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Hoehn and Yahr staging of Parkinson's disease in relation to neuropsychological measures

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1. ABSTRACT

Parkinson's disease (PD) is primarily considered to be a progressive degenerative motor disease associated with the degeneration of striatal dopamine neurons. However, increasing evidence has suggested progressive cognitive and psychiatric changes as well. Forty-six patients with PD, ranging in severity from Hoehn and Yahr (H-Y) score of 1:4, were recruited from a clinic specializing in PD. Various cognitive and neuropsychological measures were used to discover if there were indeed differences due to the progression of PD. As H-Y stage significantly increased, so did age and levodopa equivalency dose of medications, both independent of one another. Years of education had a significant negative relationship with H-Y score. Measures of general cognition divulged a significant decrease as H-Y score increased. Finally, as H-Y score increased, magical ideation decreased, and religious group social support increased. Mechanistically, the significant cognitive decline occurring with H-Y staging may be linked to a reduced dopaminergic function. Significant cognitive and neuropsychological changes are associated with the progression of PD and its possible relationship to Reward Deficiency Syndrome (RDS).

2. INTRODUCTION

The Hoehn & Yahr (H&Y) system for grading severity of Parkinson's disease (PD) symptoms uses a scale of 1 to 5 to evaluate the extent of patients' clinical disability. Patients whose symptoms are in stages 1:3 are considered minimally disabled, and they are still able to lead independent lives. However, those whose symptoms are in stages 4 and 5 are considered severely disabled (1). Motor symptom severity has been associated with various neurocognitive issues, such as dementia, depression, and hallucinations. Higher H&Y scores have been linked with a more rapid cognitive decline in PD patients (2). In general, patients with higher H&Y scores report poorer quality of life (3).

The severity of idiopathic PD (IPD) has been associated with patients' degree of depression, as studies have revealed a direct correlation with Hoehn-Yahr scores/stages, as well as elevated scores on depression rating scales including the Geriatric Depression Scale (GDS) and the Montgomery-Asberg Depression Rating Scale (MADRS) (4, 5). Piozevan *et al*. (5) also found significant deficits in PD (vs. controls) in cognitive, verbal, executive, attentional and visuospatial functioning, but showed no significant relationship with the H&Y score within

PD. This contrasts with Ridder *et al.*'s (6) finding that PD patients with significantly higher (t = 2.3, p = 0.026) H&Y scores (2.7 +/-0.6. vs. 2.4 +/-0.5) have impaired contrast sensitivity, which is associated with cognitive deficits (especially executive function deficits). The increase in depressive symptoms may be linked to the fact that as H&Y scores increase, striatal dopamine decreases, as shown by decreased dopamine binding in the caudate and putamen of patients with H&Y scores of at least 1.43 compared to controls (7). Happe *et al*. (8) reported that patients with H&Y stage 2 have lower levels of dopamine binding in the striatum than patients in H&Y stage 1, which is associated with increased subjective daytime sleepiness.

Even though the focus of most PD research has been concerned with it as a neurodegenerative motor disease due to a gradual loss of dopaminergic neurons in the striatum (9), increasingly research has expanded this to include a variety of cognitive (10, 11) and psychiatric (12) impairments over the progression of the disease. Janvin *et al.* (13) reported that in PD patients, a higher H&Y score was associated with dementia. Those who were diagnosed with dementia within four years after an initial clinical and psychiatric examination had a mean H&Y score of 2.9, whereas those who did not become demented had an average score of 2.7. Verbaan *et al*. (14) used the Scales for Outcomes in Parkinson's disease-Cognition (SCOPA-COG) to evaluate cognitive impairment in PD patients (memory, attention and executive and visuospatial functioning) without being sensitive to motor symptoms. They found that a higher H&Y stage and higher Short Parkinson's Evaluation Scale (SPES)-SCOPA motor score was associated with poorer cognitive performance. They also found that severely affected patients performed significantly worse than mildly and moderately affected patients. Furthermore, Wakamori *et al*. (15) reported that PD patients in H&Y stages 3:4 had significantly impaired language function, working memory and visuospatial function compared to those in stage 2. Additionally, there was an increase in hallucinations with the increase in H&Y score.

2.1. Rationale

While it is well known that cognitive decline is linked to dopamine deficiency for various reasons as observed in the literature and even in late stage PD, there is a paucity of research on how cognitive and dopamine deficits affect neuropsychological behaviors in late stage PD patients. A review of the literature revealed that if you use the combined search terms "Parkinson's, cognitive decline and dopamine deficiency," there are forty-two listings including animal (16, 17), human clinical (18) and imaging (19) studies as well as studies simulating the effects of dopamine imbalance on cognition: from normal affect to Parkinson's disease (18, 20). Parkinson's disease duration determines the effect of dopaminergic therapy on ventral striatum function (20). Moreover, it is known that in late stage PD patients show unusual addictive –like behaviors (gambling, over –eating and drug and alcohol abuse all defined and categorized as Reward Deficiency Syndrome (RDS) behaviors (21). Some studies have indicated that hypodopaminergic function indicates a blunted reward system. Blunted reactions also show impairments of motivation, including lower cognitive ability, more rapid cognitive decline, and poorer performance (22). Furthermore, persons exhibiting blunted stress reactivity display well-established temperament characteristics, including neuroticism and impulsivity, characteristic of various behavioral disorders (23). Reward Deficiency Syndrome has been defined as an umbrella term to describe common genetic antecedents of multiple impulsive, compulsive and addictive behaviors driven by a hypodopaminergic trait/state (24). According to Linazaroso *et al*. (25) patients with PD suffer from RDS since they are particularly prone to develop addictive behaviors. Following the first association of the DRD2 Taq A1 allele and severe alcoholism (26), there are a plethora of studies (4, 378 in PubMed 7-31-17) showing this allele is increased in a remarkable list of RDS behaviors including cognitive impairment (27). It is noteworthy that Comings *et al.* (28) showed that the same gene allele (DRD2 Taq A1) compared to screened controls, was increased in PD. Moreover, Wolters *et al.* (29) also suggested that PD is associated with what they have termed the impulsive-compulsive spectrum (ICS). They indicate that ICS consists of dopamine deficiency syndrome (with immediate reward seeking behavior), dopamine dependency syndrome (with addictive behavior), dopamine dysregulation syndrome (with both addictive behavior and stereotyped behavior) and impulse control disorders (i.e., hypersexuality, binge-eating, pathological gambling and compulsive shopping). Apparently, as well as cognitive decline, these behaviors found in PD patients by Wolters *et al*. have been identified by Blum *et al*. (21, 30, 31) as RDS behaviors.

In this manuscript, we ask the question "Does late stage cognitive decline occurring in PD measured systematically by a battery of standard neuropsychological tests offer insights into links between cognitive decline and RDS?" Work by Blum *et al*. (32) suggested that cognitive decline (putatively caused by a hypodopaminergic trait/state) can be treated with agents that provide pro dopamine regulation or homeostasis. In fact, Blum *et al.* (33), suggested that the upregulation of a number of early genes, all in unique patterns within cortico-striatal, thalamic, and hypothalamic networks suggests that food/drug cues are capable of significantly altering neuronal processing in brain areas that mediate the integration of cognition, emotion, arousal, and thus the regulation of energy balance. The dopaminergic,

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enkephalinergic, and fos gene expressions are critical regulatory genetic pathways for food/drug craving behaviors. It is notable that the outcomes related to blunted stress reactivity are like those that define RDS (the behavioral, cognitive, and neural corollaries of blunted cardiovascular and cortisol reactions to acute psychological stress) (23). Thus, while previous literature shows a clear relationship between cognitive decline and RDS-like behaviors, our potential findings in this study may be the first ever data to support links between PD patients, later stage cognitive decline and hypothetically subsequent RDS behaviors.

3. METHODS

3.1. Objectives

Based on the review in the introduction, it appears that there are indeed cognitive, neuropsychological, and clinical differences throughout the progression of PD. As we had access to this population, we decided to examine any and all differences that we could find throughout the progression of PD based on the H&Y score as the dependent variable. We decided to employ a range of cognitive and neuropsychological measures. Based on previous studies suggesting a general cognitive decline in PD (14, 15) we hypothesized that with an increase in H&Y score, there would be significant decrease in mental status and cognition on the Mini-Mental State Examination (34), the Montreal Cognitive Assessment (35), and possibly the Stroop test (36). Based on previous studies of changes in religiosity (37) and magical ideation (38) in PD, we hypothesized that as H&Y score increases, there might be changes in religious matters and magical thinking associated with the progression of PD. Thus, we used the Religious Commitment Inventory (39) and the Magical Ideation Scale (40) to test this. Aside from these preconceived hypotheses, we employed a data-driven approach, free of the biases of strict hypothesis-driven approaches. Based on previous research, we were open to the possibility that there may be many cognitive, neuropsychological, and clinical differences throughout the progression of PD as measured by H&Y stage. We wanted the data to reveal correlations without restrictive hypotheses, which might obscure significance within the data. Furthermore, since we employed measures that have been used in other studies, and as replication is the cornerstone of scientific research, we wanted to potentially add to the current body of published literature, as well as finding results that are consistent with it.

3.2. Participants: behavioral experiment

In this study, all participants had previous diagnoses of idiopathic Parkinson's disease, by a board-certified movement disorders specialist, who was also the director of the Movement Disorders clinic at the Boston VA. This physician recruited patients for the study from the Veteran's Administration Health System in Boston, MA, USA**.** Furthermore, based on our recruitment out of the VA hospital, the majority were veterans.

This study was approved by the Institutional Review Board (IRB) of VA Boston Healthcare System in Jamaica Plain, Boston, MA, USA. All participants gave informed consent as specified and approved by said IRB. A consecutive sampling method was employed based on budget and time allotted for the study. The majority of our patients were recruited by their physician within the PD clinic, based on who came in during the study. Patients with PD were asked if they were interested in participating in a research study about PD. Patients who decided followed up (self-selecting) with the study were scheduled for testing. Subsequently, those who participated were paid $10 an hour for in person neuropsychological testing, and additionally $30 for mailing back the take-home packet of inventories. Exclusionary criteria included dementia or severe cognitive impairment based on measures of mental status (please refer to measures in *Procedures: neuropsychological testing*).

3.3. Procedures: neuropsychological testing

All of the patients with PD completed a battery of neuropsychological tests to assess possible comorbid dementia and cognitive impairment while on medication. These included the Mini-Mental State Examination (MMSE) (34), the Montreal Cognitive Assessment (MoCA) (35), the Wechsler Test of Adult Reading (WTAR) (41); the Matrix Reasoning test, which is a subtest within the Wechsler Adult Intelligence Scale (WAIS) (42), Digit Span Backwards (DSB); a subtest of the Wechsler Memory Scale–III; (43) and the Stroop test (36). Additionally, all patients were assessed for mood function using the Depression, Anxiety, and Stress Scale (DASS) (44); the Magical Ideation Scale (MIS) (40). Furthermore, we employed the Religious Commitment Inventory (RCI) (39); and personality traits were measured by use of the Big Five Mini-Marker (How Accurately Can You Describe Yourself?), which included The Big Five Mini-Marker scores for five subcomponents (O: openness, C: conscientiousness, E: extroversion, A: agreeableness, and N: neuroticism; meaning emotional stability) (45). Finally, as our participants consisted of those with PD, which is often comorbid with REM sleep behavior disorder (RBD), we administered the REM Behavior Disorder Questionnaire-Hong Kong (RBDQ) (46).

Determination of Levodopa equivalency dosages (LED), which were to be used in the statistical analyses, were completed by using a standardized formula. This calculation allowed us to compare the dosing levels across the variety of dopamine

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replacement therapies that our participants with PD were taking (47). All of the testing reported within this paper was completed on-medication.

3.4. Behavioral data processing and statistical analysis

A simple analysis of means was completed within Excel. Additionally, data was exported from Excel for hypothesis testing in IBM SPSS.

We employed multivariate mixed-effects linear regression analyses to test for associations between the H&Y stage of PD (dependent variable, DV) and neuropsychological and clinical measures (independent variables, IVs). All of the statistical models employed were adjusted for handedness, sex, education, and age. All of our significant findings, we further teased apart using additional regression analyses in an attempt to account for the underlying, true nature of interactions between all the significant variables. This was done by switching independent and dependent variables and collapsing across the initial DV from the original model (i.e., H&Y stage). We allowed for outcome-specific fixed effects, subject-specific effects and measure-specific random-effects. These multivariate analyses tend to provide more realistic models of the outcomes than using multiple independent regression models for each tested relationship. Since all of the information within each subject is completely utilized within such a model, we can provide more interpretable and consistent results than simpler statistical models. Moreover, the problem of multiple comparisons is removed when viewed from these models (48). These multivariate models are known to provide higher power for detecting small but clinically important differences, as compared to independent regression models for each outcome (49). All of our analyses were performed using the specific software, IBM SPSS Statistics (version 22, IBM, Armonk, NY, USA). It was evident to us that choosing these particular analyses would help divulge the exact nature and interactions between these variables.

4. RESULTS

In this study, the participants included patients (n = 46; 43 males, three females) diagnosed with idiopathic Parkinson's disease. The mean age was 69.06 years within a range of 42:89 years. Side-of-onset included 14 left-onset PD (one female) and 30 right-onset PD (two females) and two males of an unknown side-of-onset. Race/ethnicity demographics consisted of 42 Caucasians, one Asian-American, two African-Americans, and one Native-American. The majority of the participants were right handed (n = 31), some were left handed (n = 6), and some ambidextrous (n = 9). All but two (44 of the 46; 95.65%) were high school graduates. Thirty-three (71.73%) had some college experience or an associate's degree. Twenty-three (50%) had bachelor's degree. Ten (21.73%) had postgraduate degrees or at least one year of post-baccalaureate education. Years of education ranged from 4 to 22 years, with the mean at 15.03 years. The overall Hoehn and Yahr scale median score was 2 (Q1: 2, Q2: 2, Q3: 3, Q4: 4; IQR: 1). This was within a range of 1:4, with the majority being H&Y stage 2 (n = 23), and all others in stage 1 (n = 2), stage 3 (n = 17), and stage 4 (n = 4). Thus, nearly 87% (86.95%, n = 40) were in stages 2:3. Duration of PD illness had a mean across the group of 6.619 years within a range of 1:20 years (Table 1).

All results were obtained using multivariate mixed-effects linear regression analysis (Goodness-of-Fit: R^2 = 0.935) without the need to correct for multiple comparisons. Positive t scores indicated a significantly positive relationship of between the H&Y (DV) and IVs; whereas, negative t scores indicated a significantly negative relationship (Table 2). There were no significant effects of the independent variables of gender (sex), race, handedness or duration of illness on the dependent variable of H&Y stage of Parkinson's disease. However, there were significant positive relationships between the independent variables of age (t_{35} = 5.281., p = 0.000, or p < 0.001), and Levodopa equivalency dosage (LED: t_{35} = 4.266, p = 0.002) with the DV of H&Y stage. Additionally, there was a significant negative relationship between the IV of years of education (t_{35} = -3.868, p = 0.003) and DV of H&Y Stage.

As for the cognitive measures, there were significant negative relationships between the independent variables of the MoCA score (t_{35} =-2.767, p = 0.020), the MMSE score (t_{35} = -3.330, p = 0.008), Color Word score on the Stroop (t_{35} = -3.221, p = 0.009), the magical ideation score (t_{35} = -2.770, p = 0.020) and the DV of H&Y stage. Finally, we found a significant positive relationship between the IV of interpersonal religious commitment (t_{35} = 3.920, p = 0.003) and the DV of H&Y stage.

Based on the significant differences in age, education and LED as independent variables in relation to the dependent variable of H&Y stage, we needed to clarify if the differences in the cognitive measures seen with H&Y could be explained by these other factors. This necessitated the following additional analyses in an attempt to account for these initial findings.

In a regression model using age as the dependent variable, collapsing across H&Y scores, we used all other independent variables that were initially believed to be significant from the original regression model. In this analysis, only LED as an IV showed a significant negative relationship (t_{15} = -2.527, p = 0.017). We switched the variables of analysis in

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Table 1. Demographics of PD participants

Participants	N = 46		43 males			3 females
Handedness	right: 31		left: 6			Ambidextrous: 9
Side of onset	LOPD: 14 (1 female)		ROPD: 30 (2 females)			2 unknown
Age	range: 42:89 years					mean: 69.06 years
Education	range: 4:22 years					mean: 15.03 years
Duration of PD	range: 1:20 years					mean: 6.619 years
H&Y	Q1: 2	Q2: 2	Q3: 3	Q4: 4	IQR: 1	median: 2

Abbreviations: LOPD: left-onset Parkinson's disease, ROPD: right-onset Parkinson's disease, H&Y: Hoehn and Yahr stage of Parkinson's disease, Q1:Q4 = quartile values, IQR = Interquartile range (Q3 – Q1)

Table 2. Significant differences with H&Y (dependent variable)

Test (independent variables)	p-value	t-score	df
Age	0.001*	5.281	35
Education	0.003	-3.868	35
LED	0.002	4.266	35
MoCA	0.020	-2.767	35
MMSE	0.008	-3.33	35
Stroop CW	0.009	-3.221	35
MIS	0.020	-2.77	35
RCIInter	0.003	3.92	35

All results were obtained using multivariate mixed-effects linear regression analysis (R^2 = 0.935) without the need to correct for multiple comparisons. Positive *t*-scores indicate significantly positive relationship between the dependent variable and the independent variables; whereas negative *t*-scores indicate significantly negative relationship. *The p-value was < 0.001.

Abbreviations: LED: levodopa equivalency dose, MoCA: Montreal Cognitive Assessment, MMSE: Mini Mental Status Exam, Stroop CW: Stroop Color Word score, MIS: Magical Ideation Scale, RCIInter: Religious Commitment Inventory interpersonal commitment score

the opposite direction to see if LED was driving any of the results from the initial model. We conducted a regression analysis using LED as the DV, collapsing across H&Y scores. This divulged only one significant finding, that of a negative relationship (t_{15} = -2.527, p = 0.017) with age.

In the regression model, using years of education as the DV and collapsing across H&Y scores, there was only one significant finding: a negative relationship (t_{15} = -4.168, p < 0.001) with performance (IV) on the Color Word score of the Stroop test.

5. DISCUSSION

From our main regression model, age (IV) increased in a positive relationship with H&Y score (DV). Thus, in our study, individuals of greater age tended to have significantly greater PD symptomatology. Similarly, as LED (IV) increased, so did H&Y score (DV). Thus, as PD symptomatology increased, medication dosage increased. Additional analyses were employed to tease apart if age was driving this result between LED and H&Y. Using age (DV), and collapsing across H&Y scores, a significant negative relationship was revealed with LED dosage (IV). Additionally, following transitive relations, using LED (DV) and collapsing across H&Y score, revealed a significant negative relationship with age (IV). In other words, with an increase in age, independent of H&Y score and thus PD symptomatology, medication dosages decreased, as well as the converse. This appears to show that age was not indeed driving the LED dosage with PD symptomatology, as this was independent of H&Y. In fact, when using H&Y (DV) paired with LED (IV), LED flipped and showed a significant positive relationship. Therefore, results of increased medication dosage (as represented by LED) with increasing PD symptomatology (as shown with H&Y score) cannot be explained by age. In summation, with increased age, there was increased PD symptomatology (H&Y score). With an increase in PD symptomatology (H&Y), there was a need for increased medication (LED). However, this didn't translate to an apparent transitive property between LED and age, as additional analyses revealed the relationship between LED and age was negative. Therefore, age cannot account for the positive relationship divulged between increased PD symptomatology (H&Y score) and the need for increased medication (LED). Furthermore,

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there were no additional interactions with any other factor with age.

We found a significant negative effect of years of education (IV) with H&Y score (DV). Kierzynka, Kaźmierski, and Kozubski (50) provided evidence that greater levels of education appeared to act in a protective manner against the progressive cognitive impairment in PD, perhaps due to more significant mental resources. However, this does not explain the possible negative relationship with H&Y score, which is based primarily on progressive motor changes and ambulatory disability. However, Sunwoo *et al*. (51) showed that a greater educational level decreased the motor deficits in PD, despite more significant dopaminergic degeneration. Thus, it may be that higher levels of education can compensate, somehow, for both the progressive cognitive decline and motor impairment in PD.

Measures of cognition/mental status (MoCA, MMSE, Stroop Color Word as IVs) all revealed a significant negative relationship with H&Y (DV). In essence, as PD significantly worsened, so did measures of general cognitive abilities, including processing speed, attention and working memory. This is consistent with studies showing a progressive cognitive decline in PD with an increase in H&Y score (14, 15). However, it is important to acknowledge that the cognitive slowing seen in PD for the Stroop Color Word task may not necessarily be due to cognitive decline, but instead due to difficulty with motor responses (52), although comorbid depression, as the cause, could not be ruled out. Importantly, in our study, our measure of depression (DASS) failed to divulge a significant relationship with any other measure. Furthermore, in our study, Stroop Color Word scores (as an IV) in a model with years of education (as the DV) divulged a significant negative relationship. Those with greater years of education, independent of PD symptomatology as shown by H&Y score, were more likely to have poorer performance on the Stroop Color Word task. For these results, we have no explanation.

With regards to magical ideation, this significantly decreased with H&Y score. Based on a previous study (38), they found that ROPD had significantly greater magical ideation than LOPD (independent of LED). However, as the focus of this study was on H&Y stages, it is apparent that when taking all PD patients (our cohort combined both LOPD and ROPD into one group), there was a decrease in MIS with the progression of PD. As previously mentioned, with greater H&Y score, we saw a significant increase in LED. Therefore, when these results are combined, despite the increase in LED with increasing H&Y, the MIS decreased with H&Y. So, increased LED most certainly cannot account for the decreasing MIS. This would be contrary to the logic that LED (or specifically levodopa) tends to increase MIS (53). More specifically to the point, in a post-hoc regression, collapsing across H&Y score, there was no significant relationship, neither positive nor negative, between LED (as the DV) and MIS (as an IV).

Finally, with an increase in H&Y score, there was a significant positive relationship with interpersonal commitment with those of one's religious affiliation; there is an increase in time spent with others of the same religious affiliation in related social groups as PD worsens. As with any progressive and chronic illness, spending time with a social group may be a major factor in handling the situation emotionally (54), and this may even give purpose in the face of tragedy if it is based on a religious affiliation (55). In fact, Cheng *et al*. (56) divulged that social support in PD was a buffer against comorbid depression.

There were notable limitations in this study. First, the sample size was limited due to the duration of data collection which was dictated by the funding. Additionally, as this study was done out of a VA clinic, the gender tended to be skewed toward males, due to the demographics of the patient population. Finally, the number of individuals in H&Y stages 1 and 4 were low. Patients with H&Y stage 4 or greater were less likely to participate in our study because it required extensive testing. Severe cognitive issues and decreased ability to sit still would have impacted the completion of tasks in such individuals. Future research should be conducted using a lager sample size and a more gender-balanced cohort. Additionally, future research including those with higher H&Y stages (such as 4 and greater) might elucidate the cognitive changes as PD progresses to its severest impairment. However, this might be difficult to achieve. Despite these limitations, the results we have obtained clearly show a cognitive deterioration with the progression of PD.

6. CONCLUSION

PD is often viewed primarily as a degenerative motor disorder (9). However, based on our scientific literature review and our results, there are cognitive and psychiatric changes associated with the progression of PD. Our hypothesis of a significant decline in mental status and general cognition with increasing H&Y score was confirmed. Additionally, we predicted significant changes in religious interest and magical ideation when paired with an increased H&Y score; and this was seen in our findings. These results also suggest that understanding these neuropsychological impairments due to presumed dopaminergic impairment may provide further support for PD to be included within RDS.

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We believe that our results on cognitive decline and associated neuropsychological measures provide some evidence to suggest that PD should be classified as a subset of RDS. While other studies clearly show the presence of RDS-like addictive behaviors, like gambling, sex and drugs, and alcohol in PD, this is the first treatise to emphasize the importance of the RDS nosology which seemly has been observed by others. The current rationale at this stage of research must be considered a hypothesis and should encourage other neuroscientists to perform the needed experiments to support or refute our present concept.

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8. REFERENCES

1. M. M. Hoehn and M. D. Yahr: Parkinsonism: onset, progression, and mortality. 1967. *Neurology*, 57(10 Suppl 3), S11-26 (2001)

2. D. Aarsland, K. Andersen, J. P. Larsen, R. Perry, T. Wentzel-Larsen, A. Lolk and P. Kragh-Sorensen: The rate of cognitive decline in Parkinson disease. *Arch Neurol*, 61(12), 1906-11 (2004)
DOI: 10.1001/archneur.61.12.1906

3. S. Rahman, H. J. Griffin, N. P. Quinn and M. Jahanshahi: Quality of life in Parkinson's disease: the relative importance of the symptoms. *Mov Disord*, 23(10), 1428-34 (2008)
DOI: 10.1002/mds.21667

4. N. Pankratz, K. S. Marder, C. A. Halter, A. Rudolph, C. W. Shults, W. C. Nichols and T. Foroud: Clinical correlates of depressive symptoms in familial Parkinson's disease. *Mov Disord*, 23(15), 2216-23 (2008)
DOI: 10.1002/mds.22285

5. M. R. Piovezan, H. A. Teive, E. J. Piovesan, M. J. Mader and L. C. Werneck: Cognitive function assessment in idiopathic Parkinson's disease. *Arq Neuropsiquiatr*, 65(4a), 942-6 (2007)

6. A. Ridder, M. L. Muller, V. Kotagal, K. A. Frey, R. L. Albin and N. I. Bohnen: Impaired contrast sensitivity is associated with more severe cognitive impairment in Parkinson disease. *Parkinsonism Relat Disord*, 34, 15-19 (2017)
DOI: 10.1016/j.parkreldis.2016.10.006

7. J. Wang, C. T. Zuo, Y. P. Jiang, Y. H. Guan, Z. P. Chen, J. D. Xiang, L. Q. Yang, Z. T. Ding, J. J. Wu and H. L. Su: 18F-FP-CIT PET imaging and SPM analysis of dopamine transporters in Parkinson's disease in various Hoehn & Yahr stages. *J Neurol*, 254(2), 185-90 (2007)
DOI: 10.1007/s00415-006-0322-9

8. S. Happe, P. C. Baier, K. Helmschmied, J. Meller, K. Tatsch and W. Paulus: Association of daytime sleepiness with nigrostriatal dopaminergic degeneration in early Parkinson's disease. *J Neurol*, 254(8), 1037-43 (2007)
DOI: 10.1007/s00415-006-0483-6

9. P. T. Bell, M. Gilat, C. O'Callaghan, D. A. Copland, M. J. Frank, S. J. Lewis and J. M. Shine: Dopaminergic basis for impairments in functional connectivity across subdivisions of the striatum in Parkinson's disease. *Hum Brain Mapp*, 36(4), 1278-91 (2015)
DOI: 10.1002/hbm.22701

10. S. Maril, S. Hassin-Baer, O. S. Cohen and R. Tomer: Effects of asymmetric dopamine depletion on sensitivity to rewarding and aversive stimuli in Parkinson's disease. *Neuropsychologia*, 51(5), 818-24 (2013)
DOI: 10.1016/j.neuropsychologia.2013.02.003

11. M. I. Ventura, K. Baynes, K. A. Sigvardt, A. M. Unruh, S. S. Acklin, H. E. Kirsch and E. A. Disbrow: Hemispheric asymmetries and prosodic emotion recognition deficits in Parkinson's disease. *Neuropsychologia*, 50(8), 1936-45 (2012)
DOI: 10.1016/j.neuropsychologia.2012.04.018

12. E. Cubo, P. M. Martin, J. A. Martin-Gonzalez, C. Rodriguez-Blazquez and J. Kulisevsky: Motor laterality asymmetry and nonmotor symptoms in Parkinson's disease. *Mov Disord*, 25(1), 70-5 (2010)
DOI: 10.1002/mds.22896

13. C. C. Janvin, J. P. Larsen, D. Aarsland and K. Hugdahl: Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. *Mov Disord*, 21(9), 1343-9 (2006)
DOI: 10.1002/mds.20974

© 1996-2018

14. D. Verbaan, J. Marinus, M. Visser, S. M. van Rooden, A. M. Stiggelbout, H. A. Middelkoop and J. J. van Hilten: Cognitive impairment in Parkinson's disease. *J Neurol Neurosurg Psychiatry*, 78(11), 1182-7 (2007) DOI: 10.1136/jnnp.2006.112367

15. T. Wakamori, T. Agari, T. Yasuhara, M. Kameda, A. Kondo, A. Shinko, S. Sasada, T. Sasaki, T. Furuta and I. Date: Cognitive functions in Parkinson's disease: relation to disease severity and hallucination. *Parkinsonism Relat Disord*, 20(4), 415-20 (2014) DOI: 10.1016/j.parkreldis.2014.01.002

16. P. Lei, S. Ayton, A. T. Appukuttan, I. Volitakis, P. A. Adlard, D. I. Finkelstein and A. I. Bush: Clioquinol rescues Parkinsonism and dementia phenotypes of the tau knockout mouse. *Neurobiol Dis*, 81, 168-75 (2015) DOI: 10.1016/j.nbd.2015.03.015

17. R. G. Morgan, J. T. Gibbs, E. J. Melief, N. O. Postupna, E. E. Sherfield, A. Wilson, C. D. Keene, T. J. Montine, R. D. Palmiter and M. Darvas: Relative contributions of severe dopaminergic neuron ablation and dopamine depletion to cognitive impairment. *Exp Neurol*, 271, 205-14 (2015) DOI: 10.1016/j.expneurol.2015.06.013

18. S. Helie, E. J. Paul and F. G. Ashby: Simulating the effects of dopamine imbalance on cognition: from positive affect to Parkinson's disease. *Neural Netw*, 32, 74-85 (2012) DOI: 10.1016/j.neunet.2012.02.033

19. S. Hirano, H. Shinotoh and D. Eidelberg: Functional brain imaging of cognitive dysfunction in Parkinson's disease. *J Neurol Neurosurg Psychiatry*, 83(10), 963-9 (2012) DOI: 10.1136/jnnp-2011-301818

20. A. A. MacDonald, O. Monchi, K. N. Seergobin, H. Ganjavi, R. Tamjeedi and P. A. MacDonald: Parkinson's disease duration determines effect of dopaminergic therapy on ventral striatum function. *Mov Disord*, 28(2), 153-60 (2013) DOI: 10.1002/mds.25152

21. K. Blum, R. C. Wood, E. R. Braverman, T. J. Chen and P. J. Sheridan: The D2 dopamine receptor gene as a predictor of compulsive disease: Bayes' theorem. *Funct Neurol*, 10(1), 37-44 (1995)

22. M. Febo, K. Blum, R. D. Badgaiyan, D. Baron, P. K. Thanos, L. M. Colon-Perez, Z. Demortrovics and M. S. Gold: Dopamine homeostasis: brain functional connectivity in reward deficiency syndrome. *Front Biosci (Landmark Ed)*, 22, 669-691 (2017) DOI: 10.2741/4509

23. D. Carroll, A. T. Ginty, A. C. Whittaker, W. R. Lovallo and S. R. de Rooij: The behavioural, cognitive, and neural corollaries of blunted cardiovascular and cortisol reactions to acute psychological stress. *Neurosci Biobehav Rev*, 77, 74-86 (2017) DOI: 10.1016/j.neubiorev.2017.02.025

24. K. Blum: Reward Deficiency Syndrome. In: *The SAGE Encyclopedia of Abnormal and Clinical Psychology* Ed A. Wenzel. Sage Publications, Inc, University of Pennsylvania School of Medicine, USA (April 2017)

25. G. Linazaroso, N. van Blercom and A. Lasa: (Hypothesis: Parkinson's disease, reward deficiency syndrome and addictive effects of levodopa). *Neurologia*, 19(3), 117-27 (2004)

26. K. Blum, E. P. Noble, P. J. Sheridan, O. Finley, A. Montgomery, T. Ritchie, T. Ozkaragoz, R. J. Fitch, F. Sadlack, D. Sheffield and *et al.*: Association of the A1 allele of the D2 dopamine receptor gene with severe alcoholism. *Alcohol*, 8(5), 409-16 (1991) DOI: 10.1016/0741-8329(91)90693-Q

27. K. Blum, A. L. Chen, M. Oscar-Berman, T. J. Chen, J. Lubar, N. White, J. Lubar, A. Bowirrat, E. Braverman, J. Schoolfield, R. L. Waite, B. W. Downs, M. Madigan, D. E. Comings, C. Davis, M. M. Kerner, J. Knopf, T. Palomo, J. J. Giordano, S. A. Morse, F. Fornari, D. Barh, J. Femino and J. A. Bailey: Generational association studies of dopaminergic genes in reward deficiency syndrome (RDS) subjects: selecting appropriate phenotypes for reward dependence behaviors. *Int J Environ Res Public Health*, 8(12), 4425-59 (2011) DOI: 10.3390/ijerph8124425

28. D. E. Comings, B. G. Comings, D. Muhleman, G. Dietz, B. Shahbahrami, D. Tast, E. Knell, P. Kocsis, R. Baumgarten, B. W. Kovacs and *et al.*: The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. *Jama*, 266(13), 1793-800 (1991) DOI: 10.1001/jama.1991.03470130073032

© 1996-2018

29. E. Wolters, Y. D. van der Werf and O. A. van den Heuvel: Parkinson's disease-related disorders in the impulsive-compulsive spectrum. *J Neurol*, 255 Suppl 5, 48-56 (2008)
DOI: 10.1007/s00415-008-5010-5

30. K. Blum, B. C. Haberstic, A. Smolen, D. Han, Marlene Oscar-Berman: Keynote: Genetic Addiction Risk Score (GARS) Predicts Addiction Severity Index -MV Alcohol and Drug-Risk in a multi-centered study. 5th APAAR-TSAS 2017 Asia -Pacific Society of Alcohol and Addiction Research May 31st–June 3rd, Taipei, Taiwan (2017)

31. K. Blum, P. J. Sheridan, R. C. Wood, E. R. Braverman, T. J. Chen, J. G. Cull and D. E. Comings: The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. *J R Soc Med*, 89(7), 396-400 (1996)

32. K. Blum, S. J. Schoenthaler, M. Oscar-Berman, J. Giordano, M. A. Madigan, E. R. Braverman and D. Han: Drug abuse relapse rates linked to level of education: can we repair hypodopaminergic-induced cognitive decline with nutrient therapy? *Phys Sportsmed*, 42(2), 130-45 (2014)
DOI: 10.3810/psm.2014.05.2065

33. K. Blum, Y. Liu, R. Shriner and M. S. Gold: Reward circuitry dopaminergic activation regulates food and drug craving behavior. *Curr Pharm Des*, 17(12), 1158-67 (2011)
DOI: 10.2174/138161211795656819

34. S. Nazem, A. D. Siderowf, J. E. Duda, T. T. Have, A. Colcher, S. S. Horn, P. J. Moberg, J. R. Wilkinson, H. I. Hurtig, M. B. Stern and D. Weintraub: Montreal cognitive assessment performance in patients with Parkinson's disease with "normal" global cognition according to mini-mental state examination score. *J Am Geriatr Soc*, 57(2), 304-8 (2009)
DOI: 10.1111/j.1532-5415.2008.02096.x

35. Z. S. Nasreddine, N. A. Phillips, V. Bedirian, S. Charbonneau, V. Whitehead, I. Collin, J. L. Cummings and H. Chertkow: The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*, 53(4), 695-9 (2005)
DOI: 10.1111/j.1532-5415.2005.53221.x

36. J. Stroop: Studies of interference in serial verbal reactions *Journal of Experimental Psychology*, 18(6), 643-552 (1935)

37. E. J. Modestino, P. O'Toole and A. Reinhofer: Experiential and Doctrinal Religious Knowledge Categorization in Parkinson's Disease: Behavioral and Brain Correlates. *Front Hum Neurosci*, 10, 113 (2016)

38. E. J. Modestino, C. Amenechi, A. Reinhofer and P. O'Toole: Side-of-onset of Parkinson's disease in relation to neuropsychological measures. *Brain Behav*, 7(1), e00590 (2017)
DOI: 10.1002/brb3.590

39. E. Worthington, N. Wade, T. Hight, J. Ripley, M. McCullough, J. Berry and e. al.: The Religious Commitment Inventory–10: development, refinement, and validation of a brief scale for research and counseling. *J. Couns. Psychol*, 50 84–96 (2003)

40. M. Eckblad and L. J. Chapman: Magical ideation as an indicator of schizotypy. *J Consult Clin Psychol*, 51(2), 215-25 (1983)
DOI: 10.1037/0022-006X.51.2.215

41. H. Holdnack: Wechsler Test of Adult Reading (WTAR). The Psychological Corporation, San Antonio, TX (2001)

42. D. Wechsler: Wechsler Adult Intelligence Scale– IV (WAIS–IV). NCS Pearson, San Antonio, TX (2008)

43. A. M. Seelye, D. B. Howieson, K. V. Wild, M. M. Moore and J. A. Kaye: Wechsler Memory Scale–III Faces test performance in patients with mild cognitive impairment and mild Alzheimer's disease. *J Clin Exp Neuropsychol*, 31(6), 682-8 (2009)
DOI: 10.1080/13803390802484763

44. J. D. Henry and J. R. Crawford: The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. *Br J Clin Psychol*, 44(Pt 2), 227-39 (2005)

45. G. Saucier: Mini-markers: a brief version of Goldberg's unipolar big-five markers. *J Pers Assess*, 63(3), 506-16 (1994)
DOI: 10.1207/s15327752jpa6303_8

46. S. S. Shen, Y. Shen, K. P. Xiong, J. Chen, C. J. Mao, J. Y. Huang, J. Li, F. Han and C. F. Liu: Validation study of REM sleep behavior disorder questionnaire-Hong Kong (RBDQ-HK) in east China. *Sleep Med*, 15(8), 952-8 (2014)
DOI: 10.1016/j.sleep.2014.03.020

© 1996-2018

47. C. L. Tomlinson, R. Stowe, S. Patel, C. Rick, R. Gray and C. E. Clarke: Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord*, 25(15), 2649-53 (2010)
DOI: 10.1002/mds.23429

48. A. Gelman, J. Hill and M. Yajima: Why we (usually) don't have to worry about multiple comparisons. . *Journal of Research on Educational Effectiveness*, 5, 189–211 (2012)
DOI: 10.1080/19345747.2011.618213

49. H. Goldstein: Multilevel Statistical Models. John Wiley & Sons, Ltd, (2010)

50. A. Kierzynka, R. Kazmierski and W. Kozubski: Educational level and cognitive impairment in patients with Parkinson disease. *Neurol Neurochir Pol*, 45(1), 24-31 (2011)
DOI: 10.1016/S0028-3843(14)60056-6

51. M. K. Sunwoo, J. Y. Hong, J. J. Lee, P. H. Lee and Y. H. Sohn: Does education modify motor compensation in Parkinson's disease? *J Neurol Sci*, 362, 118-20 (2016)

52. Y. H. Hsieh, K. J. Chen, C. C. Wang and C. L. Lai: Cognitive and motor components of response speed in the stroop test in Parkinson's disease patients. *Kaohsiung J Med Sci*, 24(4), 197-203 (2008)
DOI: 10.1016/S1607-551X(08)70117-7

53. C. Mohr, H. S. Bracha and P. Brugger: Magical ideation modulates spatial behavior. *J Neuropsychiatry Clin Neurosci*, 15(2), 168-74 (2003)
DOI: 10.1176/jnp.15.2.168

54. S. Ahn, S. Kim and H. Zhang: Changes in Depressive Symptoms among Older Adults with Multiple Chronic Conditions: Role of Positive and Negative Social Support. *Int J Environ Res Public Health*, 14(1) (2016)

55. S. K. Christman and J. R. Mueller: Understanding Spiritual Care: The Faith-Hope-Love Model of Spiritual Wellness. *J Christ Nurs*, 34(1), E1-e7 (2017)

56. Y. Cheng, C. Liu, C. Mao, J. Qian, K. Liu and G. Ke: Social support plays a role in depression in Parkinson's disease: a cross-section study in a Chinese cohort. *Parkinsonism Relat Disord*, 14(1), 43-5 (2008)
DOI: 10.1016/j.parkreldis.2007.05.011

Abbreviations: PD: Parkinson's disease, DV: dependent variable, IV: independent variable, RDS: Reward Deficiency Syndrome, LOPD: left-onset Parkinson's disease, ROPD: right-onset Parkinson's disease, H&Y: Hoehn and Yahr stage of Parkinson's disease, Q1:Q4 = quartile values, IQR = Interquartile range (Q3 – Q1), LED: levodopa equivalency dose, MoCA: Montreal Cognitive Assessment, MMSE: Mini Mental Status Exam, Stroop CW: Stroop Color Word score, MIS: Magical Ideation Scale, RCIInter: Religious Commitment Inventory interpersonal commitment score

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