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Short communication

Cognitive functioning in individuals with Parkinson's disease and traumatic brain injury: A longitudinal study

Dawn M. Schiehser [a, b, *], J. Vincent Filoteo [a, b], Irene Litvan [c], Eva Pirogovsky-Turk [a, b], Stephanie L. Lessig [a, c], David S. Song [a, c]

[a] VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161, USA
[b] University of California, San Diego, School of Medicine, Department of Psychiatry, 9500 Gilman Drive, La Jolla, CA 92093, USA
[c] University of California, San Diego, Department of Neurosciences, 9500 Gilman Drive, La Jolla, CA 92093, USA

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ABSTRACT

Objective: To examine longitudinal changes in cognition in individuals with Parkinson's disease (PD) with and without a history of traumatic brain injury (TBI).
Methods: Twenty-five PD participants with a history of mild-moderate post-acute (>9 months) TBI and 25 demographically-matched PD controls without a history of TBI were administered measures of cognition (Mattis Dementia Rating Scale), mood, and motor functioning at baseline and at a two-year follow-up evaluation.
Results: Individuals with PD and a history of TBI evidenced significantly greater decrements in overall cognition over the two year follow-up period compared to those without a history of TBI. Secondary subscale analyses suggest cognitive decrements may be mainly in the area of executive function, while a trend for group differences on the memory subscale was also observed. Groups did not differ on demographic, motor function, disease severity, cognitive, and mood profiles at baseline and evidenced comparable changes in mood and motor symptoms from baseline to follow-up.
Conclusion: Findings suggest that a history of mild-moderate TBI is a risk factor for cognitive decline in individuals with PD.

1. Introduction

A history of traumatic brain injury (TBI) is associated with a greater risk of Parkinson's disease (PD), mild cognitive impairment, and dementia [1]. Yet, it remains unknown whether a history of TBI impacts the progression of cognitive impairment commonly observed in PD. Cognitive deficits in PD are frequently progressive and heterogeneous, with executive functioning and memory impairments often apparent early in the course of the disease [2,3]. Likewise, executive function and memory deficits are often observed in individuals who have a sustained a TBI [4] and can persist even 10 years after the injury [5]. Despite the clinical implications for neurocognitive deficits that occur in the aftermath of neurotrauma as well as those that co-exist with neurodegenerative disease, to our knowledge, cognition in co-occurring PD and TBI has yet to be systematically evaluated in respect to progression over time. Such an evaluation has critical prognostic implications and could help inform assessment and treatment strategies.

The purpose of this study was to examine the changes in cognitive function over time in PD patients with (PD+TBI) and without (PD-TBI) a history of TBI using a standard objective measure of cognition. It was hypothesized that compared to PD-TBI, PD+TBI participants would evidence greater decline in overall cognition.

2. Methods

2.1. Participants

Participants were 25 individuals with PD and a self-reported history of at least one post-acute (i.e., >9 months post-injury) TBI (PD+TBI) and 25 PD patients without history of TBI (PD-TBI) matched for age, gender, education, disease duration, and time between testing sessions. Participants were a convenience sample

* Corresponding author. VA San Diego Healthcare System, (151B) 3350 La Jolla Village Drive, San Diego, CA 92161, USA.
E-mail address: dschiehser@ucsd.edu (D.M. Schiehser).

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enrolled in an ongoing longitudinal study of cognition. All individuals were diagnosed with PD by a board-certified neurologist specializing in Movement Disorders based on the UK Brain Bank criteria [6] and recruited from the Movement Disorders Clinics at the University of California, San Diego and the VA San Diego. A TBI was defined as self-reported "traumatically induced physiological disruption of brain function, as manifested by at least one of the following: (1) loss of consciousness (LOC), (2) post-traumatic amnesia (PTA) for events immediately before or after the accident; (3) any alteration of consciousness (AOC), such as confusion, disorientation, or slowed thinking, at the time of the accident; and/or (4) focal neurologic deficit(s) that may or may not be transient. LOC of less than 30 min constituted a *mild* TBI and a *moderate* TBI was defined as LOC between 30 min and 24 h. Due to the retrospective nature of this study, characterization of AOC could not be determined for three PD+TBI participants. For those who reported more than one TBI, the "most significant" or "worst" TBI reported by the participant and/or LOC duration was used.

Exclusion criteria on study entry included severe psychiatric disorders (e.g., schizophrenia), substance abuse disorders, neurological disorders (e.g., stroke) other than PD or TBI, and neurosurgery (i.e., deep brain stimulation). General medical conditions, including cancer, diabetes, and heart, liver, lung, and kidney disease were surveyed via clinician-administered interview and did not differ between groups at baseline (Table 1) or follow-up ($p = 0.33$). Approval was obtained by the local ethical standards committee on human experimentation. Informed written consent was obtained from all participants.

3. Procedures

All participants were administered the Mattis Dementia Rating Scale (MDRS) [7], which consists of an overall (total) score and five individual subscales: Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory. Participants were also administered the Geriatric Depression Scale (GDS) [8] as a measure of self-reported mood and the Finger Tapping Test (FTT) as an objective index of motor function. The Movement Disorder Society-sponsored revision of Part III of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [9] and the modified Hoehn and Yahr (H&Y) were used to characterize the motor function and disease stage, respectively, of the sample at the follow-up evaluation. All other tests were administered at baseline and at follow-up (mean follow-up period = 26.4 months), and administered while participants were on their normal dosages of medication and during their "ON" state. Levodopa equivalent dosages (LED) using the criteria of Tomlinson and colleagues [10] are presented in Table 1.

3.1. Statistical analysis

Demographic and PD characteristics were compared between groups using Independent Samples *t*-tests and Chi-Square or Likelihood Ratio for categorical data. Mixed Repeated Measures Analyses of Variance (RM ANOVA) with Group (PD+TBI, PD-TBI) x Time (Baseline, Follow-up) were used to examine changes in cognition (MDRS Total score). Secondary mixed model ANOVAs were performed to examine changes in the five MDRS subscale scores as well as motor function (FTT) and mood (GDS). Post-hoc independent and paired sample *t*-tests were conducted when appropriate.

4. Results

There were no differences in demographics (age, education, gender), PD characteristics (disease duration, LED, UPDRS-Part III and H&Y scores), or medical comorbidities between the PD+TBI and PD-TBI groups (Table 1). RM ANOVA revealed no significant Group main effects or Group by Time interactions on indices of motor function (FTT), mood (GDS), or LED. There was a main effect of Time, however, for non-dominant FTT (Wilk's $\Lambda = 0.80$, $F(1, 43) = 10.9$, $p = 0.002$) and GDS (Wilk's $\Lambda = 0.91$, $F(1, 43) = 4.29$, $p = 0.044$), indicating that both groups declined equally in motor functioning and displayed equal increases in depression symptoms.

As displayed in Fig. 1, Group by Time interactions were significant for the MDRS total score (Wilk's $\Lambda = 0.820$, $F(1, 48) = 10.53$, $p = 0.002$; $\eta p2 = 0.18$), while main effects for Group or Time were not significant (p's > 0.29). Post-hoc analyses revealed PD+TBI participants achieved lower MDRS scores compared to PD-TBI at follow-up ($t = -2.04$, $p = 0.05$; $d = 0.38$), but were comparable at baseline; and while PD+TBI participants declined over the follow-up period ($t = -2.21$; $p = 0.037$; $d = 0.89$), PD-TBI participants improved ($t = 2.71$, $p = 0.012$; $d = 0.99$).

Secondary analyses of the MDRS subscales revealed significant interactions for the Initiation/Perseveration (Wilk's $\Lambda = 0.861$, $F(1, 48) = 7.76$, $p = 0.008$; $\eta p2 = 0.14$) and Memory (Wilk's $\Lambda = 0.91$, $F(1, 48) = 4.58$, $p = 0.037$; $\eta p2 = 0.09$) subscales. There was also a significant main effect of Time for the Initiation/Perseveration subscale (Wilk's $\Lambda = 0.897$, $F(1, 48) = 5.51$, $p = 0.023$; $\eta p2 = 0.10$). In post-hoc analyses, PD + TBI participants demonstrated a significant decrement on the Invitation/Perseveration subscale from baseline to follow-up ($t = -2.21$; $p = 0.009$; $d = 1.49$), which was not significant for the PD-TBI group ($p = 0.61$). Compared to the PD-TBI group, PD+TBI participants performed worse on the Invitation/Perseveration subscale during the follow-up evaluation ($t = -2.18$; $p = 0.037$; $d = 0.62$), but did not significantly differ at baseline. In regards to the Memory subscale, trends for worse performance by the PD+TBI group compared to PD-TBI ($t = -1.88$; $p = 0.07$; $d = 0.53$) as well as improvement over time in the PD-TBI group ($p = 0.086$; $d = 0.86$) were evident, while decrements over time in the PD+TBI group did not reach statistical significance ($t = -1.48$; $p = 0.15$; $d = 0.75$).

No significant effects or interactions (all p values > 0.11) were found with the other three subscales: Attention (mean [standard deviation (SD)] baseline PD+TBI = 36.3 [0.7], PD-TBI = 36.0 [1.4]; follow-up PD+TBI = 35.7 [1.2], PD-TBI = 36.1 [0.9]), Construction (mean [SD] baseline PD+TBI = 5.6 [0.8], PD-TBI = 5.4 [0.7]; follow-up PD+TBI = 5.3 [0.9], PD-TBI = 5.4 [0.9]), and Conceptualization, with the exception of a significant main effect for Time (Wilk's $\Lambda = 0.852$, $F(1, 48) = 8.32$, $p = 0.006$; $\eta p2 = 0.15$) for the latter subscale, in which both groups improved over time (mean [SD] baseline PD+TBI = 36.6 [2.6], PD-TBI = 36.6 [1.9]; follow-up PD+TBI = 37.6 [2.0], PD-TBI = 37.6 [1.4]).

5. Discussion

Individuals with PD and a history of post-acute mild to moderate TBI evidenced greater decline in cognitive functioning over time compared to those without a history of TBI, despite similar demographic, disease severity, motor and mood profiles at baseline, as well as comparable changes in LED, mood, and motor symptoms over time. Specifically, while overall cognition in PD+TBI participants declined over time, overall cognition improved in PD-TBI participants, such that at follow-up, PD+TBI participants' overall cognition was significantly worse than those who did not endorse a history of TBI.

While somewhat speculative, it appears that these cognitive decrements or changes are mainly in the areas of executive function (initiation/perseveration) and memory, albeit the latter may represent only a superficial assessment of memory due to the inherent limitations of this MDRS subscale for assessing that domain. Interestingly, memory and executive function, which are