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

PhD thesis

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1. INTRODUCTION

The hippocampus can be considered a hub in the centre of a functional loop, connecting the medial temporal lobe, basal ganglia, midbrain, and frontal lobe. The mesocorticolimbic dopaminergic projection connects the ventral tegmental area (VTA) to the medial temporal lobe, including the hippocampus, where long-term potentiation, the neurophysiological substrate of memory formation takes place.

The classical views of hippocampal long-term potentiation (LTP) do not emphasis dopaminergic modulation during the prototypical cellular LTP cascade. However, in-vivo animal experiments highlighted the dopaminergic boosting effect on the LTP.

Based on these finding, it is plausible that in early phase of Parkinson's disease (PD) mood disorders and cognitive impairments might be a consequence of dysfunctional hippocampal synaptic plasticity influenced by altered dopaminergic neurotransmission.

The dopaminergic cell loss in the nigrostriatal pathway is the neuropathological hallmark in PD. The effect of dopaminergic substitutional treatment reestablish the deficient dopamine levels in the nigrostriatal pathway but overdose the relatively intact mesolimbic projections responsible for psychiatric complications (impulsivity and psychotic symptoms). 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. Animal experiments demonstrated that LI can be facilitated by dopamine antagonists. Amphetamine and other D2 dopamine agonists attenuated visual LI in healthy subjects in a within-subject, placebo controlled study design. Given the above-mentioned evidences, non-medicated PD patients (decreased dopaminergic activity) may show an increased LI, which may be reversed by dopaminergic medications.

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 by 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 special attention to depression. We hypothesized that the volumetric changes are associated with 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.

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. To establish the diagnosis of PD, we used the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria. In order to rate the disabilities and impairments, we used the Hoehn–Yahr Scale and the Unified Parkinson's Disease Rating Scale (UPDRS).

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, negative symptoms and depression. The potential psychoactive effect of l-DOPA was evaluated with the visual analogue scale (VAS). This assessment pertained to perception, relaxation, and dysphoria.

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 .

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. The LI test, CAPE, and VASs were performed 60 minutes after the l-DOPA administration. The healthy controls received placebo, and they completed one testing session.

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 diagnosis of PD was made according to UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria.

We recorded the participant's demographic characteristics, socioeconomic status with Hollingshead Four-Factor Index, and the general intelligence with the Wechsler Adult Intelligence Scale (WAIS-R). To assess the stage of PD the patients received the Hoehn–Yahr scale (Hoehn and Yahr, 1967), and the UPDRS. 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. The exclusion criteria included the presence of mild

cognitive impairment (MCI), assessed with Movement Disorder Society Task Force guideline, impulsive-compulsive spectrum behaviour evaluated according to the criteria of Voon et al. , 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%.

3.2.2.. 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).

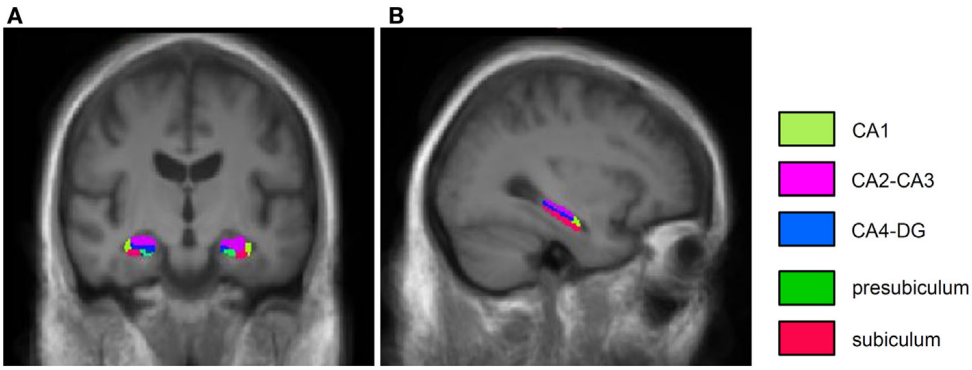
3.2.3. Experimental procedure

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), the necessary dosage was decided by the treating physician. After 24 weeks the patient and control groups completed the follow-up testing.

3.2.4. Structural Magnetic Resonance Imaging

For image processing, we used the neuGRID platform and the longitudinal pipeline of FreeSurfer v6.0 with the "hipposubfields" flag. With the automatic segmentation technique, we identified five hippocampal subregions: CA1, CA2–3, CA4–DG, subiculum, and presubiculum. (Figure 1). As the literature review does not indicate a significant left-right dissociation between hippocampal sizes, the volumetric data was averaged between the hemispheres.

Figure 1. *Coronal (A) and sagittal (B) T1-weighted images from the average output of FreeSurfer hippocampal segmentation from healthy individuals.*



3.2.5. Voxel-Based Morphometry (VBM)

A whole-brain VBM was performed to detect possible grey matter differences between PD patients and controls.

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 behavioural 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. 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.

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. For post hoc comparisons for unequal samples, we used Tukey honestly significant difference (HSD) tests. The level of statistical significance was set at alpha < 0.05.

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 2. shows the between-group differences.

Figure 2. Latent inhibition in Parkinson's patients (PD) on and off l- DOPA and healthy control subjects (CONT).

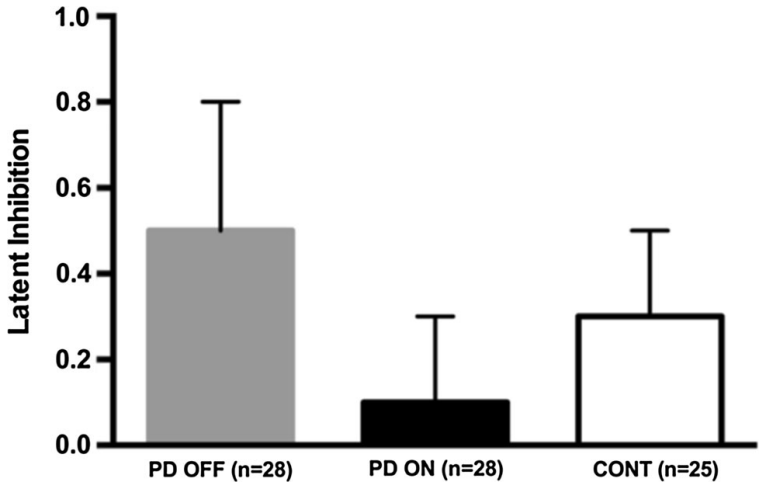


Figure 2. Latent inhibition in Parkinson's patients (PD) on and off l- DOPA and healthy control subjects (CONT). Columns are means, error bars are standard deviations. Parkinson's—OFF > controls > Parkinson's—ON (p <0.05)

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 1. 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 1. Latent inhibition, psychotomimetic effects, and CAPE values

	Parkinson's: off l-DOPA	Parkinson's: on l-DOPA	Controls
Latent inhibition[a]	0.53 (0.28)	0.13 (0.21)	0.3 (0.22)
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)

Data are mean (standard deviation)

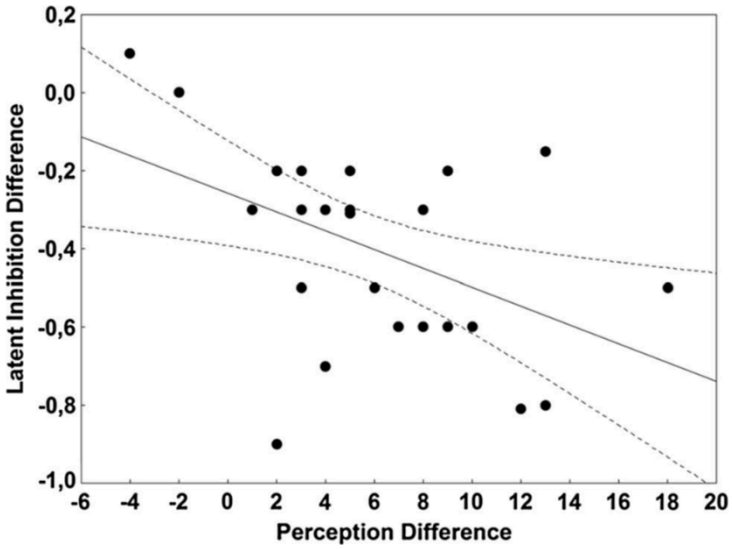
a Parkinson's—off > controls > Parkinson's—on ($p < 0.05$)

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

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 3).

Figure 3. 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 ($r> 0.2$).

4.3. 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 ($p < 0.0001$).
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 2).

Table 2. Hippocampal subfield volumes (mm^3)

	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

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 ($p < 0.0001$).*

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

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 4, Figure 5.), 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 ($-0.3 < r$s < 0.3, ps > 0.05).

Figure 4. Correlations between depressive symptoms and CA2–3 volumes before l-DOPA medication

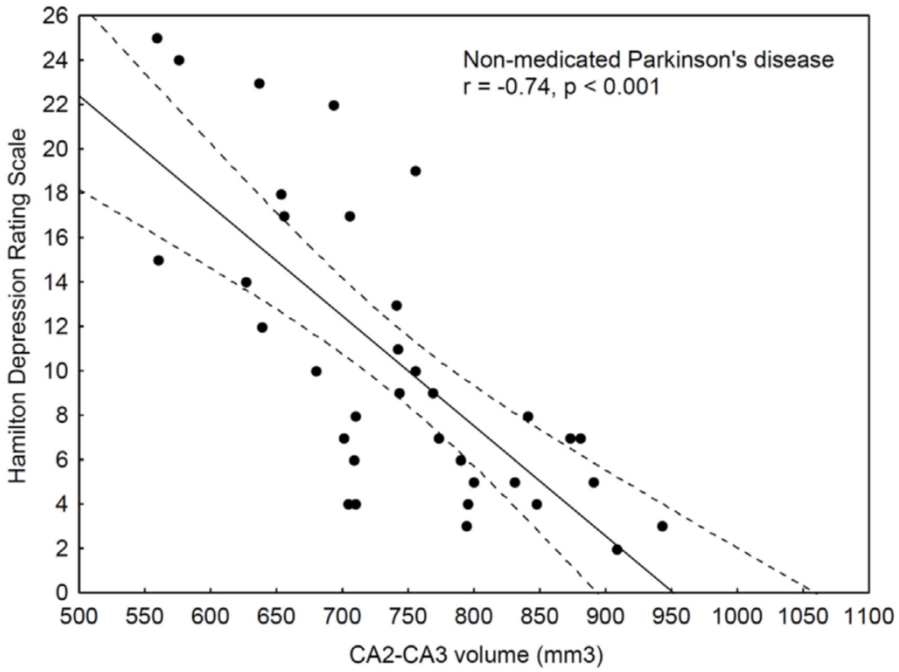
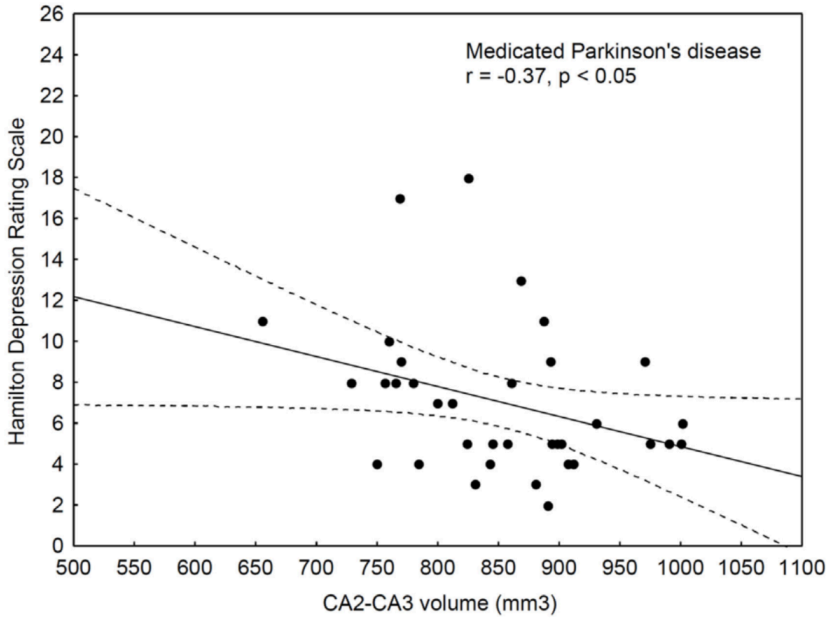


Figure 5. Correlations between depressive symptoms and CA2–3 volumes after l-DOPA medication.



4.4. Voxel-Based Morphometry

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

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.

It has been hypothesized that in PD subjective perceptual changes could originate from a distorted time perception. 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. The l-DOPA treatment might reestablish the thalamo-corical circuit responsible for timing.

Besides temporal sensing, the dopaminergic medication might modulate visual perception as well. 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 confirmed the existence of a retinal preganglionic dopaminergic circuit that is modulated by dopaminergic amacrine cells via D1 and D2 receptors.
Another significantly elevated component of our perception scale pertained to mental 'highness'. Mental highness might be a consequence of temporary mood elevation. The transient feeling of well-being is related to l-DOPA pleasure mediating effect. Dopamine supports goal-directed behaviour (directing the attention to reward-related cues) and subsequent subjective positive mood changes, but some individual personality traits might also contribute to subjective mood modulation.

5.2. Hippocampal volumes in PD patients vs. healthy controls

Our second hypothesis proposing a decreased CA2-3 and CA4-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. 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. 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. 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 behaviour. Activation of these inputs results in neuropeptide release (e.g. vasopressin from paraventricular hypothalamic nucleus) that could prolong social memory formation.

The vulnerability of the CA2 region is also proved in several psychiatric diseases including schizophrenia, depression, and anxiety. In major depressive disorder, the hippocampal volume loss affects the whole hippocampus, 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 Parkinson disease associated neurodegeneration and major depressive disorder might share several common pathways. These pathophysiological features pertain to decreased production of neurotrophic factors, reduced neurogenesis, abnormal synaptic plasticity, and enhanced neuroinflammation in the hippocampus.

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. This observation raises the possibility of an early antidepressive effects of l-DOPA, however, the exact mechanism is not clear. This finding has an important clinical significance, the amelioration of depressive symptoms might assist in quality of life improvements.

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. The literature data demonstrated that l-DOPA is able to restore neurogenesis in the DG of mice with bilateral intra-nigral 6-hydroxy-dopamine lesion, together with the improvement of Parkinson-like non-motor behaviour.

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 major depressive disorder. 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.

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.

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