Enhanced Creative Thinking under Dopaminergic Therapy in Parkinson Disease

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Objective: Creative thinking requires a combination of originality, flexibility, and usefulness. Several reports described enhanced artistic creativity in Parkinson disease (PD) patients treated with dopaminergic agents. We aimed to examine PD patients' ability to perform creativity tasks compared to healthy controls and to verify whether creativity is related to an impulse control disorder (ICD) as a complication of dopaminergic therapy.
Methods: Right-handed PD patients treated with dopamine agonists and/or levodopa, and age- and education-matched neurologically healthy controls were assessed using the Montreal Cognitive Assessment, semantic verbal fluency, Beck Depression Inventory, and Questionnaire for Impulsive–Compulsive Disorders in Parkinson Disease Rating Scale (QUIP-RS). Creativity assessment included Comprehension of Novel Metaphors (CNM), Remote Association Test, and Tel Aviv Creativity Test (TACT). Groups were compared using analyses of variance, t tests, and correlation analyses.
Results: Twenty-seven PD patients (age, mean $\pm$ standard deviation = 62 $\pm$ 7 years; education = 16 $\pm$ 3 years; disease duration = 5.8 $\pm$ 3.9 years) and 27 controls (age = 59 $\pm$ 9 years; education 17 $\pm$ 3 years) participated. PD patients performed significantly better than controls in divergent thinking tasks; specifically, the TACT-Visual for both fluency (33.48 $\pm$ 11.83 vs 25.59 $\pm$ 10.27, $p = 0.034$) and quality (15.78 $\pm$ 7.6 vs 11.19 $\pm$ 6.22, $p = 0.025$). Comprehension of Novel Metaphors was better in PD patients vs controls (0.71 $\pm$ 0.23 vs 0.55 $\pm$ 0.29, $p = 0.04$). QUIP-RS scores did not correlate with creativity measures.
Interpretation: PD patients treated with dopaminergic drugs demonstrated enhanced verbal and visual creativity as compared to neurologically healthy controls. This feature was unrelated to ICD. Dopaminergic agents might act through the reduction of latent inhibition, resulting in widening of the associative network and enriched divergent thinking.

ANN NEUROL 2014;75:935–942

The definition of creativity includes neurological, philosophical, and psychological aspects. Creative thinking is the combination of novel as well as practical ideas. Originality, flexibility, and usefulness are key features of the creative process.[1,2] Enhanced artistic production as a way of expressing creativity was reported in a variety of neuropsychiatric syndromes such as frontotemporal dementia and stroke.[3,4]

Recently, attention was drawn to reports of augmented or newly emerging artistic creativity in Parkinson disease (PD) patients treated with dopaminergic therapy.[5] A PD patient treated with L-dopa and dopamine agonists (DA) became artistically productive along with increased drive to draw paintings.[6] Another patient, originating from a family of poets, started writing poetry only a month after the initiation of dopaminergic treatment with DA and L-dopa.[7] His work was published and even won a prize. Several additional case reports described increased creativity in PD patients following the initiation of dopaminergic therapy.[6–11] Moreover, lowering the dosage or insertion of deep brain stimulation resulted in reduced creativity.[12]

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.24181

Received Feb 5, 2014, and in revised form May 8, 2014. Accepted for publication May 8, 2014.

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One of the theories for enhanced creativity in PD is connected to impulse control disorders (ICDs), a recognized complication of dopaminergic therapy.[13] ICDs comprise a spectrum of impulsive–compulsive behaviors such as compulsive gambling, eating, punding, and hobbyism. Dopamine dysregulation syndrome (DDS) is dopaminergic therapy–associated ICD. In addition to other ICD features, patients suffering from DDS tend to overuse dopaminergic therapy.[13] It was debated that obsessive drawing or writing might be interpreted as another ICD associated with dopaminergic therapy.[12,14,15] A study comparing creative drive in PD patients who declare themselves creative/noncreative and neurologically healthy controls observed that creative drive was not associated with enhanced impulsive–compulsive behavior.[15] In contrast, a survey including a self-filled ICD questionnaire, namely the Questionnaire for Impulsive–Compulsive Disorders in Parkinson Disease (QUIP),[16] and questions regarding artistic creativity before and after PD diagnosis in 290 patients showed increased prevalence of ICDs in patients experiencing enhanced creativity after PD diagnosis compared with patients who did not experience enhanced creativity.[17] In light of these observations, the aims of this study were to identify features of creative thinking in PD patients and examine whether creativity in PD patients treated with dopaminergic therapy is an expression of ICD or a distinct phenomenon.

Subjects and Methods

Right-handed PD patients and gender-, age-, and education-matched neurologically healthy controls were included. Inclusion criteria were: idiopathic PD, L-dopa and/or DA treatment, and graduation from high school in Israel (Hebrew). Exclusion criteria were parkinsonism other than idiopathic PD, history of brain surgery/deep brain stimulation, and dementia defined by Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria.[18] Mild cognitive impairment was not an exclusion criterion.

Consecutive patients were recruited through the outpatient Movement Disorders Clinic at Sheba Medical Center, Tel Hashomer, Israel. All patients met the UK Brain Bank criteria for idiopathic PD.[19] The patients were tested during their "on" periods, while on their standard drug regimen. All participants gave their written informed consent. The study was approved by the Ethics Committee of Sheba Medical Center.

All patients were examined by a neurologist specializing in movement disorders (A.F.-S., S.H.-B., O.S.C., or R.I.) using the motor subsection (part III) of the United Parkinson's Disease Rating Scale.[20] None of the participants met the criteria for depression (assessed by Beck Depression Inventory [BDI][21]), dementia (according to DSM-IV,[18] Montreal Cognitive Assessment [MoCA],[22] and Frontal Assessment Battery), or ICD (according to DSM-IV[18] and the Quip Rating Scale (QUIP-RS).[23] The L-dopa equivalent daily dose (LEDD) was calculated for each patient as described in the literature.[15] All tests were performed in Hebrew.

Verbal and Creativity Tests

VERBAL FLUENCY. One phonological (words starting with the letter b, eg, *bet* in Hebrew) and 2 semantic categories (animals and fruits/vegetables) were used.[24]

REMOTE ASSOCIATION TEST. Subjects are presented with a triplet of seemingly unrelated words (eg, *cottage, swiss, cake*) and are required to find a fourth word that is related to each of these words (eg, *cheese*). The Remote Association Test (RAT)[25] has been used to investigate linguistic creativity.[26] We used the Hebrew version of the RAT,[27] containing 25 triplets with varying degree of difficulty.

TEL AVIV UNIVERSITY CREATIVITY TEST. This test is a battery of creativity tests in Hebrew, which includes different measures of divergent thinking. The Tel Aviv University Creativity Test (TACT)[28] comprises 4 open question subtests: 2 verbal (alternative uses and pattern matching) and 2 visual (similarities and line meanings). Scoring is based on fluency (number of responses) and quality (originality of responses). Fluency score was calculated by counting the number of different answers, and quality score by 3 independent judges evaluating the originality and applicability of responses to stimuli for unique answers only (answers that appeared in only 5% or less of the sample).[28] We used a shorter version of the TACT, which included 1 TACT-Verbal subtest (alternative uses) and 1 TACT-Visual subtest (line meanings).

NOVEL METAPHORS. Subjects are presented with 2-word expressions, which either can have a literal, conventional metaphoric, or novel metaphoric meaning, or can be meaningless. Subjects are asked to decide whether the 2 words comprise a semantically meaningful expression.[29] We implemented a shortened offline version of this task. Twenty word pairs of each kind (literal, conventional metaphors, novel metaphors, unrelated) were presented to the subjects, who indicated the semantic relatedness of the word pairs. Only accuracy of success was measured. The main interest of the present study is in the comprehension of the novel metaphors (NMs) that requires semantic flexibility (ie, sense creation). Comprehension of the other meaningful word pairs requires mainly sense retrieval, because they are already represented in the lexicon.

ICD Evaluation Tests

QUIP-RS[23] is a rating scale for the severity of ICD and related symptoms, based on the former QUIP, which is a validated screening tool for PD-related ICD, but is not suitable for evaluating severity of symptoms or to monitor changes over time. QUIP-RS includes 7 questions for each ICD: compulsive gambling, buying, eating, sexual behavior, punding, hobbyism, and medication use. Each question is scored from 0 to 4 based on frequency of behaviors in the preceding 4 weeks (0 = never;

TABLE 1. Demographic and Cognitive Assessment Scores of Participants

Characteristic	PD, n = 27	Controls, n = 27	p
Age, yr	62 ± 7	59 ± 9	0.199
Gender, M/F	11/17	16/12	
Education, yr	16 ± 3	17 ± 3	0.091
MoCA, mean ± SD (range)	26.3 ± 1.6 (24–30)	27.1 ± 1.3 (25–30)	0.077
BDI	6 ± 4	4 ± 4	0.310
LEDD, mg	481 ± 430	—	
PD duration, yr	6 ± 4	—	
UPDRS III	24 ± 9	—	

BDI = Beck Depression Inventory; F = female; LEDD = mean L-dopa equivalent daily dose; M = male; MoCA = Montreal Cognitive Assessment; PD = Parkinson disease patients; UPDRS III = Unified Parkinson Disease Rating Scale, part III (motor).

4 = very often). Because PD patients were consecutively recruited, we did not know a priori the presence/absence or severity of their ICD.

Data Analysis

RAT and verbal fluency tasks were analyzed using a 2-tailed independent samples *t* test, to examine the differences between PD patients and controls. For the NMs task, accuracy of the different conditions were subjected to a repeated measures analysis of variance (ANOVA), with NM condition serving as within-subject factor and group serving as between-subject factor. A similar analysis was conducted on TACT fluency and quality scores. In all analyses, Mauchly's test of sphericity was performed for all repeated measures factors and, whenever this was found to be significant, Greenhouse–Geisser corrections were applied.

QUIP-RS scores were analyzed in 3 ways, as previously reported[23]: total QUIP-RS scores, total ICD score (sum of items 1–4), and hobbyism–punding score (sum of items 5 and 6). Correlation analysis was performed between QUIP-RS scores and creativity measures.

To examine a possible association between LEDD and creative ability, we conducted 2 different analyses. First, we performed a Pearson correlation analysis of all variables for the PD group, to examine any significant relation between the LEDD variable and all other variables. We then sorted the PD group data based on their LEDD and analyzed, via a tertile split, the differences in creative ability between the lowest versus highest LEDD group.

Results

Twenty-seven PD patients (age, mean ± standard deviation = 62 ± 7; education = 16 ± 3; disease duration = 5.8 ± 3.9 years) and 27 controls (age = 59 ± 9; education = 17 ± 3 years) participated. MoCA and BDI scores are depicted in Table 1. No differences were found between patients and controls concerning age, education, MoCA, and BDI.

Verbal Fluency

No significant differences were found in the amount of words generated by both groups in all 3 verbal fluency tasks (phonological: 12.6 ± 3.47 PD vs 13.11 ± 4.53 controls, $p > 0.1$; semantic: animals, 21.89 ± 4.81 PD vs 21.12 ± 6.04 controls, $p > 0.1$; fruits/vegetables, 20.31 ± 4.87 PD vs 19.92 ± 5.34 controls, $p > 0.1$).

Remote Association Test

The number of correct responses was similar (8.96 ± 5.09 in PD vs 8.19 ± 4.98 in controls, $p > 0.1$).

NM Task

Analysis revealed a significant effect for NM condition ($F_{3,156} = 64.119$, $p < 0.001$) and a significant interaction effect between NM condition and group ($F_{3,156} = 3.871$, $p = 0.011$). This interaction stemmed from differences in the accuracy rates of the PD and control group in the recognition of NMs (0.71 ± 0.23 in PD vs 0.55 ± 0.29 in controls, $p = 0.04$). The 2 groups did not differ on any of the 3 other expression types (Fig 1).

TACT

A significant effect for TACT subtest ($F_{1,52} = 59.151$, $p < 0.001$ and $F_{1,52} = 30.2$, $p < 0.001$, for fluency and quality analyses, respectively) was found. Whereas the TACT-Verbal subtest significantly generated more responses (fluency) in both groups, the TACT-Visual subtest significantly generated more unique, creative (quality) answers. Furthermore, a significant effect was found for group ($F_{1,52} = 4.741$, $p = 0.034$ for fluency and $F_{1,52} = 5.331$, $p = 0.025$ for quality analyses), in the sense that the PD group generated more responses and

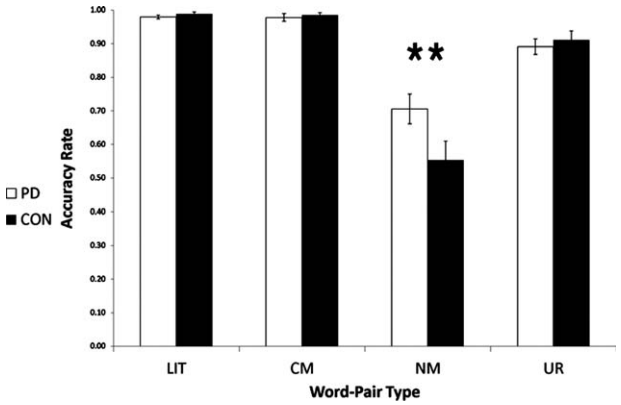

FIGURE 1: Comprehension of novel metaphors task. X-axis: the different word pair types. Y-axis: percentage of successful recognition (error bars represent standard error). The accuracy rates of Parkinson disease patients was better than those of controls in the recognition of novel metaphors ($p = 0.04$). CM = conventional metaphoric meaning; CON = healthy control subjects; LIT = literal meaning; NM = novel metaphoric meaning; PD = Parkinson disease patients; UR = unrelated.**

more qualitative responses than the control group (Fig 2).

QUIP-RS

Table 2 summarizes subjects who scored above cutoff for both ICD and hobbyism–punding as defined by Weintraub et al.[23] No significant correlation was found between QUIP-RS scores, total ICD score, and punding-hobbyism score and creativity measures (verbal fluency, RAT, TACT, NMs) for patients or controls.

LEDD Analysis

Correlation analysis between creative measures (verbal fluency, RAT, TACT, NMs) and LEDD revealed a positive trend between LEDD and the TACT-Visual quality scores ($r[27] = 0.344$, $p = 0.079$, 2-tailed). A significant negative correlation was found between LEDD and the semantic verbal fluency task of the animal category ($r[27] = -0.406$, $p = 0.036$, Table 3).

We then sorted the PD group data based on their LEDD and analyzed, via a tertile split, lowest LEDD (n = 9, mean dose = 148.53 ± 75.29mg), highest LEDD (n = 9, mean dose = 961.03 ± 449.68mg), and moderate LEDD (n = 9, mean dose = 442.82 ± 108.97mg). A LEDD subset (lowest LEDD/highest LEDD) × TACT quality subtest (TACT-Verbal/TACT-Visual) repeated measures ANOVA was conducted. This analysis revealed a significant main effect for TACT quality subtest ($F_{1,16} = 15.943$, $p = 0.001$) and interaction between group and TACT subtest quality scores ($F_{1,16} = 4.569$, $p = 0.048$). A post hoc analysis (corrected for multiple comparisons) revealed that this significant interaction effect is due to a significant simple effect between group and the TACT-Visual quality scores, in the sense that the high-LEDD group resulted in a significantly higher amount of creative responses in the TACT-Visual subtest (19.11 ± 6.60 in highest LEDD group vs 12.44 ± 6.39 in lowest LEDD group, $p = 0.045$, Fig 3).

Discussion

The results of our study indicate that PD patients treated with dopaminergic therapy reveal enhanced verbal and visual creative thinking compared to healthy subjects. This augmentation in creative thinking does not correlate with ICD.

These results support a genuine change in neuropsychological processes underlying creativity such as enhanced originality, flexibility, and elaboration

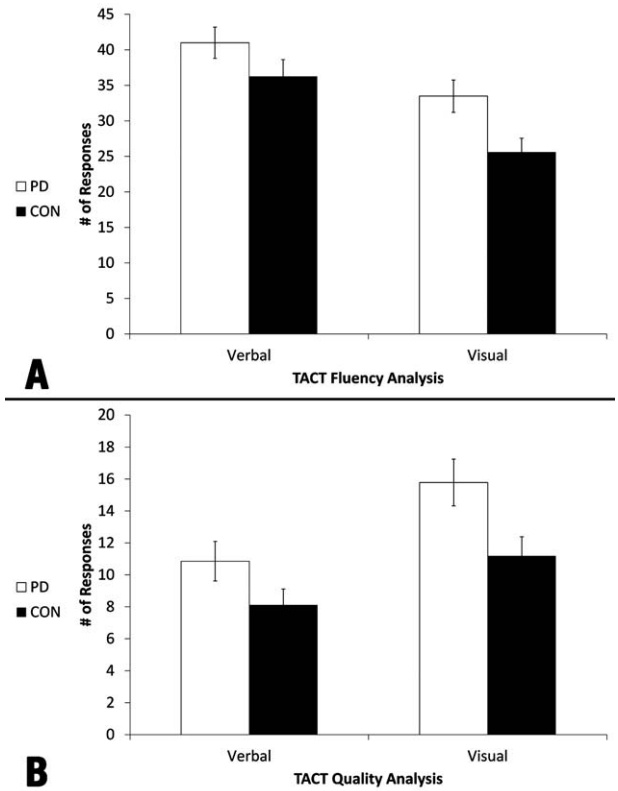

FIGURE 2: Tel Aviv University Creativity Test (TACT) analysis. (A) TACT fluency. (B) TACT quality analysis. X-axis: the 2 TACT subtests, TACT-Verbal and TACT-Visual. Y-axis: mean amount of answers (fluency) or amount of unique responses (quality). Error bars depict standard error. A significant effect for TACT subtest was found for fluency (A; $p < 0.001$) and for quality (B; $p < 0.001$). (A) The TACT-Verbal subtest significantly generated more responses (fluency) in both groups. (B) The TACT-Visual subtest significantly generated more unique, creative (quality) answers in both groups. A significant effect was found for group for fluency (A; $p = 0.034$) and quality (B; $p = 0.025$) analyses, in the sense that the Parkinson disease group generated more responses and a larger number of high quality responses than the control group. CON = healthy control subjects; PD = Parkinson disease patients.

TABLE 2. QUIP-RS Total and Number (%) of Subjects with ICD Item above Cutoff Score[a]

	PD Patients	Controls
Gambling	0/27 (0)	0/27 (0)
Buying	2/27 (7.4)	0/27 (0)
Sex	1/27 (14.4)	0/27 (0)
Eating	3/27 (11.1)	3/27 (11.1)
Hobbyism–punding	6/27 (22.2)	5/27 (18.5)
>1 ICD	2/27 (7.4)	2/27 (7.4)
Total QUIP-RS, mean score ± SD[b]	14.2 ± 12.1	13.4 ± 9.5[c]

[a]Cutoff scores are derived from Weintraub et al.[23]
[b]Range = 0–96. For comparison between PD and controls, QUIP-RS total was calculated excluding item 7, which relates to compulsive medication use, because controls score 0 for this item.
[c]QUIP-RS scores were not different in PD patients versus controls ($p = 0.768$).
ICD = impulse control disorder; PD = Parkinson disease; QUIP-RS = Questionnaire for Impulsive–Compulsive Disorders in Parkinson Disease Rating Scale; SD = standard deviation.

TABLE 3. Correlation Scores between LEDD and Creativity Measures

Score	*r*	*p*
RAT	0.11	0.59
VF_S_A	0.1	0.62
VF_S_FV	−0.41	0.04[a]
VF_P	−0.14	0.47
TACT Verb-F	−0.11	0.59
TACT Vis-F	−0.07	0.75
TACT Verb-Q	0.11	0.57
TACT Vis-Q	0.34	0.08[b]
CNM_LIT	−0.01	0.96
CNM_CM	−0.1	0.64
CNM_NM	0.07	0.74
CNM_UR	−0.24	0.23

[a]$p < 0.05$; [b]$p < 0.1$.
CNM_CM = comprehension of novel metaphors–conventional metaphors word pairs; CNM_LIT = comprehension of novel metaphors–literal meaning word pairs; CNM_NM = comprehension of novel metaphors–novel metaphors word pairs; CNM_UR = comprehension of novel metaphors–unrelated word pairs; *p* = statistical probability value of correlation score; *r* = correlation score; RAT = Remote Association Test; TACT = Tel Aviv University Creativity Test; TACT Verb-F = TACT verbal fluency scores; TACT Verb-Q = TACT verbal quality scores; TACT Vis-F = TACT visual fluency scores; TACT Vis-Q = TACT visual quality scores; VF_P = verbal fluency phonology task; VF_S_A = verbal fluency semantic animal category; VF_S_FV = verbal fluency semantic fruits and vegetables category.

demonstrated in the superior performance of PD patients in the TACT-Visual and the novel metaphor comprehension task. Thus, PD patients seem to perform better on tasks that tap major components of creative thinking[29]: divergent thinking and combinational novelty.

Metaphor comprehension without referral to novel associations was examined previously in PD as a dimension of pragmatic language processing and was found either impaired[30,31] or more recently deficient only in those PD patients with problems in working memory.[32] In the present study, we used novel metaphors and only examined nondemented patients.

The performance on 2 other linguistic tasks, verbal fluency and RAT, was similar for PD patients and controls. As for the verbal fluency task, PD patients did not differ from controls, suggesting that basic linguistic abilities were preserved. This observation is relatively surprising, because previous studies have shown that both phonemic and especially semantic verbal fluencies are impaired in nondemented PD patients.[33] We found a significant inverse correlation between LEDD and semantic verbal fluency. This could possibly reflect a U-shaped relationship, or alternatively suggest that patients with higher LEDD suffer from more advanced PD and thus demonstrate lower verbal fluency.

One of the research questions was the possibility of creativity being driven by impulsive–compulsive behavior.

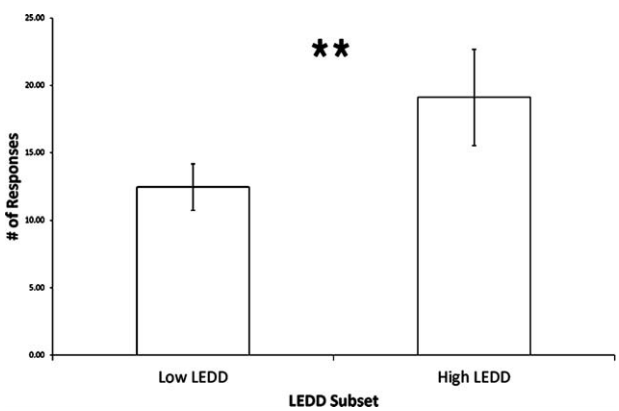

FIGURE 3: Tel Aviv University Creativity Test (TACT) visual quality scores of low and high L-dopa equivalent daily dose (LEDD) groups. X-axis: LEDD subsets (low LEDD, high LEDD). Y-axis: mean amount of quality responses (error bars depict standard error). A significantly higher amount of creative responses in the TACT-Visual subtest was observed in the highest LEDD group versus the lowest ($p = 0.045$).**

QUIP-RS scores did not correlate with creativity measures, suggesting that these occur independently. It is yet undetermined, however, what the correlation is between QUIP-RS score and the clinical picture of ICD and related disorders. Previous studies investigating the possible association between creativity and compulsive disorders used different scales. Canesi et al[15] used a different screening instrument that does not measure severity of symptoms. In their study, patients defining themselves as creative/noncreative had similar impulsivity scores.[15] They concluded that increase in creative drive is not related to ICD in PD patients treated with dopaminergic medications. Joutsa et al[17] used the QUIP as a screening tool and found an association between ICD and an increase in creative ability. However, the evaluation of creativity in their study was only subjective and did not include quantitative and qualitative objective creativity testing. It is possible that patients who suffer from ICD do "create" more, but it is not certain that their products have an original, useful value. Considering the relationship between ICD and creativity, it is a common observation that some innovators work compulsively on their projects. Simonton's "Darwinian theory of creativity" provides a mechanism by which obsessive dedication to solving a problem may trump other failings in producing creative solutions.[34]

The limitations of the QUIP-RS,[23] which was used in the present study, primarily stem from it being a relatively new rating scale with limited clinical or research experience. Patients with adequate cutoff values for ICD do not necessarily fulfill the clinical definition of ICD based on DSM-IV.[18,23] In addition, only QUIP (scoring by dichotomy), but not QUIP-RS (scoring by severity), was validated in normal controls.[35] The frequency of ICD behaviors in our normal controls measured by QUIP-RS are in concordance with those reported in a QUIP study.[35]

Two mechanisms are proposed for the role of dopamine in the creative process. Latent inhibition (LI) is the ability of the brain to filter irrelevant stimuli; reduction of this ability is observed in psychosis, whereas it is increased when antipsychotics are used. Reduced LI might thus enhance divergent thinking by widening (or loosening) the associative network, enhancing creative thinking. LI was also associated with high creative achievements. Carlsson et al[36] reported that reductions in LI, that is, a failure to screen out previously irrelevant stimuli, might also contribute to original thinking, particularly in combination with high intelligence quotient (IQ). In their meta-analysis of studies conducted on youthful high-IQ samples, they showed that high lifetime creative achievers had significantly lower LI scores compared to low creative achievers. A proposed neuroanatomical mechanism underlying reduced LI is the nucleus accumbens and its afferent connections that have been found to be influenced by dopamine levels.[1,37]

Another possible mechanism mediating the relations between dopamine and creativity is novelty-seeking behavior; creative people tend to be novelty seekers.[1] This tendency has been linked to the areas that either contain dopaminergic neurons or receive dopaminergic innervation, that is, the ventral striatum, substantia nigra, ventral tegmental area of the midbrain, and hippocampus. It was debated, however, whether increased novelty seeking occurs only in PD patients with ICD. In our patients, we did not find a correlation between ICD and creativity measures, suggesting that creativity is not a possible expression of obsessive creative drive or productivity. A positive correlation was found between LEDD and creativity measures in the current study. Higher LEDD was associated with higher scores in the TACT-Visual task analyzed for quality of responses. Several case studies also suggested that artistic talent is dose or deep brain stimulation dependent.[5,8,11,38] Enhanced creativity under dopaminergic treatment in PD may suggest that DA receptor hypersensitivity is necessary for this response. In line with the above explanations for the role of dopamine in creative thinking, we suggest that PD patients treated with dopaminergic agents may benefit from reduction of LI and possibly from enhanced novelty-seeking tendencies, leading to better performance on specific creativity tasks that require divergent thinking and novel conceptual combinations.

The present study has some limitations, including a small sample of patients and relatively high variability in the range of LEDD and treatment duration. This variation might have affected the pattern of results (eg, limited dose effects). In addition, a wider array of cognitive, linguistic, and creativity tasks could have given us more specific and detailed information on the creativity profile of these patients. Creativity tests are correlated with creative thinking, but high scores may not be sufficient for genuine creative production.

Focusing on nondemented patients may have generated sample bias. In addition, because we used verbal creativity tests, one inclusion criteria was graduation from high school in Israel, generating possible bias with an educated sample, nonrepresentative of the general population of PD. Another sample bias may derive from our testing patients on medication. Furthermore, this study is cross-sectional, focusing on a single point in time, without studying the relationship between dopaminergic treatment duration and creative ability. A longitudinal

study on PD patients, before and after the initiation of dopaminergic medication, could detect changes in creativity directly related to dosage and duration of dopaminergic treatment.

It is possible that a subset of PD patients are especially prone to creativity, in parallel to a subtype of frontotemporal dementia patients, with frontal cortex sparing and focal degeneration in the left anterior temporal lobe, who show facilitation of artistic skills.[39] Future studies should address these limitations to establish the relation between PD, dopamine, and the enhancement of basic creative thinking. Correlation with functional imaging may supply more valuable information regarding neurophysiological mechanisms underlying the creative thinking process.

Authorship

A.F.-S.: conception, design, data collection, data interpretation, writing, editing. Y.N.K.: data collection, data analysis, data interpretation, writing, editing. O.S.C.: design, editing. S.H.-B.: design, editing. R.I.: conception, design, data analysis, data interpretation, writing, editing.

Potential Conflicts of Interest

Nothing to report.

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