3.8)	14.1 (3.9)
Socioeconomic status	37.7 (9.1)	37.5 (10.6)
BMI (kg/m^2)	24.7 (7.6)	24.9 (8.1)
IQ	106.8 (11.0)	104.6 (11.0)
Montreal Cognitive Assessment	29.0 (3.2)	28.7 (2.9)
RAVLT—learning	42.8 (7.5)	41.8 (7.9)
RAVLT—recall	9.8 (2.7)	9.4 (2.5)
RAVLT—recognition	15.9 (2.1)	15.7 (1.9)
Semantic fluency	20.6 (4.4)	20.1 (5.0)
Phonological fluency	13.8 (4.2)	14.0 (4.5)
Visual Form Discrimination Test	31.0 (1.6)	31.2 (1.7)
Benton Facial Recognition Test	49.8 (2.7)	49.5 (2.6)

Table 3. ***Study 2.*** *Clinical measures of the patients with PD*

Data are mean (SD). Results from the baseline, non-medicated condition were compared with those from the follow-up, medicated condition by two-tailed t-tests.

	Baseline	Follow-up	t	p
UPDRS total	38.3 (5.1)	33.5 (5.7)	3.46	0.001
UPDRS motor	25.4 (3.8)	20.7 (4.4)	3.95	0.0003
HAM-D	11.6 (7.0)	7.6 (4.0)	2.45	0.02
HAM-A	3.5 (2.7)	4.0 (3.4)	-0.50	0.62

3.3.3. Experimental procedure

After implementing the neuropsychological batteries at baseline, the patients received l-DOPA therapy for 24 weeks (mean dose at follow-up: 450.0 mg/day, range: 300–600 mg/day), the necessary dosage was decided by the treating physician. After 24 weeks the patient and control groups completed the follow-up testing.

3.3.4. Structural Magnetic Resonance Imaging

For the hippocampal subfield segmentation, we followed the protocol published by Marizzoni et al. (2015) which provided a valid test-retest reproducibility between 13 sites in 65 elderly patients (Marizzoni et al., 2015). The protocol included a structural T1 volume measurement at baseline and follow-up sessions. [Philips Achieva 3 T scanner, magnetization- prepared rapid acquisition gradient echo, 3D sagittal acquisition, square field of view = 256 mm, acquisition matrix: 256 × 256, voxel size:1mm×1mm×1mm,TI=900ms,TE(shortest)=3.16ms, flip angle: 9 degrees, no fat suppression, full k space, no averages, acquisition time: 6 min and 50 s, acceleration factor: 2]

For image processing, we used the neuGRID platform and the longitudinal pipeline of FreeSurfer v6.0 with the “hipposubfields” flag (Reuter et al., 2012). After a within-session averaging of T1-weighted images, we performed an automatic hippocampal subfield segmentation (Van Leemput et al., 2009).

Image processing included the following steps:
(1) correction for within-subject head motion;
(2) removal of non-brain tissue using a hybrid watershed/surface deformation algorithm;
(3) affine registration to Talairach space;
(4) segmentation of cortical and subcortical structures with a Probabilistic Brain Atlas (Fischl et al., 2012).

With the automatic segmentation technique, we identified five hippocampal subregions: CA1, CA2–3, CA4–DG, subiculum, and presubiculum **(Figure 4).** Due to right-left anterior temporal lobe volumetric asymmetries, the hippocampal volumes were set by the total intracranial volume (Jack et al., 1989). Due to small volumes and scarce longitudinal reproducibility data, the fimbria and hippocampal fissure was not included in the segmentation (Li et al., 2016; Chou et al., 2010). As the literature review does not indicate a significant left-right dissociation between hippocampal sizes, the volumetric data was averaged between the hemispheres.

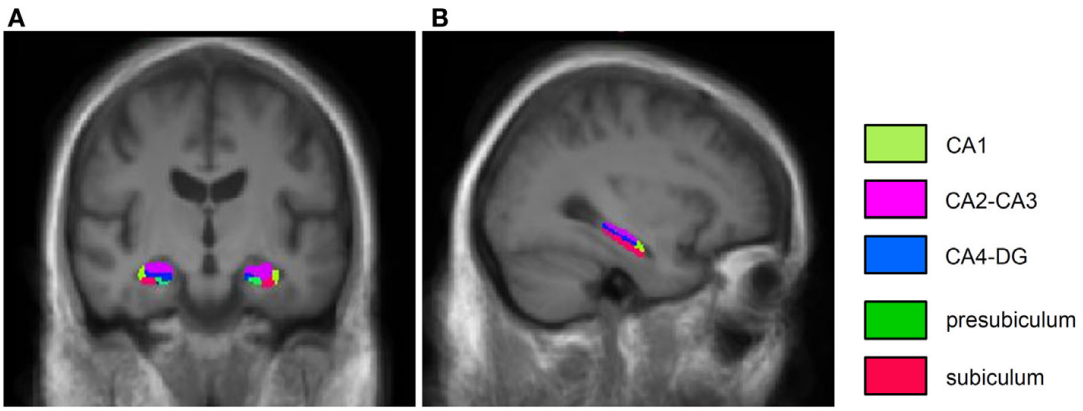

Figure 4. *Coronal (A) and sagittal (B) T1-weighted images from the average output of FreeSurfer hippocampal segmentation from healthy individuals.*

In 15 healthy control individuals, we validated the FreeSurfer hippocampal subfield measurement against the widely used AdaBoost machine-learning segmentation method (Beyer et al., 2013; Morra et al., 2008; Apostolova et al., 2010). AdaBoost employs statistical rules for subfield segmentation based on numerous voxel-specific features (e.g., image gradients, local curvatures, classification of gray or white matter, and stereotaxic position of the hippocampus) using a training dataset. The AdaBoost algorithm labels each voxel in MRI images to be segmented and delineates hippocampal subfields. AdaBoost can detect hippocampal atrophy at least as effectively as manual segmentation and FreeSurfer (Morra et al., 2010). Intraclass correlation coefficients (ICCs) between AdaBoost and FreeSurfer delineations were calculated using a two-way random ANOVA model with absolute agreement (McGraw et al., 1996). We found good to excellent ICCs according to the definition of Cicchetti (Cicchetti, 1994) (CA1: 0.68; CA2– CA3: 0.76; CA4–DG: 0.79; subiculum: 0.67; presubiculum: 0.74).

Finally, we evaluated the test–retest reliability of automated FreeSurfer measures by calculating Pearson's correlation coefficients between subfield values measured at baseline and follow-up. We found high correlation coefficients indicating good test–retest reliabilities (CA1: 0.82; CA2–CA3: 0.81; CA4–DG: 0.80; subiculum: 0.84; presubiculum: 0.84).

3.3.5. Voxel-Based Morphometry (VBM)

A whole-brain VBM was performed to detect possible gray matter differences between PD patients and controls. We used the VBM8 toolbox of SPM8 and the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra toolbox under a MATLAB 7.14 platform (MathWorks, Natick, MA, USA) (Ashburner et al., 2007; 2009).

Image analysis involved the following steps:

(1) segmentation of the raw MRI images in native space into gray matter, white matter, and cerebrospinal fluid;

(2) normalization of images to gray matter and white matter templates in stereotactic space;

(3) automatic segmentation of normalized images;

4) smoothing (8-mm, full-width, half-maximum Gaussian kernel).

DOI:10.14753/SE.2021.2379

We applied the general linear model for the statistical analysis of VBM data (voxel-wise estimation of the local amount of gray matter) with total gray matter volume as a covariate. The voxel-wise threshold was $p < 0.001$, uncorrected (extent threshold: $K = 20$ voxels). The extent threshold was determined with AlphaSim employing Monte Carlo simulations (number of iterations: 1,000, alpha-level: 0.05) (Ward et al., 2002).

DOI:10.14753/SE.2021.2379

3.3. DATA ANALYSIS

We used STATISTICA 12 (StatSoft, Tulsa) software package for data analysis. To test the assumption of normal distribution and inhomogeneity of variance we used Kolmogorov–Smirnov test and Levene's tests, respectively. In the behavioral studies, LI, CAPE, and VAS values were entered into a one-way analysis of variance (ANOVA) to determine the differences among PD-off (unmedicated), PD-on (medicated), and healthy control volunteers. The ANOVAs were followed by planned F tests. Pearson's product-moment correlation coefficients were calculated between LI and VAS difference values (PD-on minus PD-off) and the clinical symptoms. In the ANOVA exploring regional hippocampal differences, the experimental group (PD patients vs. control individuals) was defined as the between-subjects factor. The assessment sessions (baseline: non-medicated state in PD vs. follow-up: PD patients on l-DOPA) and hippocampal subfields were considered as within-subject factors. For post hoc comparisons for unequal samples, we used Tukey honestly significant difference (HSD) tests. Cohen's effects size values (d) were also calculated. The results were interpreted according to the standard classification: $d = 0.2$ was considered as small effect size, while $d = 0.8$ was considered as large effect size (Cohen, 1988). Differences in demographics data were assessed by two-tailed Student's t-test. The associations between scales assessing depression (HAM-D), anxiety (HAM-A), PD symptoms (UPDRS total and motor subscales), and hippocampal subfield volumes was estimated with Pearson's product-moment partial correlations. The correlation coefficients were calculated by Fisher r-to-z transformation. For the correction of multiple comparisons, we used the false discovery rate (FDR) method. The level of statistical significance was set at alpha < 0.05.

DOI:10.14753/SE.2021.2379

4. RESULTS

4.1. Latent inhibition

The one-way ANOVA showed a significant main effect [$F(2,78)=19.7$, $p<0.001$, $\eta^2 = 0.34$]. Figure 5. shows the between-group differences.

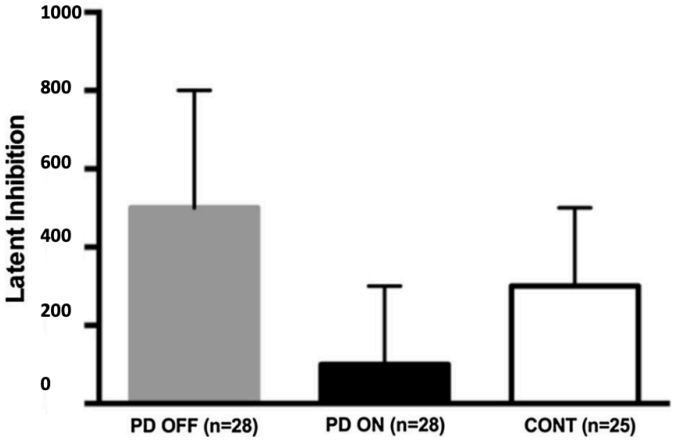

Figure. 5. *Latent inhibition in Parkinson's patients (PD) on and off l- DOPA and healthy control subjects (CONT). Columns are means, error bars are standard deviations. Parkinson's—OFF > controls > Parkinson's—ON (p <0.05)*

Drug-naïve PD patients presented significantly higher latent inhibition as compared with the control volunteers [$F(1,78) = 11.92$, $p = 0.001$], while PD patients on replacement therapy showed the reversed pattern: their LI values were significantly lower than that of the control individuals [$F(1,78) = 6.90$, $p = 0.01$]. As expected, medicated PD patients were characterized by significantly lower LI than patients off l-DOPA [$F(1,78) = 6.90$, $p = 0.01$]. We did not find any gender differences in LI between male and female patients with PD ($p>0.2$). Laterality (right vs. left onsets of motor symptoms) did not affect LI ($p>0.2$).

4.2. CAPE and VASs

The CAPE and VAS scores are depicted in **Table 4.** The variance analysis showed that from the VASs profile only perception differed significantly among the three groups (PD-on, PD-off, control) [$F(2,78) = 25.1$, $p<0.001$, $\eta^2 = 0.39$]. In PD patients on dopaminergic therapy we recorded higher scores on the perception scale [$F(1,78) = 29.52$, $p <0.001$]. The results were not significant in the case of non-medicated PD patients compared to the control group ($p = 0.34$).

Similarly, medicated PD patients displayed higher perception scores than non-medicated PD patients [$F(1,78) = 43.66$, $p<0.001$]. There were no main effects of the group for relaxation and dysphoria VASs and all CAPE values ($p>0.1$).

Table 4. *Latent inhibition, psychotomimetic effects, and CAPE values*

Data are mean (standard deviation)
a Parkinson's—off > controls > Parkinson's—on ($p < 0.05$)
b Parkinson's—on > Parkinson's—off = controls ($p < 0.05$);
off: patients before l-DOPA intake; on: the same patients after l-DOPA intake

	Parkinson's: off l-DOPA	Parkinson's: on l-DOPA	Controls
Latent inhibition[a]	530.6 (280.1)	130.4 (210.5)	300.9 (220.6)
Perception[b]	1.9 (2.2)	7.6 (4.4)	2.4 (2.1)
Dysphoria	0.9 (1.5)	1.4 (1.6)	0.9 (1.2)
Relaxation	9.9 (3.7)	9 (4.9)	11.1 (5.2)
CAPE positive	20 (5.6)	21.6 (6.2)	19.2 (4.8)
CAPE negative	17.7 (3.8)	18.3 (4.1)	18.5 (5.0)
CAPE depressive	11.7 (2.4)	10.4 (3.1)	10.6 (2.9)

DOI:10.14753/SE.2021.2379

4.3. Correlation between changes in LI and perception scores

We determined the possible relationship between changes in LI and perception scores. Specifically, we calculated the correlation between LI on vs. off l-DOPA (LI_{on} minus LI_{off}) and perception VAS on vs. off l-DOPA (VAS_{on} minus VAS_{off}). We found that lower LI scores were associated with a more pronounced increase in perception scores ($r = -0.47$, $p = 0.01$) **(Figure 6).**

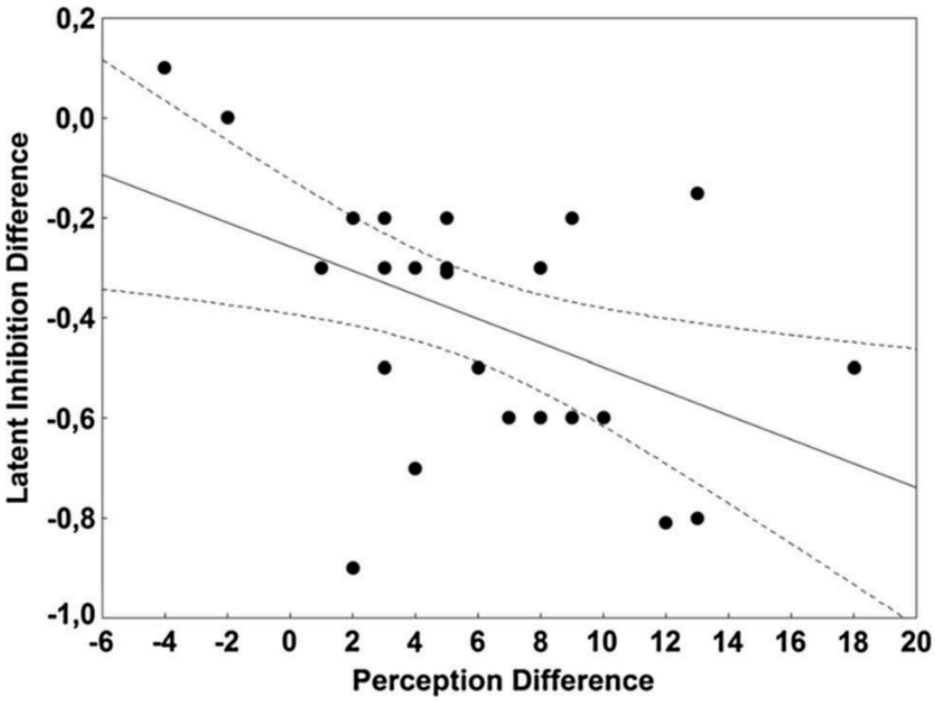

Figure 6. *Correlation between differences in perceptual experiences and LI (l-DOPA—on minus l-DOPA—off). The dotted lines show 95 % confidence intervals*

We also examined the correlation between the perception VAS scores and LI in the whole group (patients off and on l-DOPA, control subjects). The results revealed that higher perception scores were associated with lower LI ($r = -0.50$, $p<0.01$). The other VAS score changes did not correlate with LI changes, and there were no significant correlations among LI, VAS, and UPDRS scores ($r> 0.2$).

4.4. Hippocampal subfield volumes

The segmented hippocampal subfield images are presented in Figure 4. Hippocampal subfield volumes are shown in Table 5.

The results of ANOVA indicated a significant difference between PD patients and control subjects (a main effect of experimental group) [$F(1,63) = 4.01$, $p < 0.05$, $\eta^2 = 0.06$]. There was still significant main effect of assessment session (baseline vs. follow-up) [$F(1,43) = 30.54$, $p < 0.001$, $\eta^2 = 0.33$] and hippocampal subfields [$F(4,252) = 384.51$, $p < 0.001$, $\eta^2 = 0.86$]. We found two-way interactions between group and assessment session [$F(1,63) = 15.91$, $p < 0.001$, $\eta^2 = 0.20$], and assessment session and hippocampal subfields [$F(4,252) = 15.69$, 2 $p < 0.001$, $\eta^2 = 0.20$]. Most importantly, there was a three-way interaction among experimental group, assessment session, and hippocampal subfields [$F(4,252) = 13.59$, $p < 0.001$, $\eta^2 = 0.18$]. The Turkey HSD analysis on three-way interaction ANOVA (experimental group, assessment sessions and hippocampal volumes) showed a significantly smaller CA2–3 volumes in drug-naïve PD patients compared to healthy individuals ($p < 0.0001$). Cohen's effect size values ($d = 0.87$) also indicated a strong effect before L-DOPA, while, after the treatment, the d-value ($d = 0.15$) suggested a weak between-group effect. We did not detect any more significant volume changes between PD patients and control group neither at the first assessment ($ps > 0.7$) nor at the follow-up ($ps > 0.7$) **(Table 5).**

Table 5. *Hippocampal subfield volumes (mm^3)*

*At baseline, PD patients did not receive medications. Follow-up measurements were conducted after 24 weeks of l-DOPA treatment in the patient group. Healthy control subjects did not receive any medications. Hippocampal subfield volumes (mm^3) from the patients and control subjects were compared with ANOVA and Tukey's HSD tests (*p < 0.0001). Effect size values (Cohen's d) were also calculated. 95% CI: 95% confidence interval.*

	PD (n=35)			control (n=30)			Effect size
	Mean	SD	95% CI	Mean	SD	95% CI	d
Baseline CA1	342.3	69.3	318.5–366.1	350.6	70.8	324.1–377.0	0.12
CA2–3*	742.3	97.9	708.7–776.0	831.6	88.6	798.5–864.7	0.87
CA4–DG	543.5	73.5	518.2–568.7	567.8	66.1	543.2–592.5	0.34
Subiculum	589.3	75.2	563.5–615.1	574.6	90.9	540.7–608.6	0.18
Presubiculum	388.5	87.8	358.3–418.7	415.2	77.8	386.2–444.3	0.32
Follow-up CA1	345.0	71.6	320.4-369.6	355.6	73.0	328.4–382.9	0.15
CA2–3	851.7	83.4	823.1–880.3	838.6	88.0	805.7–871.5	0.15
CA4–DG	564.3	80.8	536.5–592.0	569.3	60.2	546.8–591.8	0.06
Subiculum	572.8	76.0	546.7–599.0	576.2	98.1	539.6–612.9	0.05
Presubiculum	386.0	91.0	354.8–417.3	418.5	79.6	388.7–448.2	0.38

In the PD group, during the follow-up, we found a significant volume enlargement in CA2-3 subregions (non-medicated vs. medicated state, $p < 0.001$). We did not observe other significant hippocampal volume changes between the assessments ($p > 0.5$).

4.5. Correlations between hippocampal subfield volumes and clinical symptoms

We determined the partial correlations between the hippocampal subregional volumes and clinical variables (UPDRS total and motor symptoms, HAM-D, and HAM-A) corrected for age, gender and education. The severity of depression, as measured by the HAM-D scores, correlated negatively with CA2-3 hippocampal volumes at both baseline and follow-up assessments ($r_{baseline} = -0.74$ and $r_{follow\text{-}up} = -0.37$, ps < 0.05) (**Figure 7, Figure 8.**), although the correlation coefficient at follow-up was significantly smaller than that at baseline ($Z = -2.25$, $p = 0.02$). Similarly, at the baseline assessment, higher anxiety scores correlated with smaller hippocampal volumes ($r_{baseline} = -0.47$, $p < 0.05$), although this association was not significant at follow-up. We did not find any relevant association between the remaining hippocampal subfields and UPDRS/HAM-D/HAM-A scores ($-0.3 <$ rs < 0.3, ps > 0.05). The FDR corrections indicated statistically significant relationship only between baseline depressive symptoms and CA2-3 volume.

DOI:10.14753/SE.2021.2379

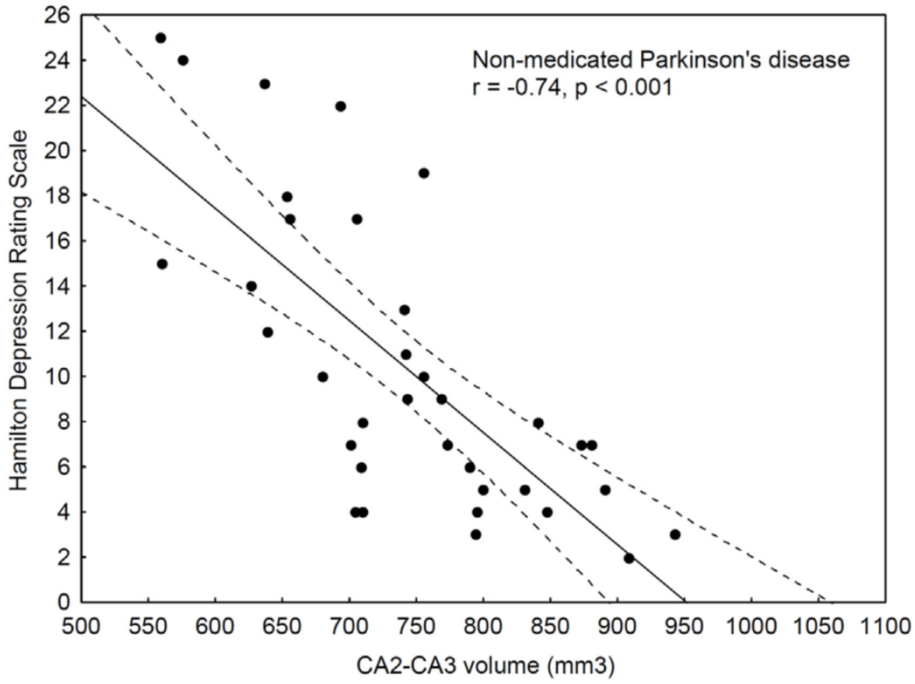

Figure 7. *Correlations between depressive symptoms and CA2–3 volumes before l-DOPA medication*

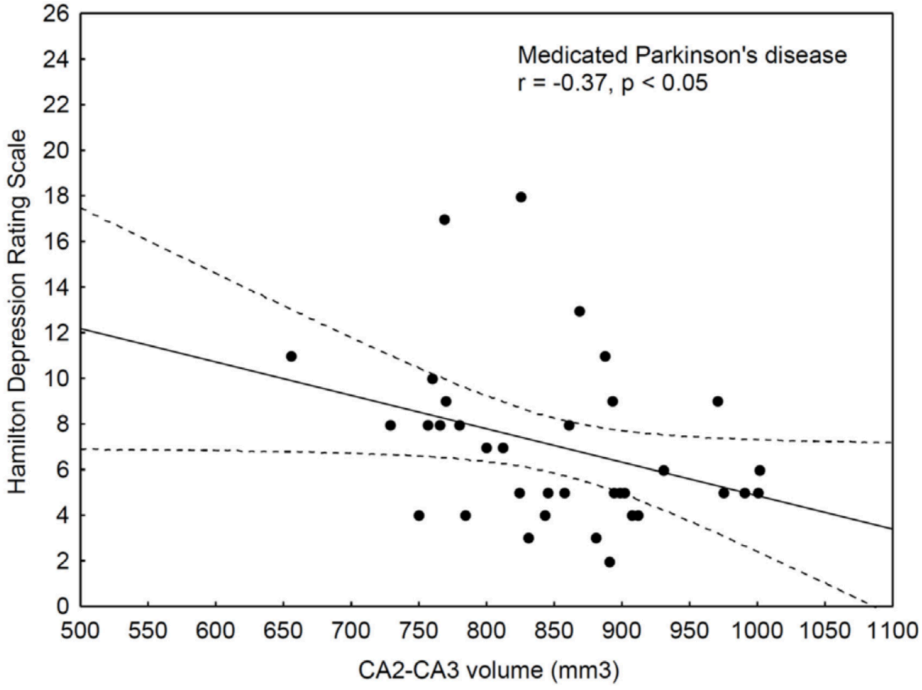

Figure 8. *Correlations between depressive symptoms and CA2–3 volumes after l-DOPA medication.*

DOI:10.14753/SE.2021.2379

4.6. Voxel-Based Morphometry

There was no significant difference in gray matter volume between PD patients and control subjects even at the screening threshold ($p < 0.001$, uncorrected).

DOI:10.14753/SE.2021.2379

5. DISCUSSION

5.1. Psychomimetic effect of a single-dose of l-DOPA

Our results confirm that even a single dose of l-DOPA has a psychoactive effect in drug-naïve PD patients. Patients on dopaminergic therapy encountered personal changes in their inner thinking process, time perception, and mental 'highness'. The patients did not experience subclinical psychosis-like symptoms (no significant changes in VAS dysphoria and CAPE positive symptoms) suggesting that in the initial stage of PD the psychiatric effect of a single l-DOPA dose differs from chronic mental changes caused by long-term replacement therapy.

Although, in our study, the patients on l-DOPA therapy scored higher on CAPE positive symptom questionnaire compared to controls, the results did not reach statistical significance ($p=0.14$). However, in healthy individuals receiving haloperidol or l-DOPA, Andreou et al. (2015) reported a linear association between CAPE scores sensory perception and overconfidence in errors (Andreou et al., 2015).

It has been hypothesized that in PD subjective perceptual changes could originate from a distorted time perception. According to the results of an early study, PD patients tend to overestimate time (Austin and Hayward 1969). Artieda et al. (1992) reported impaired temporal discrimination in PD patients for paired-pulse tactile auditory and visual stimuli. The deficit in all three sensory modalities were ameliorated after a single dose of 250 mg l-DOPA/25 mg carbidopa administration. The exact mechanism how the dopaminergic drugs modulate perception is not exactly understood. It has been suggested that the impairments in sensory information processing are a result of a deficient striatopallidal function. The basal ganglia are responsible to maintain focused attention, thus an attentional deficit could explain the abolished stimuli recognition (Artieda et al., 1992).

It has been suggested that dysfunctions in attentional set-shifting, which is mediated by connections between the basal ganglia and the prefrontal cortex, might play a role in the above-mentioned altered time appraisal. This condition is termed 'migration effect'. By implementing a task to estimate the duration of different visual signals (8 and 21 seconds) PD patients OFF medication tended to overrate the 8-second duration signal

and underrate the 21-second signal, so the peak estimations showed a numerical convergence (Allman and Meck 2012).

Another possible explanation points toward the pathologically increased pallidal inhibitory output to thalamus, resulting in deficient synchronization in thalamo-cortical circuits responsible for rhythmicity recognition. Reduction in rhythmic neural firing might impair circadian functions and internal time perception (Artieda et al., 1992).

Another approach of a deficient ’internal clock’ in PD patients came from the study of Lanage et al. (1995). In a verbal time estimation task, PD patient off l-DOPA medication underrated the time intervals. The time appreciation deficit was normalized after the l-DOPA medication (Lange et al., 1995).

The neurobiological model of human time perception could be explained in the context of information manipulation. In several pathological conditions (autism, ADHD, schizophrenia, PD) there is an apparent distortion in time perception. Hence, there is no specific organ to appreciate the elapsed time, from a psychological perspective it can be defined as the quantity of sensory responses to specific stimuli. These responses by definition are characterized by a subjective feeling (intensity) of perception (sensation) which is in a linear relationship with the magnitude of the external stimuli (Allman and Meck, 2012).

The Striatal Beat frequency theory might explain the dopaminergic boosting effect of time perception. It has been hypothesized that the sensing a ’to be’ time signal synchronize the synaptic weight between the cortical and thalamic neural populations. Thus, these neurons should undergo a phase reset in order to rich a synchronous oscillatory mode. Dopaminergic release from VTA resets the cortical neurons, while the dopamine from substantia nigra resets the dorsal striatal neurons.

The resulted synchronous oscillatory activation is sensed by basal ganglia input cells (medium spiny neurons), that considers these regularly occuring synaptic weights as time intervals. The striatal output via the direct and indirect pathway travels to thalamus, than to the cortex keeping under control the ability to adjust the the periodic oscillations. (Allman and Meck, 2012).

Neuroimaging studies demonstrated the role of basal ganglia in motor and perceptual timing. fMRI studies during a synchronization-continuation finger-tapping paradigm demonstrated reduced activity in supplementary motor area, with a concomitant

high cerebellar activation during temporal processing. These findings are in line with the functional neuroanatomical changes in PD: the striatal inhibitory output through fronto-striatal motor loops might alter some cortical areas (particularly the supplementary motor area), and these altered cortical operations seems to be overtaken by the cerebellum (Jones et al., 2014).

Besides temporal sensing, the dopaminergic medication might modulate visual perception as well. Prolonged latencies on visual evoked potentials (approximately 145 milliseconds binocularly) have been reported in PD patients. After l-DOPA administration, the latencies decreased and became closer to normal values. The authors suggested that the dopaminergic neurotransmission might boost the synapses in the optic pathway, but the exact level remained questionable, however the retinal level was already suspected (Bodis-Wollner et al., 1982).

Decreased PERG amplitudes and prolonged PVEP latencies in MPTP treated monkey PD models also confirmed the impairments in visual perception. Following Sinemet (levodopa/carbidopa) administration, the monkeys presented an immediate, but transient improvement in PVEP and PERG amplitude and latency. The explanation of these results is based on the discovery of D2 receptors in layer V. and VI. of the visual cortex, proofing the dopaminergic modulatory role in visual perception (Ghilardi et al., 1988).

Nowadays, these controversies regarding the background mechanism of the role of dopamine in the visual system seem to be clarified. Foveal vision impairment, also considered as a non-motor PD symptom, is the most reasonable explanation of visual impairment observed in PD patients. PERG studies with sinusoidal grating stimuli confirmed the existence of a retinal preganglionic dopaminergic circuit that is modulated by dopaminergic amacrine cells via D1 and D2 receptors (Bodis- Wollner et al., 2009).

Another significantly elevated component of our perception scale pertained to mental ’highness’. The definition of mental ‘highness’ is not as equivocal as in case of time perception: participants were asked to rate the statement ‘I feel high’ on the VAS, whereas in the case of time perception, the question was more straightforward (‘The passing of time was altered.’) (Kleinloog et al., 2014).

Mental highness might be a consequence of temporary mood elevation. The transient feeling of well-being is related to l-DOPA pleasure mediating effect. For

example Rutledge et al. (2015) in healthy young adults performed a value-oriented decision making gambling task, and they found that l-DOPA (50 mg of l-DOPA and 37.5 mg of benserazide) administration boosted the feeling of well-being, but the happiness feeling related to small gambling rewards was more significantly increased compared to control group (Rutledge et al. 2015).

Interestingly, Liggins et al. (2012) in healthy volunteers did not detect dopamine related positive mood changes after the administration of different Sinemet regimens (100 mg/25mg respectively 200 mg/50 mg). However, the researchers agreed on the idea that dopamine supports goal-directed behavior (directing the attention to reward-related cues) and subsequent subjective positive mood changes they raise the possibility that some individual personality traits might also contribute to subjective mood modulation (Liggins et al., 2012).

In DDS, the complication of long-term l-DOPA treatment is characterized by an excessive ’pleasure seeking behavior’ due to a pathological need (abuse) of treatment. Therefore, it is an ideal platform to study functional brain changes behind the hedonistic behavior (i.e., to measure directly the subjective effects of l-DOPA). Evans et al. (2006) used PET to study patients with DDS and to compare them to a PD group. In the DDS group, they found an augmented activity in ventral striatum, explaining functionally drug induced stereotype behaviors. The ventral striatal overactivity correlated with subjective l-DOPA ’wanting’, but not ’liking’. Furthermore, there was a negative correlation between ’wanting’ and ’liking’, suggesting the evolvement into l-DOPA tolerance (Evans et al., 2006).

To analyze in more detail the magnitude of l-DOPA psychomimetic effect, we compared our results with similar studies conducted with psychoactive pharmaceuticals. When measuring the VAS profile in healthy volunteers, the perception score was the highest for increasing doses of the ketamine (20 mg/70 kg/h during 1 h followed by 40 mg/70 kg/h for another hour): 74.1, followed by repeated doses (2, 6, and 6 mg with 90 min intervals) of Δ^9-tetrahydrocannabinol: 33.1. The effect of 80 nmol/l morphine resulted in a 9.1 perceptual score. Subjects receiving 600 mg/l ethanol for 2.5 hours reported 7.6 points increase in perceptual score, a similar change that we reported in our l-DOPA study. The validity and general reproducibility of our study design is supported

by the similar placebo VAS scores (1.9 in PD-off l-DOPA and 2.4 in controls) (Kleinloog et al., 2014).

Despite an intriguing scientific background, LI in PD is not an extensively studied research area. Lubow et al. (1999) conducted a similar study in drug-naïve PD patients to address the relationship between LI, gender, and the laterality of the PD symptom onset. LI was assessed with a visual search task consisting of a pre-exposure phase with a stable target-distractor rule and a test phase with varying targets (either from the pre-exposure phase or novel shapes). LI was measured as reaction time during target detection. Female patients with right-sided symptom onset had a higher LI, while male patients with right-sided onset and female patients with left-sided onset did not show LI (Lubow et al., 1999). Our results were partially consistent with these findings: PD patients off l-DOPA displayed higher LI than the controls, but it was not related to gender or symptom laterality. However, the absence of significant differences may be due to our small sample size and low statistical power. A novel finding extending the observations of Lubow et al. (1999) was that l-DOPA markedly decreased LI in PD patients receiving a single dose of l-DOPA.

5.2. Hippocampal volumes in PD patients vs. healthy controls

Our second hypothesis proposing a decreased CA2-3 andCA4-DG volumes in the PD group compared to controls was partially supported: the volumetric reduction affected only the CA2-3 subfields.

Traditional neuropathological studies indicated that PD is a neurodegenerative disease with cytoskeletal changes resulting in the accumulation of Lewy bodies in the perikarya and Lewy neurites near the axonal hillock. The abnormal inclusions consist of abnormally phosphorylated neurofilaments, ubiquitin, and α-synuclein. The limbic and motor systems are particularly vulnerable to these cytoskeletal changes, the affected neurons are subjected to earlier neural cell death. The exact reason why some brain regions are prone to neurodegeneration is not completely understood. Immunostaining methods confirmed the presence of a dense Lewy neurites in the CA2 hippocampal sector which might explain our finding regarding the observed volumetric reduction of this sector (Braak and Braak, 2000).

A more extended hippocampal volume reduction was reported in the study of Pereira et al. (2013). They examined the learning performance of 36 PD patients with and without visual hallucinations and correlated the results with seven hippocampal subfield volumes. The PD patients showed hippocampal volume reduction affecting the CA2-3 and CA4-DG subfields compared to controls. The group of PD patients with hallucinations presented a more pronounced CA2-3 volume decrease and smaller subicular volume. PD patients with visual hallucinations showed lower Mini Mental State Examination scores (but the scores did not indicate dementia), as well as impaired verbal learning and recall as compared to PD patients without visual hallucinations and healthy controls (Pereira et al., 2013). The pronounced hippocampal volume decrease might be due to a more prolonged disease state as compared to our study population. But our finding regarding the CA2-3 volume loss supports the idea that hippocampal structural alterations affect primarily the CA2-3 region in the early disease stage.

5.3. Correlation between hippocampal volume loss and depressive symptoms

We investigated the link between the extent of hippocampal volume reductions and mood changes. The etiology PD depression is multifactorial: some authors emphasize the reactive nature of mood disturbance, the importance of environmental factors, the social burden of a chronic illness (Sandoval-Rincon et al., 2015), but other authors state that it is rather an intrinsic, neurotransmitter-mediated phenomenon (Beyer et al., 2013). Depression is common in PD. According to a recent meta-analysis, major depressive disorder (MDD) appears in 17% in PD patients, with a pooled prevalence of 22.9% (Goodzari et al., 2016).

We found that CA2-3 subregional volumes loss correlated with the depressive symptoms in the early stages of PD.

The CA2 subregion's selective vulnerability in PD related mood disturbance might be due to its neuroanatomic connectivity. The CA2 receives inputs from septum, raphe nucleus, amygdala and hypothalamic regions, thus it might be implicated in affective and for social behavior (Chevaleyre et al., 2016). Activation of these inputs results in neuropeptide release (e.g. vasopressin from paraventricular hypothalamic

nucleus) that could prolong social memory formation, especially memory acquisition from 30 minutes to 7 days after the release (Smith et al., 2016).

Several neuroimaging reports aimed to characterize the brain structure modifications in PD related depression. PET and SPECT analysis of depressed PD patients without cognitive impairment showed modified metabolic activity in frontal lobe, striatum, and limbic system including the hippocampus, amygdala, thalamus, and anterior cingulate cortex compared to non-depressed PD patients without cognitive impairment or to healthy controls (Huang et al., 2013).

Following these findings, T1-weighted volumetric imaging in a similar study population suggested that depressive symptoms in PD might be associated with decreased prefrontal, parietal, insular, and limbic (anterior cingulate cortex and amygdala) grey matter volume (Kostic et al., 2010). However other reports did not find any volumetric differences in the limbic system of depressed vs. non-depressed PD patients (Berg et al., 1999).

fMRI studies conducted on depressed and non-depressed PD patients emphasized the role of the limbic thalamus in the pathogenesis of PD related mood disorder. Using a visual event-related fMRI paradigm (a presentation of Eckman's faces), depressed PD patients showed decreased activity in the left dorsomedial thalamic nucleus and dorsomedial prefrontal cortex compared to PD patients without affective symptoms (Cardoso et al., 2009).

The dorsomedial thalamis nuclei functions as a relay module, conveying dopaminergic projections from several anatomical areas, including the hypothalamus, periaqueductal gray matter, ventral mesencephalon, and the lateral parabrachial nucleus. However, the above mentioned dopaminergic connections are not similar with the affected traditional dopaminergic pathways in PD, but it is possible, that the dopaminergic degeneration affects them as well, with a consequent impact on mood regulation (Cardoso et al., 2009).

According to a VBM study conducted on cognitively intact PD patients (with approximately 3 years of disease duration), more severe depressive symptoms correlated negatively with bilateral hippocampal and amygdalar volumes. The correlations were positive between the depressive symptoms and anterior cingulate cortex. Van Mierlo et al. (2015). This effect might be a consequence of amygdalar Lewy body depositions. Van

Mierlo et al. (2015) suggested a similar pathomechanism in PD associated depression and MDD. Sustained stress through the activation of the hypothalamic-pituitary axis leads to elevated cortisol levels. The hippocampal region express glucocorticoid receptors, thus, high levels of corticosteroids might lead to decreased hippocampal synaptic plasticity, impaired neurogenesis, and lower expression of neurotrophic factor expression that ultimately results in hippocampal volume loss (Van Mierlo et al., 2015). Animal models showed a gender difference in corticosteroid sensitivity related depression: prenatal stress in mother rats resulted in elevated anxiety levels only in male offspring (Brunton et al., 2010).

In summary, the results of metabolic and structural alteration are not conclusive, but the involvement of the frontostriatal pathway in PD associated mood disorders seems to be an important pathological component (Wen et al., 2016).

The vulnerability of the CA2 region is also proved in several psychiatric diseases including schizophrenia, depression, and anxiety (Cole et al., 2010; Narr et al., 2004; Cha et al., 2016).

In MDD, the hippocampal volume loss affects the whole hippocampus (Kim et al., 2019), not just a circumscribed area as is our case. In our view, the limited hippocampal volume loss in our depressive PD patients could be explained with the early disease stage.

It is plausible that PD associated neurodegeneration and MDD might share several common pathways.

Neuropathological studies performed in patients with MDD highlighted glial pathology in brain structures critical for affective regulation such as prefrontal cortex, anterior cingulate cortex, and amygdala. Damage in glial cells through altered glutamate and GABA recycling and homeostasis leads to a depleted nutrient supply that might contribute to early cell death (Sibille et al., 2013).

The neurotrophic hypothesis posits that reduced levels of brain-derived neurotrophic factor in the hippocampus might be in the background of impaired neurogenesis that contributes to neurodegeneration (Zhao et al., 2008).

Another feasible cause of altered synaptic plasticity and consequent neural loss in both diseases might be inflammatory mechanism. Various cytokines, including interleukin-1α (IL-1α) and interferon-γ (IFN-γ), have been found in post-mortem

prefrontal cortex and peripheral nerves of MDD patients. It has been hypothesized that the presence of these cytokines could interpret the common symptom of 'sickness behavior' in infection and depression (Kim et al., 2016).

Our most important finding is related to the second assessment when PD patients received l-DOPA: the depressive symptoms ameliorated, and their correlation with the CA2– 3 volume was less pronounced.

A meta-analysis conducted on effectiveness of pharmacological options in PD associated depression found a possible benefic effect of dopamine agonist pramipexole. The authors stated that the positive mood changes could be explained as an indirect, benefic effect of an imporoved motor control (Sandoval-Rincon et al., 2015).

Similarly, Barone et al. in a placebo- controlled study (2010) reported the amelioration of the depressive sympotoms after pramipexole administration (Barone et al., 2010).

However, the exact mechanism is not clear, the literature data and our resuls proof the positive mood changing effect of dopaminergic medications. This finding has an important clinical significance, the amelioration of depressive symtomps might assist in quality of life improvements (Sandoval-Rincon et al., 2015).

.

5.4. l-DOPA treatment effect on hippocampal subfield

According to our results, 24-week treatment of dopaminergic medication restored the CA2-3 volumes. It can be hypothesized that l-DOPA can restore the hippocampal structural alterations the initial stages of PD. There are several possible background explanations.

Chiu et al. (2015), investigating the role of dopamine in hippocampal synaptic plasticity, suggested a key and lifelong role of two neural cell populations: one located in the subgranular zone (SGZ) of hippocampal dental gyrus, and the other placed at the subventricular zone (SVZ) of the lateral ventricle. In physiologic conditions, progenitor cells from the SGZ rich the dentate gyrus granular layer and turn into mature granule neurons. Similarly, precursor neurons from the SVZ migrate to olfactory bulb and became interneurons. It has been suggested that in a dopaminergic deficient condition, the precursor cell differentiation is downregulated, probably explaining the pathomechanism

of non-motor functions. Animal models aimed to determine whether dopaminergic medication (l-DOPA and/or pramipexol) can modify the neural cell proliferation in the SGZ and SVZ, enhance the motor functions, and non-motor PD symptoms. In pharmacologically induced toxic PD mice model (bilateral intranigral 6-ODHA injection), 20 weeks treatment either with pramipexol or l-DOPA increased the progenitor cell count in the olfactory bulb and hippocampal granule cell layer, proofing a reestablished neurogenesis. Clinically, the animals showed a positive mood changes (less depressed and anxious) (Chiu et al., 2015).

A different approach suggests that the dopaminergic therapy is able to restore the neurotrophic factor synthesis. It is hypothesized that the dopaminergic therapy, through D1 and D2 receptor stimulation, might enhance the nerve growth factor (NGF) and the glial cell – line derived neurotrophic factor (GDNF) synthesis. The augmented activation of these neurotrophic factors stimulates the astrocytes, boosting the neural life span (Ohta et al., 2010).

From a broader view, dopamine, besides the well-known role in movement- and mood disorders, is also a regulator of the immune function. Discovering dopaminergic receptors in human leukocytes highlighted the neurotransmitter's role in immune response. For example, in PD an abnormal T cell-mediated immune response is characterized by a reduced D3 receptor expression linked to reduced interferon-gamma synthesis (Sarkar et al., 2009).

Stage dependent alpha-synuclein depositions (Lewy bodies and Lewy neurites) are a well know pathological hallmark in PD. In- vivo imaging studies proved that alpha-synuclein promotes microglial activation in alpha-synuclein enriched regions, including the substantia nigra and the olfactory bulb. The alpha-synuclein activated microglia undergoes structural and functional changes: the cell shape is changed (from ramified structure into amoeboid shape). The modified microglia contributes to a region specific inflammatory responses via toll-like receptor-activated proinflammatory cytokines such as IL-6, IL-1, and TNF-alpha. The abundant microglia in the substantia nigra makes this region highly susceptible to inflammation-mediated damage (Chen et al., 2016).

Immunological studies in PD patient's substantia nigra and CA2 hippocampal region confirmed the link between the alpha-synuclein pathology, high levels of toll-like receptor expression, and pathologically modified microglia (Doorn et al., 2014). Based

on these evidences, targeting the toll-like receptors could be a possible new therapeutic approach in PD (Béraud et al., 2012).

In our study we considered several patient related individualfactors to obtain the most relevant results.

First, our subjects have been asked to take care not to change their body weight and physical activity habits during the study time. We based these restrictions on the fact that in AD patients, bilateral anterior hippocampal atrophy negatively correlated with the body mass index. Therefore, it can be hypothesized that any bodyweight increase might affect negatively the resistance of the neurovascular system, making the brain more vulnerable to atrophy (Ho et al., 2011). Moreover, it is not likely that non-specific factors may selectively affect the CA2–3 region.

To detect any potential volume loss outside the hippocampal region, we performed whole-brain VBM. We did not find any volumetric differences in extra-hippocampal regions in PD patients with intact cognitive functions compared to control subjects. Our finding is consistent with other VBM studies that did not reveal any significant gray matter loss between PD-MCI patients and healthy controls (Dalaker et al., 2010; Yarnall et al., 2014).

Two other VBM meta-analyses in PD failed to prove hippocampal gray matter reduction in cognitively intact PD patients. The first VBM analysis, exploring the structural brain differences in patients with idiopathic PD without cognitive impairment (compared to healthy controls), found grey matter reduction in left inferior frontal gyrus, expanding to superior temporal gyrus and insula, compared to healthy controls. The involvement of the orbitofrontal cortex might explain some of the depressive symptoms, executive dysfunctions, and the disturbances in sensory information processing. The reduced gray matter at the superior temporal gyrus contributes to impairments in social interactions, whereas the insula is involved in autonomic dysfunctions (Pan et al., 2012). Similarly, the second VBM study exploring the grey matter differences between non-demented PD patients and healthy controls found reduced grey matter in the left frontal lobe, parietal lobe, and anterior cingulate cortex in PD cases (Shao et al., 2014).

The fact that VBM did not reveal hippocampal volume loss in our patients is neither surprising nor contradictory. Whole-brain VBM without region of interest analysis using hippocampal masks fails to detect even larger hippocampal atrophy than that found in our study (Bergouignan et al., 2009).

5.5. Limitations

Our study is not without limitations.

First, the validity of FreeSurfer hippocampal segmentation has been questioned, although the results are not conclusive (Wisse et al., 2014). These concerns pertain to the processing of low-resolution T1- weighted MR images where the visualization of hippocampal gray and white matter is difficult compared to other methods using high-resolution T2-weighted scans. In FreeSurfer software, the hippocampal subfield segmentation method is guided along the longitudinal axis from the coronal slices, which might not follow the precise boundaries recommended by anatomical atlases. For example, with FreeSurfer, the evaluation of hippocampal atrophy in MCI and AD reported CA2-3 atrophy, which is contradictory to post-mortem stereological cell counting method describing CA1 volume loss (Rossler et al., 2002).

Imaging studies aimed to compare the reproducibility and reliability of hippocampal subfield segmentation using automated segmentation method versus manual delineation. In 133 subjects including healthy adults, patients with MCI and Alzheimer's disease the results showed that the largest variance refers to CA1 zone. Both methods resulted in a moderate interrater reliability: the highest values applied for the whole hippocampus in MCI patients (0.74) and healthy individuals (0.67). The CA2-3 and CA4-DG subfields received a mean value of 0.62 in MCI patients. Assessing the subiculum, the variance was above 0.5 in all three subgroups. The CA1 subregion had the lowest intraclass correlation coefficient (0.02). De Flores et al. (2015), based on these findings, concluded "the correlations between FreeSurfer and manual measurements were reasonable for the SUB (subiculum) and CA2–3-4-DG subfields pooled together" (p. 472) (de Flores et al., 2015).

Yushkevich et all. (2015) found that manual segmentation and FreeSurfer can similarly detect volumetric differences in CA2–3 in clinical and healthy populations (Yushkevich et al., 2015).

The most important advantage of FreeSurfer is test-retest reliability. A multi-site study in 65 healthy elderly subjects confirmed the volumetric and spatial reproducibility, making the FreeSurfer software a valid segmentation method across different scanners, analytical software, and experimental samples (Marizzoni et al., 2015).

Another advantage is that FreeSurfer does not require high-resolution T2-weighted scans with hippocampal focus, which is sensitive for motion and other types of MRI artifacts (Yushkevich et al., 2015). Finally, in a group of healthy individuals, we found convincing correlations between FreeSurfer measures and data obtained from the AdaBoost machine-learning segmentation protocol, which is frequently used in clinical populations (Beyer et al., 2013).

The second limitation is that our study did not include a clinical group receiving placebo. We have no information about spontaneous changes in hippocampal structure during the early course of PD. However, it is unlikely that the CA2–3 region might undergo a spontaneous volume expansion. A critical question for future studies is when and why medication-related volume compensation is lost, and it eventually turns into progressive atrophy.

The third main limitation is that the sample size was small. However, the obtained significance level for CA2–3 was convincing with a Cohen's effect size larger than 0.8 **(Table 5).** The critical three-way interaction in the ANOVA was also highly significant with a large effect size according to Cohen's criteria (0.18) (Cohen et al., 1988). It is important to note that it is difficult to recruit de novo, non-medicated PD patients because general practitioners often start various medications (e.g. antidepressants) before the final diagnosis of PD.

DOI:10.14753/SE.2021.2379

6. CONCLUSIONS

1. In the first part of our study, we demonstrated the psychomimetic effect of a single dose of l-DOPA in newly diagnosed, drug-naïve PD patients. After the medication, the patients scored higher on VAS profile evaluating the perceptual changes. We hypothesized that dopaminergic medication might boost various perceptual dimensions such as thinking, passing of time, and mental ‘‘highness’’. This effect might be due to dopamine mediated reduction of LI.

2. We demonstrated the hippocampal involvement in non-demented, early phase PD patients. In our second study, we found a circumscribed volume loss in CA2 hippocampal subregion in cognitively intact, newly diagnosed PD patients compared to age- and gender-matched healthy controls. These results indicate that neurodegenerative changes affect the hippocampal formation at an early phase of PD.

3. Our results provide evidence for the relationship between hippocampal volume reductions and PD associated mood disorders. In non-medicated PD patients, more severe depressive and anxiety symptoms correlated with smaller CA2-3 subfield volumes. After a 24-week l-DOPA therapy, the depressive symptoms ameliorated, and the correlation with CA2-3 volume was less pronounced. The CA2-3 regional atrophy is also reported in MDD. This common alteration raises the possibility of a shared pathway between mood disorders and neurodegenerative disease. The shared and potential contributing factors pertain to glial cell loss, reduced levels of neurotrophic factors, mitochondrial dysfunction, and neuroinflammation. The amelioration of depressive symptoms after l-DOPA administration raise the possibility of the antidepressant effect of l-DOPA.
Desipte the significant prevalence of depression in PD patients just a few clinical trials investigated the exact benefit of l-DOPA treatment. The actuality of this clinically important hypothesis was raised by american neuroscientists as well, in an ongoing clinical trial they investigate the possibe antidepressant effect of l-DOPA in older adults (https://clinicaltrials.gov/ct2/show/NCT03761030).

DOI:10.14753/SE.2021.2379

4. Our follow-up assessment revealed that a 24-week l-DOPA treatment can restore the hippocampal structural alterations in the early stage of PD. The exact mechanism is not clear, but it is plausible that the dopaminergic medication is able to restore neurogenesis in the DG, enhance the neurotrophic factor synthesis, and has a benefic immunomodulatory effect.

DOI:10.14753/SE.2021.2379

7. SUMMARY

Aim: To investigate the hypothesis that patients with Parkinson's disease (PD) present an altered hippocampal volume that might be in correlation with mood disorders and cognitive functions. We also intended to address the psychoactive effect of a single dose of l-DOPA and the short-term outcome of the replacement therapy on hippocampal structural changes and depressive symptoms.

Methods: In Study 1, 28 de novo PD patients and 25 healthy controls were assessed with a visual search task measuring latent inhibition (LI). The psychotic-like experiences were tested with Community Assessment of Psychic Experiences (CAPE) scale, and the psychotomimetic effect (perception, relaxation, and dysphoria) with visual analog scales (VAS) before and after l-DOPA administration. In Study 2, 35 drug-naïve, newly diagnosed, cognitively intact PD patients and 30 control individuals underwent structural magnetic resonance imaging. The hippocampal subfield segmentation was carried out with FreeSurfer v6.0. The clinical characteristics were evaluated with Unified Parkinson's Disease Rating Scale, Hamilton Depression Rating Scale, and Hamilton Anxiety Rating Scale. Assessments were performed when the patients did not receive medications and after 24 weeks of l-DOPA treatment.

Results: Study 1: We found enhanced LI in drug-naïve PD patients and decreased LI in medicated PD patients compared to the control group. The l-DOPA administration resulted in a significant decline in LI in PD. The VAS profile indicated higher scores of perceptual experiences (changes in subjective feelings in thinking, time perception, and mental ''highness'') in treated PD patients. We found a negative correlation between LI and perceptual experiences. Study 2: Non-medicated PD patients showed reduced CA2–CA3 hippocampal volume that correlated with the severity of depressive symptoms. A course of 24 weeks of l-DOPA therapy restored the hippocampal structural alterations and ameliorated the affective symptoms.

Conclusions: We conclude that a single dose of l-DOPA has a significant psychomimetic effect, possibly via the reduction of LI. Early stage, drug-naïve PD patients with preserved memory functions presented a circumscribed CA2-CA3 atrophy. Our study confirms the relationship between the hippocampal atrophy in early stage PD and non-motor symptoms. The l-DOPA replacement therapy at initial phase is able to normalize the hippocampal structural anomalies and ameliorate the depressive symptoms.

DOI:10.14753/SE.2021.2379

8. ÖSSZEFOGLALÁS

Célkitűzés: Hipotézisünk szerint nem demens Parkinson-kóros (PK) betegek hippokampusz térfogata összefüggést mutat a kognitív teljestőképességgel és a hangulatzavarokkal. Továbbá célunk volt az egyszeri l-DOPA adagolás pszichomimetikus hatásának jellemzése, illetve a szubsztitúciós kezelés hippokampusztérfogatra és a depresszív tünetekre gyakorolt hatásának vizsgálata.

Módszer: Vizsgálat 1.: 25 egészséges személy és 28 frissen diagnosztizált PK beteg esetében a látens gátlást egy vizuális keresési feladattal vizsgáltuk a dopaminerg kezelés előtt és után. A pszichózis-szerű tünetek értékelésére a Community Assessment of Psychic Experiences skálát alkalmaztuk. A pszichomimetikus hatást (percepció, relaxáció és diszfória) vizuális analóg skálával (VAS) mértük fel.

Vizsgálat 2.: 35 kezeletlen, frissen diagnosztizált, megtartott kognitív teljestőképességű PK beteg és 30 kontroll személy esetében a hippokampusz alrégióit strukturális mágneses rezonancia felvételek alapján, a FreeSurfer v 6.0 program segítségével szegmentáltuk. A klinikai jellemzőket a Movement Disorders Society-féle Egységesített Parkinson-kór Pontozó Skála, a Hamilton-féle depresszió és szorongás skála segítségével értékeltük. A felméréseket először a kezelés előtt, majd 24 héttel az l-DOPA terápia után végeztük.

Eredmények: Vizsgálat 1.: A kezeletlen PK betegek esetében hosszabb, míg a kezelt páciensek esetében rövidebb látenciájú látens gátlást találunk az egészséges személyekhez viszonyítva. Az l-DOPA kezelés jelentősen csökkentette a látens gátlás hatását. A VAS eredményei szerint l-DOPA hatásra fokozódott a perceptuális alteráció (szubjektíven megváltozott gondolkodás, időérzékelés és a mentális 'emelkedettség' érzése). A látens gátlás mértéke és a perceptuális alteráció között fordított összefüggést találtunk. Vizsgálat 2.: A kezeletlen PK betegek esetében CA2-3 alrégiónál térfogatcsökkenést találtunk, amely összefüggést mutatott a súlyosabb depressziós tünetekkel. 24 hét l-DOPA kezelés helyreállította az észlelt strukturális eltérést és klinikailag javított a depresszió mértékén.

Következtetés: A látens gátlás látenciájának csökkentése és a klnikai becslőskálák által bizonyítható az egyszeri l-DOPA adag pszichomimetikus hatása. A PK korai stádiumában megtartott memóriafunkciók mellett a hippokampusz CA2-CA3 alrégiója szelektíven érinett. A kezdeti stádiumban a szubsztitúciós terápia átmeneti javulást eredményezett az agyi strukturális és a nem-motoros klinikai eltérésben is.

9. REFERENCES

Aarsland D, Larsen JP, Cummins JL, Laake K. (1999) Prevalence and clinical correlates of psychotic symptoms in Parkinson disease: a community-based study. Arch Neurol, 56: 595-601.

Allman MJ, Meck WH. (2012) Pathophysiological distortions in time perception and timed performance. Brain, 135: 656–677.

Andreou C, Bozikas VP, Luedtke T, Moritz S. (2015) Associations between visual perception accuracy and confidence in a dopaminergic manipulation study. Front Psychol, 6: 414.

Apostolova LG, Beyer M, Green AE, Hwang KS, Morra JH, Chou YY, Avedissian C, Aarsland D, Janvin CC, Larsen JP, Cummings JL, Thompson PM. (2010) Hippocampal, caudate, and ventricular changes in Parkinson's disease with and without dementia. Mov Disord, 25: 687–695.

Apostolova LG, Morra JH, Green AE, Hwang KS, Avedissian C, Woo E. (2010) Automated 3D mapping of baseline and 12-month associations between three verbal memory measures and hippocampal atrophy in 490 ADNI subjects. Neuroimage, 51:488–499.

Artieda J, Pastor MA, Lacruz F, Obeso JA. (1992) Temporal discrimination is abnormal in Parkinson's disease. Brain, 115: 199–210.

Ashburner J. (2007) A fast diffeomorphic image registration algorithm. Neuroimage, 38: 95–113.

Ashburner J. (2009) Computational anatomy with the SPM software. Magn Reson maging, 27: 1163–1174.

Austin G, Hayward W. (1969) Time perception in patients with depressed consciousness and Parkinson's disease I. Experimental results. Confin Neurol, 31:22– 36

Bartsch T, Wulff P. (2015) The hippocampus in aging and disease: From plasticity to vulnerability. Neuroscience, 309: 1-16.

Barone P, Poewe W, Albrecht S, Debieuvre C, Massey D, Rascol O, Tolosa E, Weintraub D. (2010) Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 9: 573-580.

Béraud D, Maguire-Zeiss KA. (2012) Misfolded α-synuclein and Toll-like receptors: therapeutic targets for Parkinson's disease. Parkinsonism Relat Disord, 18: 17-20.

Berg D, Supprian T, Hofmann E, Zeiler B, Jäger A, Lange KW, Reiners K, Becker T, Becker G. (1999) Depression in Parkinson's disease: brainstem midline alteration on transcranial sonography and magnetic resonance imaging. J Neurol, 246: 1186–1193.

Bergouignan L, Chupin M, Czechowska Y, Kinkingnehun S, Lemogne C, Le Bastard G, Lepage M, Garnero L, Colliot O, Fossati P. (2009) Can voxel based morphometry, manual segmentation and automated segmentation equally detect hippocampal volume differences in acute depression?. Neuroimage, 45: 29–37.

Beyer MK, Bronnick KS, Hwang KS, Bergsland N, Tysnes OB, Larsen JP, Thompson PM, Somme JH, Apostolova LG. (2013) Verbal memory is associated with structural hippocampal changes in newly diagnosed Parkinson's disease. J Neurol Neurosurg Psychiatry, 84: 23–28.

Bodis-Wollner I, Yahr MD, Mylin L, Thornton J. (1982) Dopaminergic deficiency and delayed visual evoked potentials in humans. Ann Neurol, 11: 478–483.

Bodis-Wollner I. (2009) Retinopathy in Parkinson Disease. J Neural Transm, 116: 1493–1501.

Braak H, Braak E (2000). Pathoanatomy of Parkinson's disease. J Neurol, 247: 3–10.

Brunton PJ Russell JA. (2010) Prenatal social stress in the rat programmes neuroendocrine and behavioural responses to stress in the adult offspring: sex-specific effects. J. Neuroendocrinol, 22: 258–271.

Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT. (2004) Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain, 127: 791–800.

Calabresi P, Castrioto A, Di Filippo M, Picconi B. (2013) New experimental and clinical links between the hippocampus and the dopaminergic system in Parkinson's disease. Lancet Neurol, 12: 811–821.

Cardoso EF, Maia FM, Fregni F, Myczkowski ML, Melo LM, Sato JR, Marcolin MA, Rigonatti SP, Cruz AC, Barbosa ER, Amaro E. (2009) Depression in Parkinson's disease: convergence from voxel-based morphometry and functional magnetic resonance imaging in the limbic thalamus. Neuroimage, 47: 467–472.

Cha J, Greenberg T, Song I, Blair Simpson H, Posner J, Mujica-Parodi LR. (2016) Abnormal hippocampal structure and function in clinical anxiety and comorbid depression. Hippocampus, 26: 545-553.

Chen JQ, Szodoray P, Zeher M. (2016) Toll-Like Receptor Pathways in Autoimmune Diseases. Clin Rev Allergy Immunol, 50: 1-17.

Chevaleyre V, Piskorowski RA. (2016) Hippocampal area CA2: an overlooked but promising therapeutic target. Trends Mol Med, 22: 645–655.

Chiu WH, Depboylu C, Hermanns G, Maurer L, Windolph A, Oertel WH, Ries V, Höglinger GU. (2015) Long-term treatment with l-DOPA or pramipexole affects adult neurogenesis and corresponding non-motor behavior in a mouse model of Parkinson's disease. Neuropharmacology, 95: 367–376.

Chou KL, Amick MM, Brandt J, Camicioli R, Frei K, Gitelman D, Goldman J, Growdon J, Hurtig HI, Levin B, Litvan I, Marsh L, Simuni T, Tröster AI, Uc EY. (2010) A

recommended scale for cognitive screening in clinical trials of Parkinson's disease. Mov Disord, 25: 2501–2507.

Cicchetti DV. (1994) Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychol Assess 6:284–290.

Cirino PT, Chin CE, Sevcik RA, Wolf M, Lovett M, Morris RD. (2002) Measuring socioeconomic status: reliability and preliminary validity for different approaches. Assessment, 9: 145–155.

Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd Auflage. Hillsdale, 1988.

Cole J, Toga AW, Hojatkashani C, Thompson P, Costafreda SG, Cleare AJ, Williams SC, Bullmore ET, Scott JL, Mitterschiffthaler MT, Walsh ND, Donaldson C, Mirza M, Marquand A, Nosarti C, McGuffin P, Fu CH. (2010) Subregional hippocampal deformations in major depressive disorder. J Affect Disord, 126: 272-277.

Costa C, Sgobio C, Siliquini S, Tozzi A, Tantucci M, Ghiglieri V. (2012) Mechanisms underlying the impairment of hippocampal long-term potentiation and memory in experimental Parkinson's disease. Brain, 135: 1884–1899.

Dalaker TO, Zivadinov R, Larsen JP, Beyer MK, Cox JL, Alves G, Bronnick K, Tysnes OB, Antulov R, Dwyer MG, Aarsland D. (2010) Gray matter correlations of cognition in incident Parkinson's disease. Mov Disord, 25: 629–633.

de Flores R, La Joie R, Landeau B, Perrotin A, Mezenge F, de La Sayette V, Eustache F, Desgranges B, Chételat G. (2015) Effects of age and Alzheimer's disease on hippocampal subfields: comparison between manual and FreeSurfer volumetry. Hum Brain Mapp, 36: 463–474.

Doorn KJ, Moors T, Drukarch B, van de Berg W, Lucassen PJ, van Dam AM. (2014) Microglial phenotypes and toll-like receptor 2 in the substantia nigra and hippocampus of incidental Lewy body disease cases and Parkinson's disease patients. Acta Neuropathol Commun, 2: 90.

Double KL, Halliday GM, McRitchie DA, Reid WG, Hely MA, Morris JG. (1996) Regional brain atrophy in idiopathic Parkinson's disease and diffuse Lewy body disease. Dementia, 7: 304–313.

Evans AH, Pavese N, Lawrence AD, Tai YF, Appel S, Doder M, Brooks DJ, Lees AJ, Piccini P. (2006) Compulsive drug use linked to sensitized ventral striatal dopamine transmission. Ann Neurol, 59: 852–858.

Fischl B. (2012) FreeSurfer. Neuroimage, 62: 774–7781.

Freitas ME, Hess CW, Fox SH. (2017) Motor Complications of Dopaminergic Medications in Parkinson's Disease. Semin Neurol, 37: 147-157.

Gao LL, Zhang JR, Chan P, Wu T. (2017) Levodopa Effect on Basal Ganglia Motor Circuit in Parkinson's Disease. CNS Neurosci Ther, 23: 76-86.

Geffe S, Schindlbeck KA, Mehl A, Jende J, Klostermann F, Marzinzik F. (2016) The single intake of levodopa modulates implicit learning in drug-naïve, de novo patients with idiopathic Parkinson's disease. J Neural Transm, 123: 601–610.

Ghilardi MF, Bodis-Wollner I, Onofrj MC, Marx MS, Glover AA. (1988) Spatial frequency-dependent abnormalities of the pattern electroretinogram and visual evoked potentials in a parkinsonian monkey model. Brain, 111: 131–149.

Goodarzi Z, Mrklas KJ, Roberts DJ, Jette N, Pringsheim T, Holroyd-Leduc J. (2016) Detecting depression in Parkinson disease: A systematic review and meta-analysis. Neurology, 2016 87: 426-437.

Hamilton TJ, Wheatley BM, Sinclair DB, Bachmann M, Larkum ME, Colmers WF. (2010) Dopamine modulates synaptic plasticity in dendrites of rat and human dentate granule cells. Proc Natl Acad Sci, 107: 18185-1890.

Haukvik UK, Westlye LT, Mørch-Johnsen L, Jørgensen KN, Lange EH, Dale AM, Melle I, Andreassen OA, Agartz I. (2014) In vivo hippocampal subfield volumes in schizophrenia and bipolar disorder. Biol Psychiatry, 77: 581-588.

Ho AJ, Raji CA, Saharan P, DeGiorgio A, Madsen SK, Hibar DP, Stein JL, Becker JT, Lopez OL, Toga AW,Thompson PM. (2011) Hippocampal volume is related to body mass index in Alzheimer's disease. Neuroreport, 22: 10–14.

Hoehn MM, Yahr MD. (1967) Parkinsonism: onset, progression and mortality. Neurology, 17: 427–442.

Hornykiewicz O. (2010) A brief history of levodopa. J Neurol, 257: 249–252.

Huang C, Ravdin L, Nirenberg M, Piboolnurak P, Severt L, Maniscalco JS, Solnes L, Dorfman BJ, Henchcliffe C. (2013) Neuroimaging markers of motor and nonmotor features of Parkinson's disease: an 18F fluorodeoxyglucose positron emission computed tomography study. Dement Geriatr Cogn Disord, 35: 183–196.

Hughes AJ, Daniel SE, Kilford L, Lees AJ. (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry, 55: 181–184.

Jack CR, Twomey CK, Zinsmeister AR, Sharbrough FW, Petersen RC, Cascino GD. (1989) Anterior temporal lobes and hippocampal formations: normative volumetric measurements from MR images in young adults. Radiology, 172: 549–554.

Jimenez-Urbieta H, Gago B, de la Riva P, Delgado-Alvarado M, Marin C, Rodriguez-Oroz MC. (2015) Dyskinesias and impulse control disorders in Parkinson's disease: from pathogenesis to potential therapeutic approaches. Neurosci Biobehav Rev, 56: 294–314.

Jones CR, Jahanshahi M. (2014) Motor and perceptual timing in Parkinson's disease. Adv Exp Med Biol, 829: 265–290.

Junqué C, Ramirez-Ruiz B, Tolosa E, Summerfield C, Marti MJ, Pastor P, Gómez-Ansón B, Mercader JM. (2005) Amygdalar and hippocampal MRI volumetric reductions in Parkinson's disease with dementia. Mov Disord, 20: 540–544.

Kéri S. (2011) Solitary minds and social capital: latent inhibition, general intellectual functions and social network size predict creative achievements. Psychol Aesth Creat Arts, 5: 215–221.

Kim HK, Nunes PV, Oliveira KC, Young LT, Lafer B. (2016) Neuropathological relationship between major depression and dementia: a hypothetical model and review. Prog Neuropsychopharmacol Biol Psychiatry, 67: 51–57.

Kleinloog D, Rombouts S, Zoethout R, Klumpers L, Niesters M, Khalili-Mahani N, Dahan A, van Gerven J. (2014) Subjective Effects of ethanol, morphine, D(9)-tetrahydrocannabinol, and ketamine following a pharmacological challenge are related to functional brain connectivity. Brain Connect, 5: 641–648.

Konings M, Bak M, Hanssen M, van Os J, Krabbendam L. (2006) Validity and reliability of the CAPE: a self-report instrument for the measurement of psychotic experiences in the general population. Acta Psychiatr Scand, 114: 55–61.

Kostic V, Agosta F, Petrovic I, Galantucci S, Spica V, Jecmenica-Lukic M, Filippi M. (2010) Regional patterns of brain tissue loss associated with depression in Parkinson disease. Neurology, 75: 857–863.

Kuhn S, Musso F, Mobascher A, Warbrick T, Winterer G, Gallinat J. (2012) Hippocampal subfields predict positive symptoms in schizophrenia: first evidence from brain morphometry. Transl Psychiatry, 2:127-129.

Laakso MP, Partanen K, Riekkinen P, Lehtovirta M, Helkala EL, Hallikainen M, Hanninen T, Vainio P, Soininen H. (1996) Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: an MRI study. Neurology, 46: 678–681.

Lang A, Fahn S. Assessment of Parkinson's disease, in Quantification of Neurological Deficit, Butterworths, Boston, 1989: 285–309.

Lange KW, Tucha O, Steup A, Gsell W, Naumann M. (1995) Subjective time estimation in Parkinson's disease. J Neural Transm, 46: 433–438.

Lemon N, Manahan-Vaughan D. (2006) Dopamine D1/D5 receptors gate the acquisition of novel information through hippocampal long-term potentiation and long-term depression. J Neurosci, 26: 7723-7729.

Li X, Li D, Li Q, Li Y, Li K, Li S, Han Y. (2016) Hippocampal subfield volumetry in patients with subcortical vascular mild cognitive impairment. Sci Rep, 6:20873.

Liggins J, Pihl RO, Benkelfat C, Leyton M. (2012) The dopamine augmenter L-DOPA does not affect positive mood in healthy human volunteers. PLoS One, 7: 28370.

Lim HK, Hong SC, Jung WS, Ahn KJ, Won WY, Hahn CI. (2013) Automated segmentation of hippocampal subfields in drug-naive patients with Alzheimer disease. AJNR Am J Neuroradiol, 34: 747–751.

Litvan I, Goldman JG, Troster AI, Schmand BA, Weintraub D, Petersen RC, Mollenhauer B, Adler CH, Marder K, Williams-Gray CH, Aarsland D, Kulisevsky J, Rodriguez-Oroz MC, Burn DJ, Barker RA, Emre M. (2012) Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord, 27: 349–356.

Lubow RE, Dressler R, Kaplan O. (1999) The effects of target and distractor familiarity on visual search in de novo Parkinson's disease patients: latent inhibition and novel pop-out. Neuropsychology, 13: 415–423.

Lubow RE, Kaplan O, Abramovich P, Rudnick A, Laor N (2000) Visual search in schizophrenia: latent inhibition and novel pop- out effects. Schizophr Res, 45: 145–156.

MacDonald PA, MacDonald AA, Seergobin KN, Tamjeedi R, Ganjavi H, Provost JS, Monchi O. (2011) The effect of dopamine therapy on ventral and dorsal striatum-mediated cognition in Parkinson's disease: support from functional MRI. Brain, 134: 1447-1463.

Marizzoni M, Antelmi L, Bosch B, Bartres-Faz D, Muller BW, Wiltfang J, Fiedler U, Roccatagliata L, Picco A, Nobili F, Blin O, Bombois S, Lopes R, Sein J, Ranjeva JP, Didic M, Gros-Dagnac H, Payoux P, Zoccatelli G, Alessandrini F, Beltramello A,

Bargalló N, Ferretti A, Caulo M, Aiello M, Cavaliere C, Soricelli A2, Salvadori N, Parnetti L, Tarducci R, Floridi P, Tsolaki M, Constantinidis M, Drevelegas A, Rossini PM, Marra C, Hoffmann KT, Hensch T, Schönknecht P, Kuijer JP, Visser PJ, Barkhof F, Bordet R, Frisoni GB, Jovicich J. (2015) Longitudinal reproducibility of automatically segmented hippocampal subfields: a multisite European 3T study on healthy elderly. Hum Brain Mapp, 36: 3516–3527.

McGraw KO, Wong SP. (1996) Forming inferences about some intraclass correlation coefficients. Psychol Methods, 1: 30–46.

Morra JH, Tu Z, Apostolova LG, Green AE, Avedissian C, Madsen SK, Parikshak N, Hua X, Toga AW, Jack CR, Weiner MW, Thompson PM. (2008) Validation of a fully automated 3D hippocampal segmentation method using subjects with Alzheimer's disease mild cognitive impairment, and elderly controls. Neuroimage, 43: 59–68.

Morra JH, Tu Z, Apostolova LG, Green AE, Toga AW, Thompson PM. (2010) Comparison of AdaBoost and support vector machines for detecting Alzheimer's disease through automated hippocampal segmentation. IEEE Trans Med Imaging, 29: 30–43.

Mountjoy CQ, Roth M. (1982) Studies in the relationship between depressive disorders and anxiety states. J Affect Disord, 4:127–147.

Nagy H, Levy-Gigi E, Somlai Z, Takáts A, Bereczki D, Kéri S. (2012) The effect of dopamine agonists on adaptive and aberrant salience in Parkinson's disease. Neuropsychopharmacology, 37: 950–958.

Narr KL, Thompson PM, Szeszko P, Robinson D, Jang S, Woods RP, Kim S, Hayashi KM, Asunction D, Toga AW, Bilder RM. (2004) Regional specificity of hippocampal volume reductions in first-episode schizophrenia. Neuroimage, 21: 1563-1575.

Neves G, Cooke SF, Bliss VP. (2008) Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. Nature Reviews Neuroscience, 9: 65-75.

Nicoll RA, Roche KW. (2013) Long-term potentiation: peeling the onion. Neuropharmacology, 74: 18-22.

O'Keefe J, Dostrovsky J. (1971) The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely- moving rat. Brain Res, 34: 171-175.

Ohta K, Kuno S, Inoue S, Ikeda E, Fujinami A, Ohta M. (2010) The effect of dopamine agonists: the expression of GDNF, NGF, and BDNF in cultured mouse astrocytes. J Neurol Sci, 291: 12–16.

Pan PL, Song W, Shang HF. (2012) Voxel-wise meta-analysis of gray matter abnormalities in idiopathic Parkinson's disease. Eur J Neurol, 19: 199–206.

Pereira JB, Junque C, Bartres-Faz D, Ramirez-Ruiz B, Marti MJ, Tolosa E. (2013) Regional vulnerability of hippocampal subfields and memory deficits in Parkinson's disease. Hippocampus, 23: 720–728.

Polner B, Moustafa AA, Nagy H, Takáts A, Gyöfi O, Kéri S. (2016) Dopamine improves exploration after expectancy violations and induces psychotic-like experiences in patients with Parkinson's disease. Neurosci Lett, 616: 132–137.

Reuter M, Schmansky NJ, Rosas HD, Fischl B. (2012) Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage, 61: 1402–1418.

Riekkinen P, Kejonen K, Laakso MP, Soininen H, Partanen K, Riekkinen M. (1998) Hippocampal atrophy is related to impaired memory, but not frontal functions in non-demented Parkinson's disease patients. Neuroreport, 9: 1507–1511.

Rossler M, Zarski R, Bohl J, Ohm TG (2002). Stage-dependent and sector-specific neuronal loss in hippocampus during Alzheimer's disease. Acta Neuropathol, 103: 363–369.

Rutledge RB, Skandali N, Dayan P, Dolan RJ. (2015) Dopaminergic modulation of decision making and subjective well-being. J Neurosci, 35: 9811–9822.

Sandoval-Rincon M, Saenz-Farret M, Miguel-Puga A, Micheli F, Arias-Carrion O. Rational pharmacological approaches for cognitive dysfunction and depression in Parkinson's disease. (2015) Front Neurol, 6: 71.

Sarkar C, Basu B, Chakroborty D, Dasgupta PS, Basu S. (2010) The immunoregulatory role of dopamine: an update. Brain Behav Immun, 24: 525–528.

Sesack SR, Grace AA. (2010) Cortico-Basal Ganglia reward network: microcircuitry. Neuropsychopharmacology, 35: 27-47.

Shao N, Yang J, Shang H. (2015) Voxelwise meta-analysis of gray matter anomalies in Parkinson variant of multiple system atrophy and Parkinson's disease using anatomic likelihood estimation. Neurosci Lett, 587: 79–86.

Sibille E, French B. (2013) Biological substrates underpinning diagnosis of major depression. Int J Neuropsychopharmacol, 16: 1893-1909.

Smith AS, Williams Avram SK, Cymerblit-Sabba A, Song J, Young WS. (2016) Targeted activation of the hippocampal CA2 area strongly enhances social memory. Mol Psychiatry, 21: 1137-1344.

Strange BA, Witter MP, Lein ES, Moser EI. (2014) Functional organization of the hippocampal longitudinal axis. Nat Rev Neurosci, 15: 655-669.

Swerdlow NR, Stephany N, Wasserman LC, Talledo J, Sharp R, Auerbach PP. (2003) Dopamine agonists disrupt visual latent inhibition in normal males using a within-subject paradigm. Psychopharmacology, 169: 314-320.

Van Leemput K, Bakkour A, Benner T, Wiggins G, Wald LL, Augustinack J. (2009) Automated segmentation of hippocampal subfields from ultra-high resolution in vivo MRI. Hippocampus, 19: 549–557.

van Mierlo TJ, Chung C, Foncke EM, Berendse HW, van den Heuvel OA. (2015) Depressive symptoms in Parkinson's disease are related to decreased hippocampus and amygdala volume. *Mov Disord,* 30: 245–252.

Voon V, Fox SH. (2007) Medication-related impulse control and repetitive behaviors in Parkinson disease. Arch Neurol, 64: 1089–1096.

Ward BD. AlphaSim. (2002). Available from: http://afni.nimh.nih.gov/

Weiner I, Feldon J. (1987) Facilitation of latent inhibition by haloperidol in rats. Psychopharmacology, 91: 248–253.

Weiner I, Lubow RE, Feldon J. (1988) Disruption of latent inhibition by acute administration of low doses of amphetamine. Pharmacol Biochem Behav, 30: 871–878.

Weintraub D, Burn DJ. (2011) Parkinson's disease: the quintessential neuropsychiatric disorder. Mov Disord, 26: 1022–103.

Wen MC, Chan LL, Tan LC, Tan EK. (2016) Depression, anxiety, and apathy in Parkinson's disease: insights from neuroimaging studies. Eur J Neurol, 23: 1001–1019.

Wisse LE, Biessels GJ, Geerlings MI. (2014) A critical appraisal of the hippocampal subfield segmentation package in FreeSurfer. Front Aging Neurosci, 6: 261.

Wolters EC. (1999) Dopaminomimetic psychosis in Parkinson's disease patients: diagnosis and treatment. Neurology, 52: 10-13.

Yarnall AJ, Breen DP, Duncan GW, Khoo TK, Coleman SY, Firbank MJ, Nombela C, Winder-Rhodes S, Evans JR, Rowe JB, Mollenhauer B, Kruse N, Hudson G, Chinnery PF, O'Brien JT, Robbins TW, Wesnes K, Brooks DJ, Barker RA, Burn DJ. (2014) Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study. Neurology, 82: 308–316.

Yushkevich PA, Pluta JB, Wang H, Xie L, Ding SL, Gertje EC, Mancuso L, Kliot D, Das SR, Wolk DA. (2015) Automated volumetry and regional thickness analysis of hippocampal subfields and medial temporal cortical structures in mild cognitive impairment. Hum Brain Mapp, 36: 258–287.

Zhao C, Deng W, Gage FH. (2008) Mechanisms and functional implications of adult neurogenesis. Cell, 132: 645-660.

10. LIST OF OWN PUBLICATIONS

Publications related to PhD thesis:

Györfi O, Nagy H, Bokor M, Kéri S. (2016) Behavioural aspects of a modified crosstalk between basal ganglia and limbic system in Parkinson's disease. Neuropsychopharmacol Hung, 18:87-92.

Polner B, Moustafa AA, Nagy H, Takáts A, **Györfi O**, Kéri S. (2016) Dopamine improves exploration after expectancy violations and induces psychotic-like experiences in patients with Parkinson's disease. Neurosci Lett, 616:132-137.

Györfi O, Nagy H, Bokor M, Kelemen O, Kéri S. (2017) A single dose of L-DOPA changes perceptual experiences and decreases latent inhibition in Parkinson's disease. J Neural Transm, 124:113-119.

Györfi O, Nagy H, Bokor M, Moustafa AA, Rosenzweig I, Kelemen O, Kéri S. (2017) Reduced CA2-CA3 Hippocampal Subfield Volume Is Related to Depression and Normalized by l-DOPA in Newly Diagnosed Parkinson's Disease. Front Neurol, 8:84.

Györfi O, Nagy H, Bokor M, Kéri S. (2018) Insights into the structure and function of the hippocampal formation: Relevance to Parkinson's disease. Ideggyogy Sz, 71:15-24.

Other publications:

Macerollo A, Varga ET, **Györfi O**, Kobeleva X, Paterson RW, Sellner J.: The European Association of Young Neurologists and Trainees in 2013: striking a blow for European junior neurologists. Eur J Neurol 2013; 20: 54-58.

Sauerbier A, Macerollo A, **Györfi O**, Balicza P, Moarcas M, Papp V, Zis P, Klingelhoefer L, Saifee T, Struhal W, Sellner J.: Insufficient global health education in European neurological post-graduate training: a European Association of Young Neurologists and Trainees survey. Eur J Neurol 2016; 23:1680-1683.

Manhalter N, **Györfi O**, Boros E, Bokor M, Fazekas F, Dénes Z, Fabó D, Kamondi A, Erőss L.: Case report of a woman with anti amphiphysin positive stiff person syndrome. Ideggyogy Sz. 2017; 70:213-216.

DOI:10.14753/SE.2021.2379

11. ACKNOWLEDGMENTS

Throughout the writing of this dissertation, I have received a great deal of support and assistance. I would first like to thank my supervisor Professor Szabolcs Kéri, whose expertise was invaluable in the formulating of the research topic and methodology in particular. His advice and encouragement both research as well as on my career have been priceless.

I specifically appreciated Dr. Magdolna Bokor's extensive personal and professional guidance and provision of precious scientific knowledge in the field of movement disorders. I am also pleased to say thank you for all my colleagues from the Department of Neurology from the National Institute of Psychiatry and Addictions for stimulating discussions.

I would like to thank my parents and my brother for all their help and support throughout this challenging work.