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Neuropsychological Outcomes Following Psychosocial Intervention for Depression in Parkinson's disease

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Abstract

The purpose of this paper is to describe neuropsychological outcomes in people with Parkinson's disease (PD) following their participation in an NIH-sponsored, randomized-controlled trial of cognitive-behavioral treatment for depression. Improvements in mood were associated with modest gains in verbal memory and executive functioning, over the 10-week treatment period, and accounted for greater variance in neuropsychological outcomes at the end-of-treatment, than other known correlates of cognitive functioning in PD, such as disease severity, age, and education. Baseline working memory and executive skills were also associated with depression improvement over time.

Keywords

Parkinson's disease; depression; cognition; psychosocial intervention

Depression affects approximately 50% of people with Parkinson's disease (PD){1}. This high rate of depression in PD (dPD) is of great clinical concern as dPD is associated with faster physical and cognitive deterioration{2}, poorer quality of life {3}, greater impairment in activities of daily living{4}, more rapid initiation of dopaminergic replacement treatment{4}, and heightened levels of caregiver distress{5}. In particular, the negative impact that depression has on cognitive functioning in PD has received substantial attention in the literature.

Depression has been identified as a risk factor for dementia in PD in both longitudinal and cross-sectional investigations {6,7}. Depression may also exacerbate the wide range of cognitive deficits observed in PD, including impaired global cognition, executive functions, memory, attention, and language {8,9,10,11}. These cognitive deficits may be most profound in depressed PD patients with lower levels of education {9,12} higher levels of apathy {11,13}, more severe depression {14} and a history of depression that predates the

onset of the movement disorder{ 15}. Depression may also be a more robust predictor of cognitive impairment in PD than disease severity, age of PD onset, and PD treatment regimen{ 16}.

Nonetheless, the extent to which cognition in PD improves following successful depression treatment remains to be clearly elucidated. While some dPD treatment studies have documented pre-post improvements in global cognitive functioning { 17,18}, executive skills and visual spatial ability { 19}, others have found treatment to be associated with neither negative cognitive effects nor cognitive changes of any kind { 20,21,22}. In some instances, baseline cognition (i.e., better memory, executive functions) was found to predict improved depression treatment response, though cognitive improvement did not coincide with the amelioration of depression { 23,24}. This limited data stems largely from pharmacological (antidepressant, dopamine agonist) and rTMS (repetitive transcranial magnetic stimulation) trials. To the best of our knowledge, cognitive functioning has yet to be investigated as a secondary endpoint in psychosocial treatment studies for dPD.

The purpose of this paper is to describe neuropsychological outcomes in people with PD following their participation in a cognitive-behavioral treatment (CBT) trial for depression{ 25}. We hypothesized a priori that improved depression would be associated with improvements in verbal memory (primary outcome) and executive functions (secondary outcome) following the psychosocial treatment of dPD (as these specific cognitive domains have been most consistently associated with treatment response in past treatment trials of dPD { 19, 23, 24}. Exploratory analyses also addressed 1) the impact of improved depression on attention, working memory, and verbal fluency, 2) the effect of improved secondary anxiety (a psychiatric complication highly comorbid with dPD that may complicate its course and treatment and itself impact cognition { 26} on a variety of cognitive domains) and 3) the extent to which better performance on individual neuropsychological tests over the course of the trial predicts improved mood following psychosocial intervention.

Method

Overview

A randomized-controlled trial of CBT plus clinical monitoring vs. clinical monitoring only for the treatment of dPD was conducted from April 2007 until July 2010 in the departments of Psychiatry and Neurology at Robert Wood Johnson Medical School (RWJMS). Treatment was provided for 10 weeks. The CBT protocol incorporated behavioral activation, cognitive restructuring, sleep hygiene, anxiety management, and caregiver psychoeducation. Clinical monitoring encompassed six in-depth discussions about mood and motor functioning with study staff. Participants continued on all stabilized (6 weeks) treatment regimens under the supervision of their personal physicians. Randomization was stratified by antidepressant use at baseline, such that participants taking antidepressant medications were equally represented in both treatment groups. Medication use for all purposes and mental health care utilization was tracked throughout the study. Post-enrollment changes in depression treatment (other than the study interventions) were a criterion for early termination. Ninety percent of participants completed the trial.

The study had had full RWJMS IRB approval. Written informed consent was obtained prior to the initiation of any study procedures. Participant characteristics, recruitment strategies, flow of participants through the trial, study procedures, sample size, and power calculations are detailed in the main outcome paper {25}. Key aspects of the experimental design are highlighted below.

Participants

Participants were recruited from the Richard E. Heikkila Movement Disorders Clinic at RWJMS. Enrollment criteria included: PD per NINDS Criteria {27}, a *Primary* psychiatric diagnosis of Major Depressive Disorder (MDD), Dysthymia, or Depression Not Otherwise Specified (per the SCID for DSM-IV), a Clinical Global Impression Severity Scale score of > 4 [at least moderately ill {28}], 35-85 years old, stable medication regimen 6 weeks, and a caregiver willing to participate in treatment. Significant motor fluctuations (>50% of the day), suicidality, psychosis, or possible dementia (operationally defined as a score below the 5th percentile for age on memory and at least one other subscale on the Mattis Dementia Rating Scale) {29} were exclusionary.

Measures

Neuropsychological tests and mood and disability ratings were administered at baseline and week 10 (end-of -treatment) by masters or doctoral level psychologists (or the study neurologist who completed PD symptom ratings) who were blind to treatment assignment. The primary outcome of verbal memory was assessed by the total recall, delayed recall, and recognition scores of the Hopkins Verbal Learning Test – Revised (HVLT-R){30}. The secondary outcome of executive functioning was assessed by the time taken to complete the inhibition task from the Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test {31}. Exploratory outcomes included measures of attention and working memory (Digit Span, Letter-Number Sequencing, Spatial Span scores from the Wechsler Memory Scales){32}, and verbal fluency (D-KEFS letter fluency, category fluency, category switching scores). Alternative versions of the HVLT-R and D-KEFS verbal fluency test were administered at baseline and week-10. Mood and disability measures included the Hamilton Depression Rating Scale (HAM-D 17; depression) {33}, Hamilton Anxiety Rating Scale (HAM-A; anxiety) {34} and Unified Parkinson's Disease Rating Scale (UPDRS; PD symptom severity) {35}.

Overview of Statistical Analyses—Data were analyzed with SPSS Version 18. An intent-to-treat approach was employed. In order to determine the impact of improved mood on cognition, a median split was conducted on the HAM-D change score between baseline and week-10 for the entire sample. Individuals with a change score at or above the median were classified as “more improved”. Those with a change score below the median were classified as “less improved.” Raw neuropsychological scores were converted to standard scores using accepted normative data prior to data analysis. Baseline neuropsychological data are presented in Table 1.

Data were first analyzed with mixed-models repeated measures analysis of variance. Group assignment (depression improvement – more/less), assessment point (baseline/week-10),

and their interaction were fixed effects. The group-by-time interaction was the fixed effect of interest. Results were adjusted for multiple comparisons via the Bonferroni correction within each specific hypothesis. The main effect of depression improvement was also examined to determine if higher scores on specific cognitive measures over the course of the trial were associated with a stronger likelihood of improved mood following treatment. Compound symmetry was used to model the covariance structure for all analyses.

When the group-by-time interaction was significant, follow-up stepwise linear regression analyses were conducted to determine the relative contribution of depression improvement on week-10 cognition, controlling for other relevant variables like baseline performance on the respective neuropsychological measure, PD severity (UPDRS total score), age, and education. All available participant data, coupled with a multiple imputation approach to missing data, was used in computing all regression statistics. When the main effect of “depression improvement” was significant, follow-up discriminant function analysis was conducted to determine if baseline scores on these measures (collectively) predicted improved mood over time, and the extent to which each respective cognitive test contributed to the improved outcome.

Mixed models followed by stepwise linear regression were also employed for exploratory analyses regarding anxiety improvement and cognition. If both anxiety and depression improvement predicted the same aspect of week-10 cognition in separate analyses, additional stepwise linear regression models were conducted in order to determine the relative contribution of each psychiatric complication, controlling for the other, (i.e., depression improvement was entered first, followed by anxiety improvement; the order was then reversed) to the neuropsychological domain of interest.

Results

Characteristics of the Sample

Eighty people with PD (60% male) were enrolled. On average, participants were 64.56 (10.53) years old [age range of 40-83] and had PD for 6.34 (5.51) years [89% had mild to moderate PD based on the Hoehn and Yahr Scale]. The majority of the sample was highly educated (68% had a college degree or higher), had Major Depressive Disorder (81%, $n = 65$) and a secondary anxiety disorder diagnosis (56.3%, $n = 45$).

Mixed Models Analyses

There was a significant group [depression improvement] by time interaction on week-10 total recall [$F(1,74) = 7.15$, $p = .009$; Cohen's $d = .58$] and recognition [$F(1,73) = 7.08$, $p = .007$; Cohen's $d = .72$] scores {verbal memory; PRIMARY OUTCOMES}. There was a significant group [depression improvement] by time interaction on week-10 inhibition scores [$F(1,72) = 5.58$, $p = .02$; Cohen's $d = .31$] {executive functioning, SECONDARY OUTCOME}. No significant effects of depression improvement on delayed recall, attention, working memory, or verbal fluency were observed.

There was a significant group [anxiety improvement] by time interaction on week-10 total recall [$F(1,74) = 6.63$, $p = .01$; Cohen's $d = .56$] and delayed recall [$F(1,74) = 8.48$, $p = .008$;

Cohen's $d = .62$] scores {verbal memory; EXPLORATORY OUTCOME}. There were no significant effects of improved anxiety on recognition, executive functioning, attention, working memory, or verbal fluency.

Stepwise Regression Models

Depression improvement contributed unique variance to verbal memory [total recall: 6%, $p = .009$; recognition: 11%, $p = .001$] and executive functioning [inhibition: 2%, $p = .021$] at week-10, controlling for baseline scores on each respective measure, PD severity, education, and age (Table 2). Anxiety improvement contributed unique variance to verbal memory [total recall: 5%, $p = .030$; delayed recall: 6%, $p = .008$] at week-10, in the stepwise linear regression model (Table 3).

Both depression and anxiety improvement were implicated in HVLIT-R total and delayed recall scores at end-of-treatment. [There was trend for the group (depression improvement) by time interaction on week-10 delayed recall scores ($p = .09$), so this was included in combined analyses in order to be conservative.] Results indicated that neither depression ($p = .08$), nor anxiety ($p = .37$), contributed unique variance to total recall, controlling for the other, at week-10 (when added to the stepwise regression model described above). Moreover, depression did not contribute unique variance to delayed recall ($p = .60$), controlling for anxiety. However, anxiety improvement contributed unique variance to delayed recall scores at week-10 (5%, $p = .03$), even when controlling for depression.

Exploratory Discriminant Function Analysis

Main effects of the grouping variable “depression improvement” were observed on the following tests: Inhibition/Switch [$F(1,77) = 4.24$, $p = .04$], Recognition [$F(1,76) = 4.43$, $p = .04$], Spatial Span [$F(1,76) = 4.09$, $p = .05$], Digit Span [$F(1,78) = 6.21$, $p = .02$], and Letter Number Sequencing [$F(1,78) = 6.47$, $p = .01$]. When baseline scores on these tests were entered as independent variables in a discriminant function analysis (DFA) to predict depression improvement over time, the overall model was non-significant ($p = .10$). Closer inspection of data revealed that Spatial Span and Recognition subtests had the lowest individual loadings with the overall function and were thus removed from a follow-up DFA. Results from this follow-up DFA were significant [$X^2 = 9.25$, $df = 3$, $p = .026$]. Pooled within group correlations between discriminating variables and standardized canonical discriminant functions were as follows: Letter-Number Sequencing (.894), Digit Span (.786), and Inhibition Switch (.772).

Discussion

This is the first paper to describe the impact of psychosocial intervention for depression on neuropsychological functioning in PD. Results indicate that improvements in depression were associated with small gains in verbal memory and executive functioning, following the psychosocial treatment of dPD. Moreover, higher baseline scores on measures of working memory and executive functioning were able to reliably discriminate between participants who derived greater benefits from treatment, and those who did not, over 10-weeks. Though effect sizes were modest, improvements in depression accounted for more variance in

neuropsychological outcomes at the end-of-treatment, than other known correlates of cognitive functioning in PD, such as disease severity, age, and education. Finally, changes in both depression and anxiety were implicated in gains in select aspects of verbal memory. The impact of anxiety on cognition was shared with depression for immediate recall, and a small but significant amount of unique variance was explained by anxiety only for delayed recall.

There are no additional psychosocial treatment studies for dPD with which to compare these results. However, the present findings are consistent with the published literature regarding pharmacologic and rTMS approaches for the treatment of dPD. For example, baseline verbal memory and executive functions have been associated with better antidepressant response in PD, while memory and executive skills have been found to improve following longer-term antidepressant treatment (i.e., 6 months) and short-term rTMS of the left dorsolateral prefrontal cortex, respectively {19,23, 24}. The finding of improved cognition with the amelioration of depression and anxiety is also consistent with the biological substrates of anxiety and depression in PD. Medial prefrontal cortex and cingulate cortex, in particular though not exclusively, have been implicated in mood disturbance and fluctuation in PD {36,37}. Because both PD and depression can reduce frontal cortical blood flow, it is plausible that amelioration of such metabolic changes with treatment impacts executive functions and aspects of memory. However, future studies would need to show that psychosocial treatment produces lasting or even transiently significant changes in cerebral metabolism in PD.

Additionally, the relationship between anxiety and both immediate and delayed recall, suggest an effect on encoding. This is also consistent with the shared biological substrate of depression and mood fluctuation, including anxiety, as described above.

Clinical Implications

Because baseline executive and working memory were predictive of treatment response, it is tempting to speculate whether attempts to improve executive function might improve the odds of depression treatment response in PD. Such speculation is premature given that there is only very limited evidence that remediation of executive and working memory deficits can be accomplished in PD {38} and there is no data regarding cognitive remediation in PD patients with depression. However, the present data do suggest that successful depression treatment may be associated with cognitive improvements. Thus, it may be beneficial for depression treatment to be initiated prior to cognitive remediation attempts, so that lesser cognitive deficits need to be addressed in cognitive remediation.

Another issue that arises is whether cognitively impaired PD patients can benefit from psychosocial treatment of depression. There is no data to address this issue, but extant literature on patients with Alzheimer's disease indicate that manualized psychosocial treatments for depression can be effective, although cognitive-behavioral treatments are more apt to be successful in mildly impaired patients and more behavioral strategies may need to be used in persons with moderate cognitive compromise {39}.

Limitations

The study is not of sufficient duration (i.e., 10 weeks) to assess the long-term clinical significance of the observed findings. Results also might not generalize to all dPD patients. The majority of sample had MDD, was highly educated (possibly due to a strong preference amongst this sub-group for psychotherapy as a primary intervention for depression {40}), and had a supportive caregiver. The cognitive effects of treatment may be less profound in a mildly depressed sample (with perhaps lesser cognitive dysfunction) or a sample with lower levels of education and less social support. The restricted range on variables, such as education and disease severity, observed in the sample, may also have resulted in their minimal correlation with cognition in stepwise regression analyses. Finally, sample size was modest per clinical trial standards. Additional cognitive effects may have been observed with larger numbers.

Summary and Conclusions

This study provides preliminary evidence to suggest that memory and executive functioning may improve following the successful psychosocial treatment of dPD. Anxiety, a common correlate of depression, may also influence cognitive changes in PD, and may be most relevant to the assessment of delayed recall. While a median split on depression change scores was used to define the degree of mood improvement for study participants, 78% of the “more improved” group was randomized to CBT. Thus, we believe that these results generalize to both psychosocial treatment in general and CBT in particular. Further research is needed to replicate and extend these findings.

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Table 1

Means and Standard Deviations for Baseline Neuropsychological Measures

Measure	Mean	Standard Deviation
HVLT-R Total Recall	37.06	(10.95)
HVLT-R Delayed Recall	35.96	(11.58)
HVLT-R Recognition	40.64	(11.38)
Digit Span	10.20	(3.10)
Letter-Number Sequencing	9.01	(3.59)
Letter Fluency	10.91	(3.94)
Category Fluency	10.13	(3.57)
Category Switching	9.75	(4.08)
Spatial Span	9.37	(3.24)
D-KEFS Inhibition	8.16	(4.08)

Note. – HVLT-R = Hopkins Verbal Learning Test –Revised; D-KEFS = Delis – Kaplan Executive Function System. All data presented are standardized scores (HVLT-R: $M = 50$, $SD = 10$; all other measures: $M = 10$, $SD = 3$).

Table 2

Stepwise Linear Regression Models: Depression, Memory, and Executive Skills in Parkinson's Disease

	Variables	<i>M (SD)</i>	<i>B [95% CI]</i>	β	<i>P</i>	<i>R</i> ² Change
Week 10 Total Recall	Baseline HVL-T-R Total Recall	37.06 (10.95)	0.60 [0.38, 0.82]	.56	.000	27%
	Baseline UPDRS Total Score	46.86 (17.71)	0.03 [-0.11, 0.17]	.05	.674	0%
	Education (highest level)		-0.45 [-1.74, .843]	-.07	.456	0%
	Age	64.56 (10.53)	-0.13 [-0.36, 0.10]	-.09	.269	2%
	Depression Improved (more/less)		6.21 [1.57, 10.84]	.27	.009	6%
Week 10 Recognition	Baseline HVL-T-R Recognition	40.64 (11.38)	0.38 [0.13, 0.63]	.34	.003	13%
	Baseline UPDRS Total Score	46.86 (17.71)	0.13 [-0.04, 0.30]	.15	.144	0%
	Education (highest level)		0.78 [-0.76, 2.32]	.12	.323	1%
	Age	64.56 (10.53)	-0.09 [-0.36, 0.18]	-.07	.519	2%
	Depression Improved (more/less)		9.40 [3.82, 14.97]	.36	.001	11%
Week 10 Inhibition	Baseline D-KEFS Inhibition	8.16 (4.08)	0.81 [0.66, 0.95]	.80	.000	68%
	Baseline UPDRS Total Score	46.86 (17.71)	0.00 [-0.04, 0.33]	.00	.939	0%
	Education (highest level)		0.00 [-0.30, 0.31]	.00	.993	0%
	Age	64.56 (10.53)	-0.02 [-0.07, 0.04]	-.05	.563	0%
	Depression Improved (more/less)		1.29 [0.20, 2.38]	.15	.021	2%

Note. CI = confidence interval; HVL-T-R = Hopkins Verbal Learning Test – Revised; UPDRS = Unified Parkinson's Disease Rating Scale; Inhibition = Delis-Kaplan Executive Function System Color Word Interference Subtest

Table 3

Stepwise Linear Regression Models: Anxiety and Memory in Parkinson's disease

	Variables	<i>M (SD)</i>	<i>B [95% CI]</i>	β	<i>P</i>	<i>R</i> ² Change
Week 10 Total Recall	Baseline HVLTL-R Total Recall	37.06 (10.95)	0.61 [0.39, 0.83]	.56	.000	28%
	Baseline UPDRS Total Score	46.86 (17.71)	0.02 [−0.12, 0.17]	.04	.768	0%
	Education (highest level)		−0.09 [−1.47, 1.28]	−.01	.897	1%
	Age	64.56 (10.53)	−0.16 [−0.39, 0.71]	−.12	.176	2%
	Anxiety Improved (more/less)		5.45 [0.52, 10.38]	.24	.030	5%
Week 10 Delayed Recall	Baseline HVLTL-R Delayed Recall	35.96 (11.58)	0.60 [0.38, 0.82]	.56	.000	30%
	Baseline UPDRS Total Score	46.86 (17.71)	0.03 [−0.12, 0.17]	.03	.702	0%
	Education (highest level)		0.85 [−0.59, 2.29]	.10	.247	0%
	Age	64.56 (10.53)	−0.18 [−0.42, 0.05]	−.14	.130	2%
	Anxiety Improved (more/less)		6.93 [1.83, 12.03]	.28	.008	6%

Note. CI = confidence interval; HVLTL – R = Hopkins Verbal Learning Test – Revised; UPDRS = Unified Parkinson's Disease Rating Scale