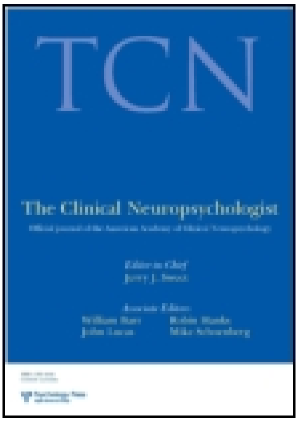

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The Case for Testing Memory With Both Stories and Word Lists Prior to DBS Surgery for Parkinson's Disease

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Patients seeking deep brain stimulation (DBS) surgery for Parkinson's disease (PD) typically undergo neuropsychological assessment to determine candidacy for surgery, with poor memory performance interpreted as a contraindication. Patients with PD may exhibit worse memory for word lists than for stories due to the lack of inherent organization in a list of unrelated words. Unfortunately, word list and story tasks are typically developed from different normative datasets, and the existence of a memory performance discrepancy in PD has been challenged. We compared recall of stories and word lists in 35 non-demented PD candidates for DBS. We administered commonly used neuropsychological measures of word list and story memory (Hopkins Verbal Learning Test, Logical Memory), along with a second word list task that was co-normed with the story task. Age-corrected scores were higher for the story task than for both word list tasks. Compared to story recall, word list recall correlated more consistently with motor severity and composite measures of processing speed, working memory, and executive functioning. These results support the classic view of fronto-subcortical contributions to memory in PD and suggest that executive deficits may influence word list recall more than story recall. We recommend a multi-componential memory battery in the neuropsychological assessment of DBS candidates to characterize both mesial temporal and frontal-executive memory processes. One should not rely solely on a word list task because patients exhibiting poor memory for word lists may perform better with stories and therefore deserve an interdisciplinary discussion for DBS surgery.

Keywords: Parkinson's disease; Verbal memory; Deep brain stimulation.

INTRODUCTION

Memory changes are a primary concern for patients with Parkinson's disease (PD), who are at an elevated risk for dementia (Aarsland, Zaccai, & Brayne, 2005). Among non-demented patients, cognitive difficulties are common and can include slowing, executive dysfunction (e.g., temporal ordering, organization, set-shifting), and episodic memory impairments (McKinlay, Grace, Dalrymple-Alford, & Roger,

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2010; Muslimovic, Post, Speelman, & Schmand, 2005; Pahwa, Paolo, Tröster, & Koller, 1998; Weintraub, Moberg, Culbertson, Duda, & Stern, 2001). Executive impairments have been attributed to disruption of fronto-subcortical systems (Alexander, DeLong, & Strick, 1998; Taylor, Saint-Cyr, & Lang, 1986; Zgaljardic, Borod, Foldi, & Mattis, 2003). An accurate assessment of memory is a crucial goal in the neuropsychological evaluation of candidates for deep brain stimulation (DBS) because cognitive impairment may increase surgical risk. Neuropsychological evaluation helps to identify individuals with PD dementia or Dementia with Lewy Bodies, who are less likely to benefit from DBS, and aids in decisions regarding selection of surgical site (pallidum vs subthalamic nucleus) based on cognitive status (Okun et al., 2007).

The assessment of memory can take many forms. Initial correlational research suggested that tests evaluating memory for word lists versus stories were essentially interchangeable (Delis, Cullum, Butters, Cairns, & Prifitera, 1988). Both require rapid processing of a constant stream of information that must be maintained in working memory to facilitate encoding and consolidation via hippocampal mechanisms. However, contemporary research highlights important differences (Randolph et al., 1994; Helmstaedter, Wietzke, & Lutz, 2009; Wicklund, Johnson, Rademaker, Weitner, & Weintraub, 2006). Performance on story tasks typically benefits from intrinsic semantic organization of the material, while word list tasks require one to *self-generate* organizational strategies. Memory for word lists, compared to stories, has been associated with cognitive measures of executive function (Tremont, Halpert, Javorsky, & Stern, 2000). Patients with focal frontal lobe lesions (Kopelman & Stanhope, 1998) and executive dysfunction (Brooks, Weaver, & Scialfa, 2006) exhibit worse memory for unrelated words than semantically related information. Conversely, memory for semantically related information, including stories, may be more directly related to temporal lobe integrity (Lezak, Howieson, & Loring, 2004; Tremont et al., 2000).

Because many patients with PD exhibit slowing and executive dysfunction, it logically follows that these patients would perform worse on word list memory tasks than story memory tasks. At least three studies have examined this issue. One provided empirical support for this performance discrepancy but did not assess memory with common clinical instruments (Hartikainen, Helkala, Soininen, & Riekkinen, 1993). Another reported the opposite finding (better memory for word lists than for stories) but used tasks developed from different normative samples (Dulay et al., 2008). The third did not observe a discrepancy between word list and story recall in PD using "co-normed" tests from the Repeatable Battery for Assessment of Neuropsychological Status (RBANS), a relatively easy tool that employs a single normative sample (Beatty et al., 2003). These highly discrepant results raise the possibility that performance differences on word list versus story tests may reflect differences in tests' normative properties rather than PD-related "executive" impairment. The pragmatic importance of this issue relates to the assumption that all memory measures are equivalent during clinical decision making. Poor performance on one word list memory task sensitive to PD-type executive impairment may be inaccurately attributed to dementia (false positive).

The purpose of the present study was to directly test two competing hypotheses for why patients with PD may perform worse on word list versus story memory tests. Performance discrepancies may reflect: (a) a disease effect related to reduced executive skills in PD; (b) an artifact of different test normative properties. To address these hypotheses we administered co-normed memory tests (story and a word list task from the Weschler Memory Scale-III), and the Hopkins Verbal Learning Test (HVLT). The HVLT has been commonly used as a word list task and was developed from a different normative sample.

METHOD

Participants

Participants included 35 patients with probable idiopathic PD being considered for DBS at the University of Florida Center for Movement Disorders and Neurorestoration. Diagnoses were made according to UK brain bank criteria by fellowship-trained neurologists specializing in movement disorders (Hughes, Daniel, Kilford, & Lees, 1992). Patients were excluded if they evidenced dementia according to recent Movement Disorder Society recommendations (Dubois et al., 2007). Specifically, participants were excluded if they scored below 26 on the Mini-Mental State Exam and below 136 on the Mattis Dementia Rating Scale. A total of 32 participants self-identified as white, and 3 as Hispanic.

Memory measures

Wechsler Memory Scale-Third Edition (WMS-III; Wechsler, 1997). The normative sample used to develop the WMS-III was a geographically and demographically diverse group of 1250 individuals. Older groups reported relatively lower education than the rest of the sample (Lezak et al., 2004). Two WMS-III subtests were used in this study:

Logical Memory: Two brief stories are presented orally. Patients are asked to freely recall each story immediately after it was read and again 25–35 minutes later.

Word List: This test includes four learning trials of 12 unrelated words, an interference learning trial of 12 new words, and a delayed recall trial of the initial 12 words 25–35 minutes later. Patients are told they would be tested after a delay.

Hopkins Verbal Learning Test (HVLT; Benedict, Schretlen, Groninger, & Brandt, 1998). The normative sample used to develop the Hopkins Verbal Learning Test (HVLT) was a relatively homogenous group of 541 individuals living in the northeastern United States reporting an average of 13.8 years of education (Benedict et al., 1998). This test involves three learning trials for 12 words belonging to three semantic categories and a delayed recall trial 20–25 minutes later. No interference list is presented, and patients are not told they will be tested after a delay.

Other cognitive and motor measures

We created composites representing four cognitive domains: executive functioning, processing speed, working memory, and language. The executive functioning domain comprised Trail Making Test (Part B), Controlled Oral Word

Association Test (COWAT), and the Stroop Test (Color-Word trial). The processing speed domain comprised Trail Making Test (Part A), the Digit Symbol subtest from the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III), and the Stroop Test (Word Reading trial). The working memory domain comprised Digit Span Forward and Backward from the WAIS-III. The language domain comprised the Boston Naming Test (BNT) and the Vocabulary subtest from the WAIS-III.

Executive functioning (i.e., inhibition, set-shifting and directed search), processing speed, working memory and motor functioning have all been associated with fronto-subcortical circuitry. Language measures including confrontation naming and vocabulary have been associated with temporal lobe integrity and were included as a control domain (Lezak et al., 2004).

Procedures

Informed consent was obtained according to university and federal guidelines. Cognitive assessments used for pre-DBS screening were completed over 2 days while patients were on dopaminergic medications. Day 1: patients underwent a standardized neuropsychological assessment that included WMS-III Logical Memory and HVLT. Day 2: patients were administered the WMS-III Word List subtest during a research visit. Motor testing off and on dopaminergic medications was conducted by neurologists using the Unified Parkinson's Disease Rating Scale (UPDRS-III; Fahn, Elton, & Committee, 1987).

Statistical analyses

Using normative data provided by test publishers for each patient's age group, performances on the memory tasks were converted to T-scores (mean = 50, standard deviation = 10). Primary aims were assessed with repeated-measure analyses of variance. Cognitive composite scores were calculated as averaged *z*-scores derived from raw scores on each test within a domain. Williams' *t*-tests were used to evaluate the statistical significance of differences in Pearson correlation magnitudes (Steiger, 1980; Williams, 1959).

RESULTS

Table 1 provides sample characteristics. The participants were predominantly well-educated men with moderate PD severity. Table 2 displays scores on the memory tests. Compared to age peers, patients performed statistically below the normative average (T-score = 50) on three of the four word list variables but not on either story variable.

Memory

Immediate recall scores differed across the three memory tests, $F(2, 66) = 13.909$; $p < .001$; $\eta_p^2 = .30$ (Figure 1). The two word list tasks did not differ (WMS-III, HVLT, $p = .37$). Scores on both were significantly lower than

Table 1 Sample characteristics

	Mean	*SD*
Demographic		
Age	63.0	8.9
Education (years)	14.5	2.9
Sex (M/F)	28/7	
Disease		
Disease duration (months)	136.9	56.2
UPDRS-III "on"	23.4	9.9
UPDRS-III "off"	36.5	13.3
HY (2/2.5/3)*	21/2/3	
LEDD	1102.3	577.4
Emotion		
BDI-II	10.6	6.4
AS	10.3	6.7
STAI state (percentile)	62.4	32.4
STAI trait (percentile)	58.1	32.1
General Cognitive		
MMSE	28.4	1.7
DRS-2	137.8	5.4

SD: Standard deviation; UPDRS-III: Unified Parkinson's Disease Rating Scale, Motor Section; HY: Hoehn & Yahr Stage Scale; LEDD: Levodopa equivalent daily dose; BDI-II: Beck Depression Inventory, 2nd edition; AS: Apathy Scale; STAI: State-Trait Anxiety Inventory; MMSE: Mini Mental State Exam; DRS-2: Dementia Rating Scale, 2nd edition.

*Hoehn & Yahr data were not available for nine patients.

Table 2 Mean age-adjusted T-scores on memory tasks relative to normative sample**

	Mean T-score	*SD*	*t*
HVLT Word List-1			
Immediate	42.3	12.0	−3.717*
Delay	41.6	11.3	−4.349*
WMS-III Word List			
Immediate	43.9	11.8	−3.077*
Delay	52.1	8.3	1.404
WMS-III LM (Stories)			
Immediate	51.6	12.3	0.768
Delay	54.9	10.0	2.929

*$p < .006$ in one-sample *t*-tests (test value = 50).

Normative sample T Score: Mean = 50, $SD = 10$.

WMS-III: Wechsler Memory Scale, 3rd edition; HVLT: Hopkins Verbal Learning Test.

**Normative scores for both the WMS-III and HVLT are based on age (but not sex or education).

scores on Logical Memory ($ps < .001$). *Delayed recall* scores also differed across the three memory tests, $F(1.6, 47.9) = 25.248$; $p < .001$; $\eta_p^2 = .46$. Logical Memory scores were higher than scores on both WMS-III Word List ($p < .01$) and HVLT ($p < .001$). Scores were higher on WMS-III Word list than HVLT ($p < .001$).

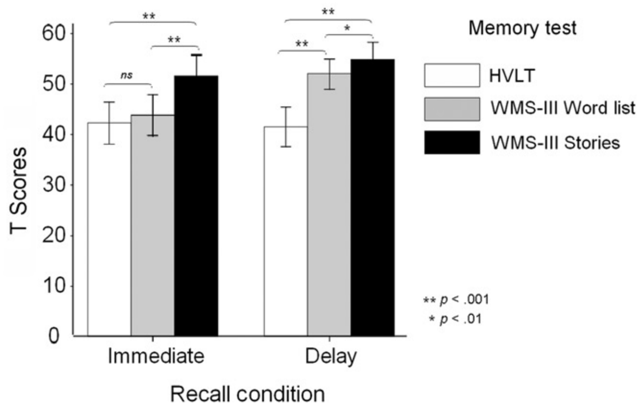

Figure 1 Age-corrected T scores on the three memory tests. HVLT: Hopkins Verbal Learning Test; WMS-III: Wechsler Memory Test, 3rd edition

Table 3. Pearson correlations between memory measures, cognitive composites, and motor severity

	Processing Speed	Working Memory	Executive Functioning	Language	UPDRS-III On
HVLT					
Immediate	.398*	.337‡	.175	.305	−.144
Delay	.502**	.058	.387*	.282	−.415**
WMS-III Word List					
Immediate	.384*	.553**	.269	.549**	−.266
Delay	.378*	.356*	.411*	.323	−.126
WMS-III Logical Memory					
Immediate	.072	.227	.174	.370*	−.162
Delay	.226	.253	.280	.290	−.234
UPDRS-III On	−.351‡	−.047	−.386‡	−.072	

$^{**}p < .01$. $^{*}p < .05$. ‡$p < .1$. WMS-III: Wechsler Memory Scale, 3rd edition; HVLT: Hopkins Verbal Learning Test; UPDRS-III: Unified Parkinson's Disease Rating Scale, Motor Portion.

Other cognitive domains

Table 3 displays correlations between the memory tasks and specific cognitive domains. Williams' *t*-tests revealed that several correlations between composites reflecting frontal-related cognition (processing speed, working memory, executive functioning) and word list variables were statistically stronger than correlations between these composites and corresponding story variables.

Processing speed: Correlations with immediate word list recall (HVLT, WMS-III) were greater than those with immediate story recall (ps $< .05$). There was a trend for a similar pattern involving delayed recall (HVLT vs Logical Memory; $t(32) = 1.40$; $p = .09$). *Working memory*: A greater correlation occurred with WMS-III Word List than with Logical Memory for immediate recall, $t(32) = 2.74$; $p < .01$. *Executive functioning*: The executive functioning composite correlated significantly with delayed recall scores for both word list tasks but not with either of the story memory variables. However, none of these pairs of correlations was statistically different ($p\text{s} > .05$).

Motor severity

Greater motor severity was associated with worse performance on HVLT Delayed. Medium-sized, non-significant relationships between UPDRS-III and Executive Functioning and Processing Speed were noted, with greater motor severity associated with worse performance (see Table 3).

DISCUSSION

These findings support the view that non-demented individuals with PD exhibit better episodic memory for stories than for word lists. We found that both immediate and delayed memory scores were significantly higher for a story task than a co-normed word list task. Similar findings have been demonstrated with non-demented patients with PD using non-standard measurement instruments (Hartikainen et al., 1993). This study is the first to document this verbal memory performance discrepancy in PD using co-normed measures. Results are in line with current theoretical conceptualizations of mesial temporal versus subcortical memory difficulties, with the former associated with encoding and storage deficits and the latter associated with higher-order encoding and retrieval deficits (Cummings, 1990; Panegyres, 2004; Perry & Hodges, 1996).

We did not replicate the findings of Beatty et al. (2003), who reported similar story and word list recall among patients with PD on co-normed measures from the RBANS. This discrepancy may relate to psychometric properties of the instruments. Specifically, a recent study examining the RBANS in a sample of non-demented patients with PD reported low reliability and validity and failed to replicate its proposed factor structure in this population (Yang et al., 2009).

Our findings support an association between fronto-subcortically mediated cognition and word list learning. Executive functioning (i.e., Trailmaking, Part B, Stroop Color-Word, verbal fluency), working memory, and processing speed are often reduced in PD (Cooper et al., 1992; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Gabrieli, Singh, Stebbins, & Goetz, 1996; Lees & Smith, 1983; Stebbins et al., 1994). Composite scores representing these domains were more consistently associated with word list recall than story recall. Further support for the hypothesis that fronto-subcortical dysfunction underlies poorer word list performance was provided by a medium-sized (Cohen, 1988) correlation between motor severity and a word list variable (HVLT Delayed). Motor severity was not associated with either story variable.

The results also highlight an influence of normative data on the size of discrepancies between story and word list recall. Specifically, WMS-III Word List scores were higher than HVLT scores. Clinicians should be cognizant of normative sample differences when drawing conclusions about the magnitude of impairments.

A relevant limitation of this study is that the order of the two word list tasks was not counterbalanced due to our unwillingness to alter standard clinical procedures during the DBS candidacy evaluation. As a result, all patients received the HVLT before the WMS-III Word List. However, we believe the impact is minimal because practice effects for word list learning tasks with different memoranda are small (Wilson, Watson, Baddeley, Emslie, & Evans, 2000). Also, our finding of *better* performance on WMS-III Logical Memory than WMS-III Word List, despite a potential practice effect that would presumably *reduce* that difference, only strengthens our conclusions.

Another potential factor that could influence recall of these different memoranda that was not explored in this study relates to the various attributes of the words used in the various tests, including frequency, length, and concreteness. While systematic differences in these attributes between the tests may not be apparent in corrected scores, it is possible that patients with PD may be more susceptible to increasing difficulty on one or more of these dimensions. Of note, there are word list tests that have been created with this issue in mind. Specifically, the Philadelphia Repeatable Verbal Learning Test includes words matched on frequency for category based on category exemplars identified using an older adult sample, and the California Verbal Learning Test is rank-based for frequency in the English language. Future studies should explore the contribution of word attributes to the detectability of impairments. Researchers and clinicians comparing word list and story tasks should be mindful of issues related to the unique properties of most story tasks, such as the inclusion of non-nouns and proper nouns, and the acceptance of certain alternative phrasings for scoring purposes.

This study highlights the importance of a multi-componential memory battery in the clinical neuropsychological assessment of patients with PD, particularly candidates for DBS. If verbal memory were assessed only with a word list task, patients could be misclassified with memory system impairment (false positive). Conversely, assessment with only a story memory task may result in a failure to identify higher-order memory deficits commonly experienced by individuals with PD (false negative). Such higher-order aspects of memory are more heavily emphasized by word list tasks, which demand that one self-generate organizational strategies. If a patient were impaired on both word list and story memory tasks, a clinician might be more confident in concluding a primary memory impairment. For DBS screenings, clinicians should not dismiss patients with poor word list memory without confirming deficits with a story task. Identification of a primary memory impairment should be brought to the attention of the multidisciplinary team as an example of a contraindication to surgery. Such an impairment might suggest that an additional pathological process is present, such as PD dementia or Alzheimer's disease. Surgical intervention in these patients is considered to pose greater risk for complications and result in less-robust outcomes (Okun et al., 2007). Similar consideration should be used in the assessment of post-DBS cognitive functioning. Compared to medically managed patients with PD, DBS patients are more likely to experience reliable declines in word list recall than in story recall (Mikos, Zahodne, Okun, Foote, & Bowers, 2010).

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