Original Article

Is Dementia in Parkinson' Disease Related to Chronic Stress, Anxiety, and Depression?

Anita Pal, Nishi Pegwal, Madhuri Behari[1], Ratna Sharma

Department of Physiology, Stress and Cognitive Electroimaging Laboratory, All India Institute of Medical Sciences, [1]Department of Neurology, Fortis Hospital, New Delhi, India

Abstract

Objectives: Stress, anxiety, and depression are known to be associated with the development of neurodegenerative disorders through interactions with the underlying pathophysiology. We hypothesized that the presence of these symptoms contributes to cognitive disturbances and dementia in Parkinson's disease (PD). The present study aimed to investigate the levels of stress, anxiety, and depression in PD patients relative to healthy individuals. **Materials and Methods:** Anxiety, stress, and depression levels were assessed using standardized questionnaires in PD without dementia (PDND, $n = 30$), PD with dementia (PDD, $n = 28$), and healthy controls (HC, $n = 26$). Arithmetic subtraction task was used as a stressor. Galvanic skin response, heart rate and salivary cortisol, and alpha-amylase were measured during baseline and after induced stress (arithmetic task). **Results:** Acute anxiety, acute stress, and depression levels were significantly higher in PDND compared to HC, whereas both acute and chronic anxiety, stress, and depression levels were significantly higher in PDD compared to PDND and HC. Cortisol and alpha-amylase levels were significantly higher in PDND compared to HC during both baseline and postarithmetic task. Posttask levels of cortisol were lower in PDD compared to PDND. **Conclusion:** This study concludes that higher levels of salivary cortisol and alpha-amylase at baseline and poststress task with normal levels of chronic stress and anxiety were associated with no dementia in PD. Presence of higher levels of acute, chronic anxiety, and stress along with depression with lower cortisol reactivity to stressor suggests onset of dementia in Parkinson's patients.

Keywords: Alpha-amylase, anxiety, cortisol, dementia, Parkinson's disease, stress

Introduction

Parkinson's disease (PD) was originally described by James Parkinson in 1817 in his "Essay on the Shaking Palsy."[1] In discussing his very first patient, he emphasized that the onset of symptoms followed an emotionally stressful event that has also been reported subsequently. An editorial in the journal Stress Medicine in 1999 on "Parkinson's and Alzheimer's disease: the surprising role of stress" and several reports subsequently suggest that stress can contribute to Parkinson disease in more than one way.[2] Chronic stress is detrimental for cognition and is responsible for generalized anxiety disorder and depression.[3,4] Depression precedes the onset of motor symptoms of PD and increases the risk for developing the disease by 2.2–3.1 folds.[5,6] In addition to depression, anxiety can develop before the onset of motor symptoms and brain changes occurring early in the disease may render the patients more likely to develop psychiatric symptoms.[7,8] Interestingly, neuropsychiatric disturbances act as a major contributor to developing dementia over time.[9,10]

Parkinson disease is one condition where chronic and progressive neurodegenerative changes lead to progressive cognitive decline with advancing disease with certain risk factors which may be dependent on the one's lifestyle. The aspects of lifestyle that need to be addressed include the stress and anxiety levels of the patients. Since the development of dementia in Parkinson's patients is a reality, it needs to be diagnosed and taken care of, and most importantly what causes dementia needs to be understood.

High levels of depression and stress along with motor symptoms in PD might be associated with overall pathophysiology of the disease. Stress in PD aggravates motor complications, reducing the quality of life, and increasing the burden of caregivers. Psychological stress and resultant comorbidities could become a challenge for proper, accurate and timely diagnosis, and therapeutic intervention. Due to the overlapping comorbidity of PD motor and stress-related psychological symptoms, it is often difficult to recognize it as a separate entity.

Does the status of stress, anxiety, and depression along with stress reactivity differ in PD patients with or without dementia relative to age-matched healthy individuals? The answer to these questions could help develop strategies to delay and at the best prevent the development of dementia in PD. We hypothesized that the scores of acute and chronic stress, anxiety, and depression along with changes in galvanic skin

Address for correspondence: Dr. Ratna Sharma, Department of Physiology, Stress and Cognitive Electroimaging Laboratory, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-mail: ratnaaiims@gmail.com

Submission: 07.08.2018 **Revision:** 24.08.2018
Acceptance: 18.09.2018 **Published:** 25.10.2019

DOI: 10.4103/aian.AIAN_341_18

response (GSR), salivary cortisol, and alpha-amylase levels would be different in Parkinson's patients with or without dementia compared to age-matched controls.

Objectives

We undertook this study with an aim to assess acute as well as chronic levels of stress, anxiety, and depression along with stress reactivity in Parkinson's patients with or without dementia compared to age-matched controls.

Materials and Methods

Subjects

PD patients diagnosed by the United Kingdom PD Brain Bank criteria[11] were recruited for the study. Information about the onset and course of the disease, initial symptoms, site of onset of disease, medical history, and medication were obtained by a semi-structured interview by the neurologist. The patients were screened on the basis of inclusion and exclusion criteria of the study and eligible patients were requested to participate in the study. Patients of both sexes, between 45 and 75 years of age, age of onset of PD of >40 years, and Hoehn and Yahr[12] stage of 1–3 were recruited. Patients with previous history of head injury with unconsciousness, stroke, drug abuse, concurrent use of sedatives, hypnotics, neuroleptic drugs, frequent syncope, hypoglycemia, epilepsy, concurrent serious illness which may shorten lifespan (malignancy if known), presence of hallucinations, other kinds of motor deficits, and psychiatric illnesses were excluded from the study. The study was approved by the ethical committee for human studies of All India Institutes of Medical Sciences (Ref. No IESC/T-158/30.3.2012). All the participants provided informed written consent to participate in the study. Mini-Mental State Examination (MMSE)[13] and Clinical Dementia Rating (CDR) scores[14] which are considered as markers of overall cognitive status and stage/severity of dementia, respectively, were used to classify the PD patients into two groups as PD patients without dementia (PDND, n = 30; MMSE = 25–30; CDR = 0–1) and PD patients with dementia (PDD, n = 28; MMSE 10–24; CDR = 0.5–3). Age- and education-matched healthy controls (HC, n = 26; MMSE = 26–30; CDR = 0) with no prior history of any neurological or psychiatric illness were recruited as controls.

Experimental procedure

Experimental procedure included assessment of anxiety, stress and depression, performance of arithmetic task to assess stress reactivity, baseline salivary sample collection, recording of electrocardiogram (ECG), and GSR during baseline (eyes closed condition) as well as during arithmetic task followed by postarithmetic task saliva sample collection. Saliva sampling has the advantage that it is noninvasive, making multiple sampling easy, and stress free. In addition to this, increase in salivary cortisol and alpha-amylase concentration in response to psychological stress considered to be correlated with serum cortisol and plasma norepinephrine, respectively.

Assessment of stress, anxiety, and depression

Stress, anxiety, and depression levels were assessed using standard inventories and scores were compared between the groups. State and trait anxiety were assessed using State-Trait Anxiety Inventory (STAI-Y1 and Y2),[15] acute stress by Acute Stress Questionnaire,[16] chronic stress by Perceived Stress Scale developed by Sheldon Cohen,[17] and depression level was assessed using Beck's depression inventory (BDI).[18]

Stress reactivity (arithmetic task)

Arithmetic task was chosen to induce mental stress because it acts as a strong stress inducer.[19] The patients were instructed to do sequential subtraction of a fixed digit from a higher order digit verbally, for example, seven from 100 and thus going toward 1/0. Any mistakes in their calculations were pointed out and they were made to repeat the same again.

Physiological parameter

To evaluate the sympathetic nervous system activity during baseline and during arithmetic task, the GSR and heart rate were recorded using leads provided by RMS POLYWRITE-D Systems. For measuring the changes in heart rate, ECG was recorded using two-lead ECG electrodes from RMS POLYWRITE-D Systems. For GSR recording, two Ag/AgCl electrodes were placed round the index and middle finger of the left hand by a Velcro flexible lightweight cable. The electrodes had a 6 mm contact area with a 1.6 mm cavity to accommodate electrode gel (ECG gel was used). The electrodes were shielded to minimize noise interference and improve recordings.

Saliva sample collection and estimation of cortisol and alpha-amylase

Saliva samples were collected before and after completion of the arithmetic calculation task for the measurement of cortisol and alpha-amylase using sterile cotton swab placed underneath the tongue for 30 s. Saliva from these swabs was squeezed into sterile Eppendorf tubes and salivary samples were immediately frozen at –20°C until analyses. All experiments were performed between 11 am and 1 pm to control for the diurnal fluctuations in the cortisol levels.

Competitive immunoenzymatic colorimetric enzyme-linked immunosorbent assay (ELISA) method was used for estimation of cortisol (Diametra, Italy) and alpha-amylase (Assay Max). For calculations, the standard curve was plotted on semi-log graph paper with concentration on X-axis and the percentage of absorbance at 450 nm on Y-axis. The best-fit line was determined by regression analysis using log-log or four-parameter logistic curve fit for deriving the concentration in the unknown sample.

Statistical analysis

STATA version 11.0 software (Stata Statistical Software: version 11 (College Station, TX: StataCorp LP) was used for statistical analyses. To compare scores of parameters, namely, STAI-Y1 and Y2, acute and chronic stress, and BDI among the groups, one-way ANOVA followed by Bonferroni correction was applied. To compare GSR, heart rate, cortisol, and alpha-amylase concentration among the groups, Kruskal–Wallis

test followed by Mann–Whitney test for group comparison were used. Paired signed rank test was applied to compare the changes during arithmetic task to baseline in all the groups.

Results

Acute anxiety ($P < 0.001$), acute stress ($P < 0.001$), and depression scores (PDD: $P < 0.0001$ and PDND: $P = 0.0008$) were significantly higher in patients of PD compared to HC. Chronic stress ($P < 0.001$) and chronic anxiety ($P = 0.004$) scores were significantly higher only for PDD patients while they were comparable in PDND patients when compared with HC. Within the Parkinson's patients group, PDD patients had higher acute and chronic anxiety (STAI-Y1 $P = 0.009$ and STAI-Y2 $P = 0.002$), acute ($P = 0.002$) and chronic stress ($P = 0.012$), and depression scores ($P = 0.0027$) compared to PDND [Table 1].

Salivary cortisol levels during baseline ($P = 0.004$) and after arithmetic task ($P = 0.002$) were higher in PDND compared to controls. PDD patients, on the other hand, were comparable to controls. PDND had higher postarithmetic task cortisol level ($P = 0.038$) compared to PDD, though baseline levels were comparable. Alpha-amylase levels were significantly higher in both groups of Parkinson's patients compared to controls during both baseline (PDND: $P = 0.05$ and PDD: $P = 0.009$) and postarithmetic task (PDND: $P = 0.042$ and PDD $P = 0.008$) [Table 1]. There was no significant change in alpha-amylase levels at baseline and postarithmetic task period when compared between PDND and PDD patient groups. When cortisol and amylase levels were compared within each group between baseline and postarithmetic task condition, cortisol levels increased significantly postarithmetic task only in HC ($P = 0.027$) and PDND ($P = 0.02$) groups, while no change was observed in amylase levels for all three groups [Table 2].

GSR was higher in PDND during baseline compared to both PDD ($P = 0.006$) and HC ($P = 0.029$), whereas during postarithmetic stress, GSR was higher only in PDND ($P = 0.027$) compared to PDD. Higher GSR was observed during arithmetic task compared to baseline in all the three groups (HC: $P = 0.005$, PDND: $P = 0.0002$, and PDD: $P = 0.0004$) [Table 2]. No significant changes were obtained in the heart rate activity when compared between the groups.

Discussion

In the present study, combined measures of stress reactivity derived in the form of levels of stress hormones and stress assessment through GSR and questionnaire-based subjective assessment provided an insight of effect of baseline and induced stress in PDND and PDD compared to HC.

Acute anxiety and acute stress along with high depression score was a feature of Parkinson's patients without dementia. Higher acute and chronic stress and anxiety accompanied with high depression were present in patients with dementia. In conclusion, high level of acute and chronic anxiety and stress along with depression distinguishes PDD from PDND. Depression, anxiety, sleep disturbances, apathy, agitation, panic attacks, and phobic disorders are reported to be the most common neuropsychiatric symptoms in PD.[20] Although existing studies have reported these changes in early-stage PDND, in the present study, the patients with and without dementia were also compared. In addition, the PDD patients

Table 1: Comparison of neuropsychological characteristics, cortisol, amylase level and galvanic skin response, in HC, PDND and PDD groups

Tests	HC ($n=26$)	PDND ($n=30$)	PDD ($n=28$)	$P<0.05$	HC versus PDND	HC versus PDD	PDND versus PDD
MMSE	29.35±0.98	27.65±1.91	22.12±2.83	<0.001	0.0006	<0.0001	<0.0001
STAI-Y1[#]	28.5±6.91	35.08±5.44	39.02±8.15	<0.001	<0.001***	<0.001***	0.009**
STAI-Y2[#]	39.65±8.98	40.97±8.71	46.76±8.62	0.0006	1.000	0.004**	0.002**
Acute stress[#]	26.76±12.16	47.6±3.26	62.54±24.43	0.001	<0.001***	<0.001***	0.002**
Chronic stress[#]	40.76±8.82	43.92±9.51	49.10±8.95	0.0006	0.43	<0.001***	0.012*
BDI[#]	4.39±2.9	8.15±5.2	11.61±6.6	0.0001	0.0008***	<0.0001***	0.0027**
Cortisol (ug/ml) (baseline)	2.33±1.59	3.92±2.16	3.11±1.99	0.009	0.004***	0.088	0.096
Alpha-amylase (U/ml) (Baseline)	134.6±85.00	196.9±95.17	218.5±101.7	0.029*	0.050*	0.009**	0.486
Cortisol (ug/ml) (postarithmetic task)	2.93±1.37	5.59±3.75	3.76±2.75	0.009	0.002***	0.651	0.038*
Alpha amylase (U/ml) (postarithmetic task)	130.4±115.6	198.2±86.82	246.7±104.4	0.011*	0.042*	0.008**	0.100
GSR (baseline)	6.33±1.67	7.31±1.66	6.07±1.96	0.009	0.029*	0.48	0.006**
GSR (arithmetic task)	7.09±1.88	8.01±1.80	7.05±1.83	0.051	0.07	0.91	0.027*

*$P<0.05$, **$P=0.001$, ***$P<0.0001$. Values are expressed as mean±SD; [#]ANOVA test followed by multiple comparison by *t*-test with Bonnferoni correction. STAI-Y1=State and Trait Anxiety Inventory form Y1, STAI-Y2=State and Trait Anxiety Inventory form Y2, BDI=Beck's Depression Inventory, GSR=Galvanic stress response. Kruskal–Wallis test followed by Mann–Whitney test for group comparison were used to compare galvanic skin response, cortisol and alpha-amylase concentration, and MMSE scores among groups. ANOVA=Analysis of variance, MMSE=Mini-Mental State Examination, SD=Standard deviation, HC=Healthy Controls, PDND=Parkinson's without dementia, PDD=Parkinson's with dementia

Table 2: Comparison of cortisol, amylase, galvanic skin response (baseline vs. arithmetic task) in HC, PDND, and PDD groups

Parameters	Groups	Baseline	Arithmetic task	$P<0.05$
Cortisol	HC	2.33±1.59	2.93±1.37	0.027*
	PDND	3.92±2.16	5.59±3.75	0.020*
	PDD	3.11±1.99	3.76±2.75	0.59
Alpha amylase	HC	134.6±85.00	130.4±115.6	0.79
	PDND	196.9±95.17	198.2±86.82	0.91
	PDD	218±101.7	264.7±104.4	0.08
GSR	HC	6.326±1.67	7.085±1.88	0.005**
	PDND	7.307±1.66	8.011±1.80	0.0002***
	PDD	6.065±1.96	7.052±1.83	0.0004***

*≤0.05, **P=0.001, ***P<0.0001. The values are presented as mean±SD. Paired signed rank test was applied. GSR=Galvanic skin response, SD=Standard deviation, HC=Healthy Controls, PDND=Parkinson's without dementia, PDD=Parkinson's with dementia

were found to be more depressed compared to both PDND and HC. The presence of depression at the early stage in PDND compared to HC along with acute anxiety and stress suggests it could be a predictor of cognitive impairment and its progression to dementia as reported earlier.[21]

High cortisol level in PDND during baseline as well after stress condition compared to HC suggests PDND patients to be prone to stress response. Salivary cortisol in response to stress has been reported to be elevated in PD patients compared to healthy age-matched controls in an earlier study.[22] Further, higher cortisol levels have been reported in depression,[23] anxiety,[24] Alzheimer's disease, and PD.[25]

In the present study, the PDD group had normal baseline cortisol levels in spite of high levels of acute as well as chronic stress. Although direct role of cortisol and alpha-amylase in the development of PD or dementia in PD has not been reported, there are evidence that supports the idea that HPA axis dysregulation and excess cortisol may be detrimental to cognition. The presence of lower cortisol levels possibly due to enhanced negative feedback at HPA axis as a result of chronic stress has been reported.[26] In addition to lower baseline cortisol levels, increased dexamethasone sensitivity and responsiveness have been reported in these studies. GSR an indirect indicator of sympathetic nervous system activity was higher during arithmetic task compared to baseline in all the groups, suggesting that the task was stressful. Stress reactivity in PDD, however, was comparable to control and in fact was lower as compared to PDND, indicating a lower responsiveness to stressor. Another possible cause for this lower responsiveness to stressor could be autonomic dysfunction which is also been reported in Parkinson's patients. Reduced cortisol reactivity to stress has been also reported in ADHD[27] which could be due to habituation to stressful conditions.[28] In PD, the acute stress increases dopamine release as an essential measure to promote adaptation and survival, whereas chronic stress decreases dopaminergic tone in various regions of the brain including the prefrontal cortex , striatum, nucleus accumbens, and frontal cortex.[29] Interaction of the altered levels of cortisol and dopamine in PD patients are expected to have serious implications for the disease. An indicator of sympathetic activation, namely, alpha-amylase levels was higher in both PDND and PDD compared to controls at rest and after the stress task. Mental stress has been reported to cause increased sweating and activation of tremor in PD patients,[30] though in the present study, no such response was seen. There is growing evidence suggesting that the experience of stress impairs cognition and that these effects may be exacerbated in advanced age and more so in disease condition such as PD. The extent and the degree of cognitive decline may differ in patients depending on the underlying pathophysiology, neurotransmitter levels, and stress hormone levels. Neuropsychiatric dysfunctions such as anxiety, stress, and depression have been proposed to be playing a pivotal role in cognitive worsening in PD.[31]

The present study concludes that questionnaire-based assessments of stress, anxiety, depression, and salivary cortisol levels may be explored to assess the presence of dementia in neurodegenerative disorders.

Financial support and sponsorship

This work was supported/funded by Department of Biotechnology (DBT) Sanction Order No. & Date: BT/PR/14844/MED/30/579/2010, September 22, 2011.

Conflicts of interest

There are no conflicts of interest.

References

1. Parkinson J. An essay on the shaking palsy 1817. J Neuropsychiatry Clin Neurosci 2002;14:223-36.
2. Parkinson's and Alzheimer's Disease: The Surprising Role of Stress. Stress Medicine– Wiley Online Library, Rosch; 1999. Available from: https://www.onlinelibrary.wiley.com/doi/abs/10.1002/%28SICI%291099-1700%28199901%2915%3A1%3C1%3A%3AAID-SMI822%3E3.0.CO%3B2-8. [Last accessed on 2018 Aug 03].
3. Herbert J. Fortnighly review. Stress, the brain, and mental illness. BMJ 1997;315:530-5.
4. Patriquin MA, Mathew SJ. The neurobiological mechanisms of generalized anxiety disorder and chronic stress. Chronic Stress (Thousand Oaks) 2017; 1:10.
5. Leentjens AF, Van den Akker M, Metsemakers JF, Lousberg R, Verhey FR. Higher incidence of depression preceding the onset of Parkinson's disease: A register study. Mov Disord 2003;18:414-8.
6. Schuurman AG, van den Akker M, Ensinck KT, Metsemakers JF, Knottnerus JA, Leentjens AF, *et al.* Increased risk of Parkinson's disease after depression: A retrospective cohort study. Neurology 2002;58:1501-4.
7. Ishihara L, Brayne C. A systematic review of depression and mental illness preceding Parkinson's disease. Acta Neurol Scand 2006;113:211-20.
8. Thanvi BR, Munshi SK, Vijaykumar N, Lo TC. Neuropsychiatric non-motor aspects of Parkinson's disease. Postgrad Med J 2003;79:561-5.
9. Emre M. What causes mental dysfunction in Parkinson's disease? Mov Disord 2003;18 Suppl 6:S63-71.
10. Aarsland D, Larsen JP, Lim NG, Janvin C, Karlsen K, Tandberg E, *et al.* Range of neuropsychiatric disturbances in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1999;67:492-6.
11. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical

diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-4.
12. Hoehn MM, Yahr MD. Parkinsonism: Onset, progression and mortality. Neurology 1967;17:427-42.
13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
14. Morris JC. The clinical dementia rating (CDR): Current version and scoring rules. Neurology 1993;43:2412-4.
15. Spielberger CD. Manual for the State-Trait Anxiety Inventory STAI (Form Y) ("Self-Evaluation Questionnaire"); 1983. Available from: http://www.ubir.buffalo.edu/xmlui/handle/10477/1873. [Last accessed on 2017 Jul 17].
16. Cardeña E, Koopman C, Classen C, Waelde LC, Spiegel D. Psychometric properties of the Stanford acute stress reaction questionnaire (SASRQ): A valid and reliable measure of acute stress. J Trauma Stress 2000;13:719-34.
17. Cohen S, Kamarck T, Mermelstein R. A Global Measure of Perceived Stress. J Health Soc Behav. 1983;24:385¨C96.
18. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
19. Jern S, Pilhall M, Jern C, Carlsson SG. Short-term reproducibility of a mental arithmetic stress test. Clin Sci (Lond) 1991;81:593-601.
20. Hanagasi HA, Emre M. Treatment of behavioural symptoms and dementia in Parkinson's disease. Fundam Clin Pharmacol 2005;19:133-46.
21. Global Parkinson's Disease Survey (GPDS) Steering Committee. Factors impacting on quality of life in Parkinson's disease: Results from an international survey. Mov Disord 2002;17:60-7.
22. Djamshidian A, O'Sullivan SS, Papadopoulos A, Bassett P, Shaw K, Averbeck BB, *et al.* Salivary cortisol levels in Parkinson's disease and its correlation to risk behaviour. J Neurol Neurosurg Psychiatry 2011;82:1107-11.
23. Bhagwagar Z, Hafizi S, Cowen PJ. Increased salivary cortisol after waking in depression. Psychopharmacology (Berl) 2005;182:54-7.
24. Vreeburg SA, Zitman FG, van Pelt J, Derijk RH, Verhagen JC, van Dyck R, *et al.* Salivary cortisol levels in persons with and without different anxiety disorders. Psychosom Med 2010;72:340-7.
25. Hartmann A, Veldhuis JD, Deuschle M, Standhardt H, Heuser I. Twenty-four hour cortisol release profiles in patients with Alzheimer's and Parkinson's disease compared to normal controls: Ultradian secretory pulsatility and diurnal variation. Neurobiol Aging 1997;18:285-9.
26. Yehuda R, Seckl J. Minireview: Stress-related psychiatric disorders with low cortisol levels: A metabolic hypothesis. Endocrinology 2011;152:4496-503.
27. Hastings PD, Fortier I, Utendale WT, Simard LR, Robaey P. Adrenocortical functioning in boys with attention-deficit/hyperactivity disorder: Examining subtypes of ADHD and associated comorbid conditions. J Abnorm Child Psychol 2009;37:565-78.
28. Northover C, Thapar A, Langley K, Fairchild G, van Goozen SH. Cortisol levels at baseline and under stress in adolescent males with attention-deficit hyperactivity disorder, with or without comorbid conduct disorder. Psychiatry Res 2016;242:130-6.
29. Ziegler DA. Cognition in Healthy Aging and Parkinson's Disease: Structural and Functional Integrity of Neural Circuits. Massachusetts Institute of Technology; 2011. Available from: http://www.dspace.mit.edu/handle/1721.1/68169. [Last accessed on 2016 May 30].
30. Callister R, Suwarno NO, Seals DR. Sympathetic activity is influenced by task difficulty and stress perception during mental challenge in humans. J Physiol 1992;454:373-87.
31. Weintraub D, Moberg PJ, Culbertson WC, Duda JE, Stern MB. Evidence for impaired encoding and retrieval memory profiles in Parkinson disease. Cogn Behav Neurol 2004;17:195-200.