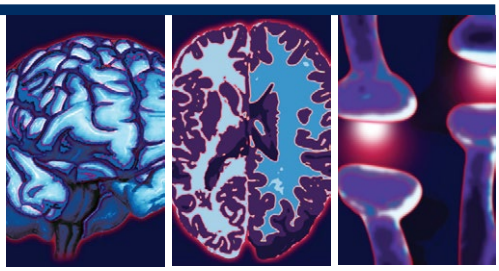

Dysphoria, dopaminergic medication and spatial memory in Parkinson's disease

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ABSTRACT

Depression is considered a potential risk factor for developing cognitive deficits and dementia during the progression of Parkinson's disease (PD). Depression and dysthymia are also among the most frequent neuropsychiatric comorbidities, especially in later stages of PD. Regardless of the depression diagnosis, clinical and subsyndromal depressive symptoms in PD patients are associated with decreased daily functioning. However, very little is known about subsyndromal depressive symptoms and their relations to cognitive function and dopamine medication in PD. Here we investigated depressive symptoms and spatial memory performance in 34 early PD patients compared to 36 matched healthy controls in a pharmaco-behavioral cross-over study. Despite that none of the PD patients fulfilled clinical criteria for major depression or dysthymia, PD patients showed elevated scores of depressive symptoms compared to healthy controls. Depressive symptom load was further negatively correlated with spatial memory performance in PD patients when off dopaminergic medication. Furthermore, it could be shown that the factor dysphoria but not retardation or vegetative symptoms of the MADRS was associated with reduced spatial memory off dopaminergic medication. Present findings indicate that under dopaminergic withdrawal affective symptoms of depression i.e., dysphoria may be associated with spatial memory deficits in early PD patients. Future studies are needed to specify the underlying mechanisms and interactions of depressive symptoms and dopaminergic treatment in PD, especially in context of clinically relevant depression.

Keywords

Depressive symptoms, Dysphoria, Dopaminergic medication, Spatial memory, Parkinson's disease

Introduction

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder of multifactorial etiology leading to massive cell loss in the substantia nigra pars compacta (SNc) and increasing nigrostriatal dopamine (DA) deficiency [1-3] as well as to disturbances of other neurotransmitters including the serotonergic system (see [4] for recent review). On the symptom level PD is characterized by motor symptoms, the cardinal symptoms being bradykinesia, rigidity, postural instability, and resting tremor (UK Brain Bank Criteria, [5]), as well as non-motor symptoms such as neuropsychiatric symptoms, including dysthymia and depression, and cognitive deficits [6]. Affective disorders, particularly depression,

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are very frequent in PD [7]. Depression rates are already substantially elevated in early disease stages, with 25-34 % of PD patients being affected [8]. Treatment with dopamine (DA) medication, specifically with DA agonists has been suggested to ameliorate depression in PD [9,10]. Cognitive deficits in PD are most prominent in the domains of memory, executive functions [11,12] and visuospatial learning and memory [13-16]. DA medication effects on cognition in PD patients follow an inverted-U shaped and individually dosage-dependent function [17-21] and have been associated with improved performance in learning, visual and verbal memory, visuospatial abilities, and frontal lobe tasks [22]. In a recent study DA medication in early PD patients has been shown to have beneficial effects on spatial memory functions subserved by the hippocampal-striatal circuitry [23]. However, given that DA depletion in the striatum follows a dorsal to lateral-ventral gradient, DA medication dosages associated with improved cognitive functions supported by the dorsal striatum might also negatively affect ventral striatal functions following the "overdose" model [24,25].

The relationship between depression and cognitive deficits in PD has been investigated so far mainly for the domain of executive functions. Depressed PD (dPD) patients show impairments in tasks of executive functions compared to non-depressed PD (ndPD) patients [26,27]. Comparison of dPD, dysthymic PD, and non-depressed PD (ndPD) patients in cognitive tests showed that dysthymic PD patients displayed more profound visuospatial and executive dysfunction relative to ndPD, whereas dPD patients exhibited even broader and more profound executive and visuospatial deficits in episodic visuospatial memory, spatial working memory and language domains [28]. These findings indicate a dose-response relationship of depression and executive functioning in PD i.e., an increase in executive function deficits with increasing load of depressive symptoms [28]. Blonder, *et al.* [29] reported a significant interaction of depression and medication status in tests of episodic memory (verbal memory and facial affect recognition), with reduced performance in dPD patients when on DA medication compared to the off medication condition. So far, the question whether depressive symptom load in non-depressed PD patients is differentially associated with cognitive performance on and off DA medication still needs to be investigated. Furthermore, it is unknown whether factors of depressive symptoms (cognitive, affective, and motor) are specifically related to cognitive performance on and off dopaminergic medication.

In a pharmaco-behavioral crossover study we aimed to investigate the depressive symptom load in early PD patients and matched healthy controls (HC). Furthermore, we examined the association of depressive symptom load and hippocampal-striatal spatial memory [23,30-32] in PD patients on versus off DA medication. Based on the findings that DA medication ameliorates depression [9,10] and cognitive performance in PD [22], specifically spatial learning and memory [23], we assumed a negative association of depressive symptom load with spatial memory performance under dopamine withdrawal (off medication). To explore the specificity of association between depressive symptom load and spatial memory on and off DA medication in early PD patients, we applied the model by Suzuki, *et al.* [33] distinguishing three factors of depressive symptoms (dysphoria, retardation and vegetative symptoms) as assessed with the Montgomery-Asberg Depression Rating Scale [34] (MADRS). Studies on neuropathological mechanisms of depression suggest that cognitive-affective symptoms of depression and performance in tasks of attention and executive function share common neural substrates which are different from the neural networks mediating vegetative symptoms of depression [35-38]. Therefore, we expected that MADRS factors dysphoria and retardation, but not vegetative symptoms will be significantly associated with spatial memory performance under dopamine withdrawal.

Methods

■ Sample

Patients were diagnosed with idiopathic PD according to UK Brain Bank criteria [5]. Patients were included in the study if they were stable on DA medication for at least three months and able to tolerate an overnight off-medication period. Exclusion criteria comprised mild cognitive impairment and dementia (Montreal Cognitive Assessment [39] (MoCA score ≤ 24) and any other neurological diseases. Only German native speakers participated in the study. The sample comprised 34 PD patients and 36 matched HC (matching criteria: age, gender, education, smoking, handedness) who provided

their written informed consent prior to study participation. The study was approved by the local ethics committee (EK 259072011).

■ Procedure and materials

During screening, all patients underwent a neurological and neuropsychiatric examination performed by a movement disorder specialist, including PD diagnosis and classification of PD subtype, assessment of Hoehn & Yahr stage and medical history. Cognitive status was assessed using the MoCA [39]. Depressive symptoms were assessed on DA medication with the MADRS [34]. Levodopa equivalent daily dose (LEDD) was computed for all PD patients according to Tomlinson and colleagues [40]. Impulsivity was assessed with the Barratt Impulsiveness Scale (BIS-11) [41].

Following study inclusion, two separate appointments were scheduled within four weeks for behavioral assessment (spatial navigation task): one with the regular DA medication (on medication) and one after an overnight medication withdrawal starting at 8 p.m. of the previous day until the end of the assessment on the following day (off medication). All assessments were scheduled in the morning. The order of medication status was counterbalanced for each patient. Each assessment started with an evaluation of motor impairment based on the Unified Parkinson's Disease Rating Scale (UPDRS) Part III [42].

■ Spatial Navigation Task

During the virtual reality-based spatial navigation task [23,30-32] participants navigated on a circular grass plane surrounded by a boundary (stone wall) using a joystick. A traffic cone served as a local intra-environmental cue and mountains, clouds and the sun were provided as distal orientation cues. Before performing the task, participants were given instructions and received training with the joystick. During encoding trials, participants were instructed to remember the location of four objects presented in sequence within the environment. Objects were pictures of neutral items (e.g., alarm clock, rubber duck, hat, and briefcase). During learning trials, participants were asked to virtually walk back to the memorized location of a cued object. They indicated the objects' position by pressing a button on the keyboard. After the button press, the object appeared in its correct location (feedback). The task included three learning trials i.e., each object was cued three times in pseudorandomized order. The initial task's transfer trials modeling hippocampal- versus striatal-dependent navigation strategies were not included into the present analyses. Evidence from an earlier study [30] indicated that the spatial memory effect was most apparent in the first trial of the learning phase, thus, we focused our analyses on the respective data. Spatial memory was calculated as the mean distance error between the correct and the memorized object position (computed as the Euclidian distance in virtual meters, vm), with a larger distance error indicating worse spatial memory.

■ Statistical analyses

Differences in demographic, neuropsychological and neuropsychiatric variables between PD patients and HC were examined with *t*-tests and Chi^2-tests. Correlations of the MADRS score with spatial memory performance on and off dopaminergic medication as well as with motor impairment were calculated as Pearson's product-moment correlation coefficients *r* (Bonferroni-corrected).Correlations of the MADRS factors with spatial memory performance on and off DA medication, clinical and neuropsychological measures were calculated as Spearman's rank correlation coefficients r_{rho} (Bonferroni corrected). MADRS factors were calculated based on a three-factor model by Suzuki, *et al.* [33]. Factor 1 ("dysphoria") comprised the MADRS items pessimistic thoughts, suicidal thoughts and reported sadness. Factor 2 ("retardation") consisted of the items lassitude, inability to feel, apparent sadness, and concentration difficulties. Factor 3 ("vegetative symptoms") comprised the items reduced sleep, reduced appetite, and inner tension. Correlation coefficients of dysphoria with spatial memory on and off medication were tested for significant difference with Stata 14.2. For this analysis, the original values were rank transformed and entered in linear regression with bootstrapping (2.000 replications, bias-corrected accelerated method). All other statistical analyses were conducted with IBM SPSS Statistics 22 and $\alpha<0.05$ indicated statistical significance.

Results

■ Sample characteristics

Table 1 summarizes the demographic, clinical and neuropsychiatric characteristics of the sample. PD patients and HC did not differ in demographic features, cognitive status and impulsivity. Most of PD patients (91.2 %) were

Table 1: Demographic and clinical characteristics of PD patients (N = 34) and healthy controls (N = 36). Data are means (standard deviations) except where noted.

	PD			HC		Chi^2 or t (df)	p value
Demographic data							
Male, [n (%)]	25	(73.5)		27	(75.0)	0.020 (1)	0.888
Age, years	59.24	(8.23)		58.92	(8.03)	0.164 (68)	0.870
Clinical characteristics PD patients							
Disease duration, years	3.85	(3.13)		-	-		
Hoehn and Yahr stage on medication (%)							
1.0	7	(20.6)		-	-	-	-
1.5	7	(20.6)		-	-		
2.0	17	(50.0)		-	-		
2.5	2	(5.9)		-	-		
3.0	1	(2.9)		-	-		
LEDD	581.03	(433.41)		-	-	-	-
UPDRS III score ON med	16.00	(6.13)		-	-	-5.156 (33)	< 0.001
UPDRS III score OFF med	19.79	(7.11)		-	-		
Neuropsychological / neuropsychiatric characteristics							
MoCA	27.76	(1.74)		27.92	(1.34)	-0.411 (68)	0.683
MADRS	2.47	(2.44)		0.75	(1.20)	3.707 (47.555)	0.001
BIS-11	52.41	(7.80)		52.08	(6.54)	0.191 (68)	0.849

PD: Parkinson's disease patients; HC: healthy controls; LEDD: levodopa equivalent daily dose; UPDRS III score ON med/OFF med: Unified Parkinson's Disease Rating Scale Part III, on and off dopaminergic medication; MoCA: Montreal Cognitive Assessment; MADRS: Montgomery-Asberg Depression Rating Scale; BIS-11: Barratt Impulsiveness Scale.

in early disease stages (Hoehn and Yahr stages 1 and 2). PD patients displayed significantly lower motor impairment (UPDRS III score) on DA medication as compared to the off medication condition. We examined the range of PD medications: two patients (5.88 %) were taking DA agonists alone, 21 patients (61.76 %) were taking DA agonists in combination with MAO-B inhibitors or NMDA-antagonists or both. The remaining 11 patients (32.35 %) received levodopa in combination with DA agonists and/or MAO-B inhibitors and/or NMDA-antagonists. Two of 34 patients were taking antidepressants.

The mean MADRS score in PD group was 2.47 (SD=2.44, range=0-9) and no patients were classified as depressed (the MADRS cutoff score is 14/15 for depression in PD; [43]. However, the MADRS score of PD patients was significantly higher compared to the MADRS score of HC (M=0.75, SD=1.20, range=0-6).

■ Correlations of depressive symptoms with spatial memory performance

In the PD group, the MADRS score showed no significant correlation with spatial memory performance when on medication (r=-0.029, p=0.869), but it was significantly associated with spatial memory performance off medication (r=0.534, p=0.001). Higher scores in spatial memory indicated worse performance. Therefore, higher depressive symptoms were associated with worse spatial memory performance when off DA medication. Motor impairment (UPDRS III score) showed no significant association with spatial memory performance on medication (r=0.091, p=0.607).

■ Correlations of MADRS factors with spatial memory off medication

Table 2 summarizes the results of Spearman's correlation coefficients of dysphoria, retardation and vegetative symptoms with spatial memory on and off medication. The MADRS factors did not show significant associations with spatial memory performance on medication, but dysphoria was significantly correlated with spatial memory off DA medication, meaning that higher symptoms of dysphoria were associated with worse spatial memory under dopamine withdrawal. Retardation displayed a moderate correlation with spatial memory off medication, yet not significant after Bonferroni correction. Vegetative symptoms did not show any significant correlation with spatial memory performance. The difference between the correlations of dysphoria with spatial memory on DA medication (r=0.587, p=0.001) and off DA medication (r=0.158, p=0.338) was found to be in trend significant (t=1.72, p=0.095, confidence interval: -0.787 – 0.937).

Table 2: Spearman's rank correlation coefficients (Bonferroni corrected) of the MADRS factors with spatial memory performance*, clinical and neuropsychiatric variables.

		Spatial memory performance		UPDRS III motor impairment		LEDD	MoCA	BIS-11
		on med	off med	on med	off med			
Dysphoria	r_{rho}	0.217	**0.558**	0.169	0.154	0.003	-0.237	0.139
	p value	0.217	**0.001**	0.340	0.385	0.986	0.177	0.435
Retardation	r_{rho}	-0.037	0.449	0.391	0.292	0.189	-0.410	0.279
	p value	0.835	0.008	0.022	0.094	0.285	0.016	0.111
Vegetative symptoms	r_{rho}	-0.062	0.164	-0.068	-0.099	-0.006	0.080	0.162
	p value	0.727	0.354	0.700	0.576	0.974	0.653	0.361

on med: on regular dopaminergic medication; off med: withdrawal from dopaminergic medication; UPDRS III: Unified Parkinson's Disease Rating Scale Part III; LEDD: levodopa equivalent daily dose; MoCA: Montreal Cognitive Assessment; BIS-11: Barratt Impulsiveness Scale.
P (Bonferroni-corrected): 0.007.
*Spatial memory performance was calculated as the mean distance error between the actual and memorized object position, higher scores indicating worse performance.

■ Correlations of MADRS factors with clinical and neuropsychiatric measures

No significant correlations of MADRS factors with clinical variables (motor impairment on and off medication, levodopa equivalent daily dose), cognitive impairment and impulsivity were observed **(Table 2)**.

Discussion

The present study aimed to investigate depressive symptom load and spatial memory performance in 34 early PD patients compared to 36 matched control subjects. In the patient group, we examined the association of depressive symptoms and spatial memory performance on and off DA medication. The main results are the following: 1) although none of the PD patients featured clinical depression, depressive symptom load in the patient group was significantly higher as compared to controls. 2) Depressive symptoms were significantly associated with reduced spatial memory performance under dopamine withdrawal (off medication). 3) Dysphoria, but not retardation or vegetative symptoms was significantly associated with reduced spatial memory off medication. 4). No significant correlations of dysphoria with clinical variables, cognitive impairment and impulsivity were observed.

Previous studies reported cognitive performance deficits in depressed as compared to non-depressed PD patients [26-28]. In the present sample, we observed that depressive symptom load was associated with reduced spatial memory performance off medication. We also found that dysphoria, but not retardation or vegetative symptoms of the MADRS was associated with reduced spatial memory off medication. We found that the difference of the associations of dysphoria with spatial memory on and off medication showed a trend to significance. Thus, dysphoria was specifically related to reduced spatial memory under dopamine withdrawal.

Retardation was moderately yet not significantly related to spatial memory off medication, and vegetative symptoms showed no correlation with spatial memory. According to the neurofunctional model of depression introduced by Mayberg, *et al.* [36-38], cognitive symptoms of depression have been associated with altered activity in the dorsal compartment comprising the medial frontal cortex, the dorsolateral prefrontal cortex, posterior cingulate and parietal cortices. In contrast, vegetative symptoms of depression have been rather related to altered activity in the ventral compartment consisting of the subgenual anterior cingulate, ventral insula, hypothalamus and rostral inferior frontal regions [36-38]. Our behavioral findings support the specific association of cognitive-affective symptoms of depression (dorsal compartment) with spatial memory. These results probably reflect the differential neural substrates of cognitive-affective and vegetative symptoms of depression [35,37,38]. Dysphoria showed no significant associations with clinical, neuropsychiatric and cognitive variables, supporting the specificity of its association with spatial memory performance. The present findings emphasize the importance of depressive symptom factor approach for the evaluation of spatial memory performance.

The neuropathology of PD is characterized by a distinct spatio-temporal dopamine depletion: the dorsal-striatal projections are affected already in mild PD, whereas the degeneration progresses only later to more ventral parts of the striatum and the mesocorticolimbic pathways [44].

Dopamine levels in the prefrontal cortex (PFC) of PD patients may even be upregulated in early PD, supposedly reflecting a compensation of the dopamine depletion in the striatum [45,46]. The effects of dopamine on cognition have been shown to follow an inverted-U-shaped function suggesting that both insufficient and excessive dopamine levels impair cognitive performance ("overdose-model" [47-49].

Neural mechanisms underlying spatial memory have been suggested to involve at least two parallel memory systems based on the hippocampus and dorsal striatum [50,51]. Specifically for spatial learning and memory, the right posterior hippocampal activation has been shown to reflect learning of boundary-related locations, whereas right dorsal striatal activation (peak in the caudate) was associated with memory of cue-related locations [30,31]. These findings confirm the relevance of both hippocampal and striatal interactions for spatial memory [23].

Our results suggest that subsyndromal depressive symptoms may be associated with spatial memory deficits under dopaminergic withdrawal. In contrast, Blonder, *et al.* [29] reported significant deficits in depressed PD patients on DA medication as compared to the off medication state in tasks of verbal memory and affective processing. Blonder, *et al.* also showed that DA medication had the opposite effect in non-depressed PD patients with enhanced performance on tasks of verbal memory and affective processing. A possible explanation for the divergent findings is that the tasks employed by Blonder, *et al.* predominantly recruited frontally mediated cognitive functions leading to overdosing in the on-medication state and the observed performance deficits. However, in our study we examined the hippocampal-striatal functions (e.g. spatial memory) in non-depressed PD patients. We observed that depressive symptoms, specifically dysphoria was associated with reduced spatial memory performance under dopamine withdrawal. In a recent study Vriend, *et al.* [52] suggest that depressive symptoms in PD are associated with dopamine loss in the caudate nucleus. According to these findings, PD patients with depressive symptoms might already show more extensive striatal dopamine deficits relative to PD patients with low or no depressive symptoms. Thus, depressive symptoms in PD patients may represent a marker of interindividual differences in striatal DA depletion contributing to the progression of cognitive decline in PD. Recent studies have shown that depression preceding the onset of PD was associated with impaired executive task performance [53,54]. Major depression has been associated with reduced reward processing and diminished reward-related activation in the ventral striatum [55] reflecting altered striatal functionality as a potential neurofunctional substrate of this disorder. Molecular imaging studies on PD depression have shown reduced dopamine transporter (DAT) availability within striatum or extra-striatal regions [56,57] as well as increased DAT density in dPD patients in the dorsal striatum [58]. In non-PD depressed patients higher DAT uptake has been reported [59,60]. Dopaminergic alterations appear to be important in primary depression and in depressive symptoms in PD.

The Spatial Navigation Task includes a motor component as subjects used a joystick to navigate. However, motor symptoms showed no significant association with spatial memory and cannot account for spatial memory performance. For the assessment off medication, patients were instructed to omit only their prescribed PD medication overnight. Other medications were held constant and therefore cannot explain the present findings.

The majority of PD patients were receiving DA agonists in combination with MAO-B inhibitors and/or NMDA-antagonists, while a smaller proportion of patients received levodopa in combination with DA agonists and a MAO-B inhibitor and/or a NMDA-antagonist. MAO-B inhibitors have been found to treat depression and anxiety in PD [61]. However, the role of MAO-B inhibitors as add-on to DA agonist treatment for cognitive and affective functions in PD has not yet been addressed. A study by Krishna and Moustafa [62] suggests that MAO-B inhibitors as an adjunct to levodopa therapy provide a better effect on cognitive function (including working memory, cognitive flexibility and probabilistic learning) and depression compared to monotherapy with levodopa or DA agonists. The authors assume that the beneficial effects of combined levodopa and MAO-B therapy on cognitive and affective measures may be the continuous dopaminergic stimulation of the basal ganglia and/or increase of the availability of monoamines. Whether the combination of DA agonists with MAO-B inhibitors and/or NMDA-antagonists may have similar positive effects, should be addressed in future studies.

Some methodological limitations need to be mentioned. The majority of PD patients in the present sample had mild PD with significant cognitive deficits being less probable. Depressive symptoms were assessed with the MADRS on medication; no reference data off medication are available. Lastly, no task on working memory and processing speed on and off medication was applied. Although the sample comprised PD patients in early disease stages, we cannot rule out potential effects of individual differences in these cognitive functions on spatial memory performance.

In the present study we demonstrated that in early PD symptoms of dysphoria, but not retardation or vegetative symptoms were specifically associated with reduced spatial memory performance under dopaminergic withdrawal. It is unknown whether these associations would be relevant and even more evident in PD samples with clinical depression. To our knowledge, this aspect has not been addressed before. The present explorative study with its methodological limitations nevertheless provides first valuable insights and may stimulate future studies to examine the relationship between depressive symptoms, DA medication and spatial memory in PD, especially in clinical PD depression. A better understanding of antidepressant treatment alone and/or in combination with dopaminergic treatment for spatial memory and executive functions would contribute to development of personalized treatment approaches, helping to improve quality of life in PD.

Funding Source

This study was funded by the German Research Foundation (Deutsche Forschungsgemeinschaft; DFG) Collaborative Research Centre 940: "Volition and Cognitive Control: Mechanisms, Modulators, Dysfunctions".

Acknowledgments

We are grateful to Susanne Guenther, Maximilian Peukert and Maria Simon for their help with patient recruitement and data acquisition. We thank Michael Hoefler for support with statistical analyses.

Conflict of Interest

A.Storch was acting on Advisory Boards (UCB Pharma) and consultancies (Britannia, Mundipharma, Pfizer), received honoraria from AbbVie, Desitin, Medtronic, GSK, MEDA Pharma, Medtronic, Mundipharma, TEVA, Lundbeck, Novartis, UCB Pharma, and received research grants from Deutsche Forschungsgemeinschaft (DFG). M. Fauser received grants from Deutsche Forschungsgemeinschaft (DFG), personal fees from UCB Pharma and MEDA Pharma.

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