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Theory of Cognitive Aging in Parkinson Disease

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Abstract

Objective: While cognitive deficits are well documented in Parkinson disease (PD), identifying a theoretical framework in which to interpret these findings has been less studied. Theories of cognitive aging suggest that processing speed is likely a critical factor in normal cognitive function that explains a large portion of the inter-individual variance associated with age-related cognitive decline. We tested the hypotheses that measures of processing speed underlie deficits in working memory and inhibition in PD as well.

Methods: We measured cognitive function in a group of 77 medicated individuals with PD without dementia and 54 controls. Participants completed a battery of behavioral tests, including measures of processing speed (SDMT), working memory (Digit Span Backward), inhibition (DKEFS Color Word Interference), attention (Digit Span Forward) and depression (GDS). We compared performance across groups using analysis of variance. In addition, we used mediation analysis to examine the effect of processing speed on the relationship between age and both working memory and inhibition.

Results: Groups were similar for age, years of education, MMSE score and premorbid IQ. Performance on measures of processing speed and inhibition were significantly worse in the PD than control group. Furthermore, we found that processing speed mediated the relationship between age and inhibition in the PD and control groups. However, the decrease in working memory performance in the PD group was a statistical trend and the relationship between working memory and age was not mediated by processing speed in either group.

Conclusion: The pattern of cognitive aging consistent with the processing speed theory may be exacerbated in PD. However, while the working memory measure was correlated with processing speed, it was not correlated with age. The processing speed theory of cognitive decline provides a framework for hypothesis testing about the complex concept of bradyphrenia.

Keywords: Processing speed; Working memory; Inhibition; Executive function; Mediation analysis

Introduction

Parkinson disease (PD) is an age-related neurodegenerative disorder that can result in a variety of cognitive deficits including impairments in processing speed [1-3], working memory [4,5] and inhibition [6,7]. In addition, elderly people with PD are at higher risk for loss of independence due to cognitive impairment [8]. In fact, there is evidence that cognitive slowing occurs independent of motor slowing in PD. For example, Sawamoto et al. [9] designed a test to specifically measure processing speed, and accuracy was used as the outcome measure. Results showed decreased performance in PD at increased speeds of stimulus presentation. However, while cognitive deficits have been consistently observed in PD, identifying a theoretical framework in which to interpret these findings has been less extensively studied.

Cognitive decline across the life span has been most successfully characterized using a multivariate model [10,11]. Age-related changes in cognitive performance have been linked to a reduction in cognitive resources. In a review of theoretical models of aging and cognition, Brown and Park [12] describe three cognitive resources that contribute to performance, specifically processing speed, working memory and inhibition. The speed at which the brain processes information has been shown to decrease with age [13,14]. For example, Deary and Ritchie [15] found decreased speed of processing for the Digit Symbol test, and experimental measures (tests of simple and choice reaction time) as well as a psychophysical measure of efficiency of early stage perceptual processing in two large groups of 70 and 83 year old participants. Furthermore, longitudinal studies indicate that decreased processing speed is associated with changes in complex cognitive abilities as we age [16-19]. For example, Ritchie et al. [20] used a visual inspection task with minimal motor requirements to measure processing speed three times over six years in a population of 70 year old participants. Results revealed a strong correlation between the slope of change for intelligence measures and processing speed measures. In fact, individual differences in speed of processing measures have been shown to account for the majority of age-related variance in measures of diverse and complex function, including working memory and inhibition (see [13] for review).Thus it has been proposed that processing speed sub serves a range of other cognitive functions, making it an explanatory construct in age-related cognitive decline [13,21-23].

Previous studies of working memory, or the amount of information that can be simultaneously stored in a temporary buffer for manipulation

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during processing [24], support this hypothesis. Working memory has been shown to decrease with age (e.g. [25-27]).Interestingly, Salthouse and Babcock [28] investigated age-related differences of three components of working memory: processing efficiency, storage capacity and coordination effectiveness. Performance declined with increased age; however the impact of age was mediated by processing speed of simple operations. Furthermore, Parkin and Java [29] found that performance on the Symbol Digit Substitution test was a strong predictor of memory performance. Thus there is ample support for the hypothesis that processing speed sub serves higher order cognitive function from the study of working memory.

Similarly, age-related decline in the performance of measures of inhibition have been associated with processing speed as well. Inhibition, or the ability to suppress attention to irrelevant or off goal-path thoughts (e.g. [30]), is important for the efficient operation of selective attention and working memory, limiting the amount of information into working memory that is not along the goal-path [31]. Inhibition is also important during parallel processing, when deficits may result in cross talk, and during language comprehension, suppressing irrelevant meanings of words of phrases [31]. Thus deficits in inhibition increase the contents of working memory with irrelevant information, resulting in competition at retrieval, which leads to poorer memory performance, increased distractibility, increased errors and increased response time. Adolfsdottir et al. [32] recently measured inhibition and switching in a longitudinal study of 123 subjects, with three samples over six years. They found that age contributed to longitudinal models of inhibition and switching as did processing speed, while measures of education and retest effects did not. Similarly, Marco et al. [33] examined inhibition, cognitive flexibility and processing speed in a group of people with agenesis of the corpus callosum and matched controls. They found that, while performance on timed measures of inhibition and flexibility were impaired, group differences could be largely explained by performance on measures of processing speed. Thus there is strong evidence that reductions in processing speed significantly contribute to the decline in measures of working memory and inhibition in healthy aging [13].

There is evidence from the study of disease supporting the processing speed theory of cognitive function, including conditions such as agenesis of the corpus callosum [33], aging and alcoholism [34] and rheumatoid arthritis [35]. However, the relationship between deficits in processing speed, working memory and inhibition in PD has not been extensively examined. In fact, it has been argued that the concept of parkinsonian bradyphrenia has not been clearly defined and should be analyzed as slowness of different cognitive processes (for review see [36]). One possible theoretical framework for understanding the complex phenomenon of bradyphrenia in PD is the processing speed theory of cognitive aging. To that end we tested the hypothesis that, as in healthy aging, measures of processing speed underlie deficits in working memory and inhibition in PD.

Methods

Participants

For this study, a group of 77 individuals with PD (48 males, 29 females) and 54 individuals without PD (29 males, 25 females) were recruited from movement disorder clinics, senior centers, support groups, and veteran's organizations. The participants were all between the ages of 54 and 80 with English as a first language. The participants with PD were all diagnosed by a movement disorders neurologist and had history of good clinical response to levodopa and/or dopamine agonist treatment. The exclusion criteria included traumatic head or spine injury, brain tumor, stroke and history of drug abuse, significant symptoms of depression (Geriatric Depression Scale score>20) and Mini Mental State Exam score less than 20. All participants with PD were being treated using dopamine replacement therapy including levodopa with carbidopa, dopamine agonists and/ or COMT inhibitors. All participants provided written, informed consent and the study was approved by an institutional review board.

Instruments

Subjects performed tests in a private room and testing lasted 2-4 h. The test battery was presented in a pseudorandomized order across participants. Participants with PD were tested during their best ON medication state (based on patient self-report), after their morning dose of medication.

Descriptive measures

- Epworth Sleepiness Scale (ESS; [37]): A short questionnaire about daytime sleepiness.
- The Frontal Lobe Personality Scale (FLOPS; [38]), now known as the Frontal Systems Behavior Scale (FrSBe), is a 46-item questionnaire designed to assess behavioral disturbances associated with damage to frontal lobe regions of the brain. Subjects are instructed to answer each item from two time points: "Before Injury" and "At Present". There are three subscales which provide measures for Apathy, Disinhibition and Executive Function [39,40]. We used the "at present" Apathy scale for further analysis.
- Geriatric Depression Scale (GDS; [41]): A measure of depressive symptoms in the form of a 30-item self-report.
- Hoehn and Yahr scale (H&Y; [42]): A measure of PD severity.
- Mini-Mental State Examination (MMSE; [43]): An estimate of general cognitive function based on orientation, registration, attention and calculation, recall and language.
- National Adult Reading Test, Revised (NART-R; [44]) is a measure of semantic memory commonly used to estimate premorbid intellectual function. The participant is asked to pronounce a series of 61 irregularly spelled words.
- The Unified Parkinson 's disease Rating Scale (UPDRS; [45]) is a clinical scale used to evaluate PD severity in multiple domains. UPDRS Part I measures mentation, behavior and mood. UPDRS Part II measures activities of daily living. UPDRS Part III measures motor performance. USDRS Part IV measures complications of therapy. A nurse practitioner trained in the use of the UPDRS administered the UPDRS interview and evaluation.

Neuropsychological tests

- Delis-Kaplan Executive Function System (D-KEFS; [46]) contains subtests used to measure executive functions including inhibition and switching based on a Stroop task (Color-Word Interference). We subtracted the completion time for the Word Naming condition from the completion time for the Inhibition condition to measure inhibition.
- WAIS-III Digit Span [47] is a measure of forward and reverse digit span using progressively longer numerical sequences to assess simple auditory attention and working memory, respectively. Digit span backward was recently validated as a diagnostic measure of cognitive impairment in PD [48].

- Symbol Digit Modalities Test (SDMT, Oral Version [49]) is a psychometric measure of processing speed and visual tracking. The participant is presented with a coding key containing nine numbers, each corresponding to a different symbol. Below the key, a series of symbols is also presented, and the participant must state the number corresponding to the symbols in order as quickly as possible. Score is the number of items successfully completed in 90 s.

Data Analysis

All statistical analysis was performed using SPSS (version 23; http://www.ibm.com/analytics/us/en/technology/spss/). Between groups comparisons were made using Multivariate Analysis of Variance (MANOVA). Pearson correlation ($p<0.05$) was used to evaluate the linear relationship between processing speed and demographic, cognitive, motor, mood and disease severity measures for participants with PD.

We also performed two mediation analyses to evaluate a presumed mediation effect of processing speed and mood variables on the relationship between age and 1) working memory and 2) inhibition (see http://davidakenny.net/cm/mediate.htm for an overview). We followed the four steps described by Baron and Kenny [50] and others [51,52] to establish mediation. We used hierarchical regression to show that either working memory or inhibition score were correlated with age to establish that there was an effect to be mediated. Second, we used a similar regression model to determine that age was correlated with the possible mediating variables (processing speed, depression and apathy). Third, we determined if the mediator affected the outcome variable (either working memory or inhibition measures) by entering both age and the mediators into a regression model with working memory or inhibition measures as the outcome variable. Further, we used this same model to determine the degree of mediation (complete or partial).The amount of mediation is called the indirect effect or the reduction of the effect of the causal variable (age) on the outcome (working memory or inhibition) due to the mediators. We used bootstrapping to test the indirect effect [53,54]. We resampled with replacement 5000 times to determine a confidence interval and p value. We used the PROCESS SPSS macro provided by Hayes and Preacher to perform this analysis [55].

Results

Group differences

Demographic and descriptive data: The PD and control groups were not significantly different in age ($F(1,129)=3.332$, $p=0.070$), years of education ($F(1,129)=2.169$, $p=0.143$), daytime sleepiness ($F(1,129)=3.545$, $p=0.062$), premorbid IQ ($F(1,129)=0.099$, $p=0.753$) and MMSE score ($F(1,129)=0.459$, $p=0.499$; Table 1). However, the PD group indicated greater symptoms of depression (GDS; $F(1,129)=12.277$, $p<0.001$) and apathy (FLOPS; $F(1,129)=9.159$, $p=0.003$) than the control group. Note that PD participants were at a relatively early disease stage (H&Y scale score, Table 2). Dopamine equivalents are listed in Table 2.

Cognitive measures

For the measure of processing speed, the PD group correctly completed fewer items in 90 s compared to the control group, with a mean difference of 8.3 items (SDMT $F(1, 129)=18.648$, $p<0.001$, Table 3). 75% of PD participants (58/77) had processing speed scores below mean control group performance. For the measure of working memory, while there was no statistically significant difference between groups (Digit Span Backward; $F(1,129)=3.818$, $p=0.053$; Table 3), there was a trend toward significance. In addition, the PD group performed the inhibition task more slowly than the control group, with a mean difference of 8.9 s (DKEFS CWI Inhibition minus Word Reading; $F(1,129)=7.785$, $p=0.006$). 57% of PD participants (44/77) took longer to complete the inhibition task than mean control group performance. There were no differences between groups for the measure of simple auditory attention (Digit Span Forward; $F(1, 129)=0.266$, $p=0.607$).

Regression analyses

For all PD participants, processing speed (SDMT) was correlated with the variables associated with cognitive aging theory (age, working memory and inhibition; Figure 1) and multiple additional variables, including measures of daytime sleepiness (ESS), depression (GDS), apathy (FLOPS), MMSE score and disease severity (UPDRS score; Tables 1 and 2). Decreased speed of processing was associated with

	N	Age (years)	Education (years)	ESS	NART-R	GDS*	FLOPS Apathy	MMSE
Control	54 (F=25)	66.0 (6.0)	16.6 (3.1)	7.0 (3.3)	113.6 (7.6)	2.8 (3.5)	24.2 (7.5)	28.8 (1.2)
PD	77 (F=29)	68.0 (6.3)	15.8 (2.8)	8.4 (4.8)	114.1 (8.5)	5.5 (5.0)	28.3 (7.6)	28.6 (1.6)

Daytime sleepiness (ESS: Epworth Sleepiness Scale), Measures of premorbid IQ (NART-R: National Adult Reading Test - Revised), Depression (GDS: Geriatric Depression Scale), apathy (FLOPS Apathy) and mental state (MMSE: Mini-Mental Status Exam)

* CO vs. PD $p<0.05$

Table 1: Demographic measures.

	Dopamine Equivalent	H&Y (median)	UPDRS Total
PD	612.2 (490.8)	2	38.2 (19.8)

Measures of disease severity (UPDRS: Unified Parkinson's Disease Rating Scale; H&Y: Hoehn and Yahr Scale), Measures of manual dexterity (FDT: Functional Dexterity Test) and mobility (mEFAP: Modified Emory Functional Ambulation Profile)

Table 2: PD specific measures.

	SDMT* (items)	Digit Span Backward° (items)	DKEFS CWI Inhibition* (s)	Digit Span Forward (items)
Control	52.4 (8.0)	7.2 (2.3)	37.7 (10.5)	10.3 (2.3)
PD	44.1 (12.6)	6.6 (1.7)	46.6 (21.6)	10.06 (2.0)

Measure of processing speed (SDMT: Symbol Digit Modalities Test), Working memory (Digit Span Backwards), Inhibition (DKEFS Color Word Interference Condition 3: Inhibition minus DKEFS Color Word Interference Condition 2: Word Reading) and attention (Digit Span Forward)

* CO vs. PD $p<0.05$

° CO vs. PD $p=0.053$

Table 3: Cognitive measures.

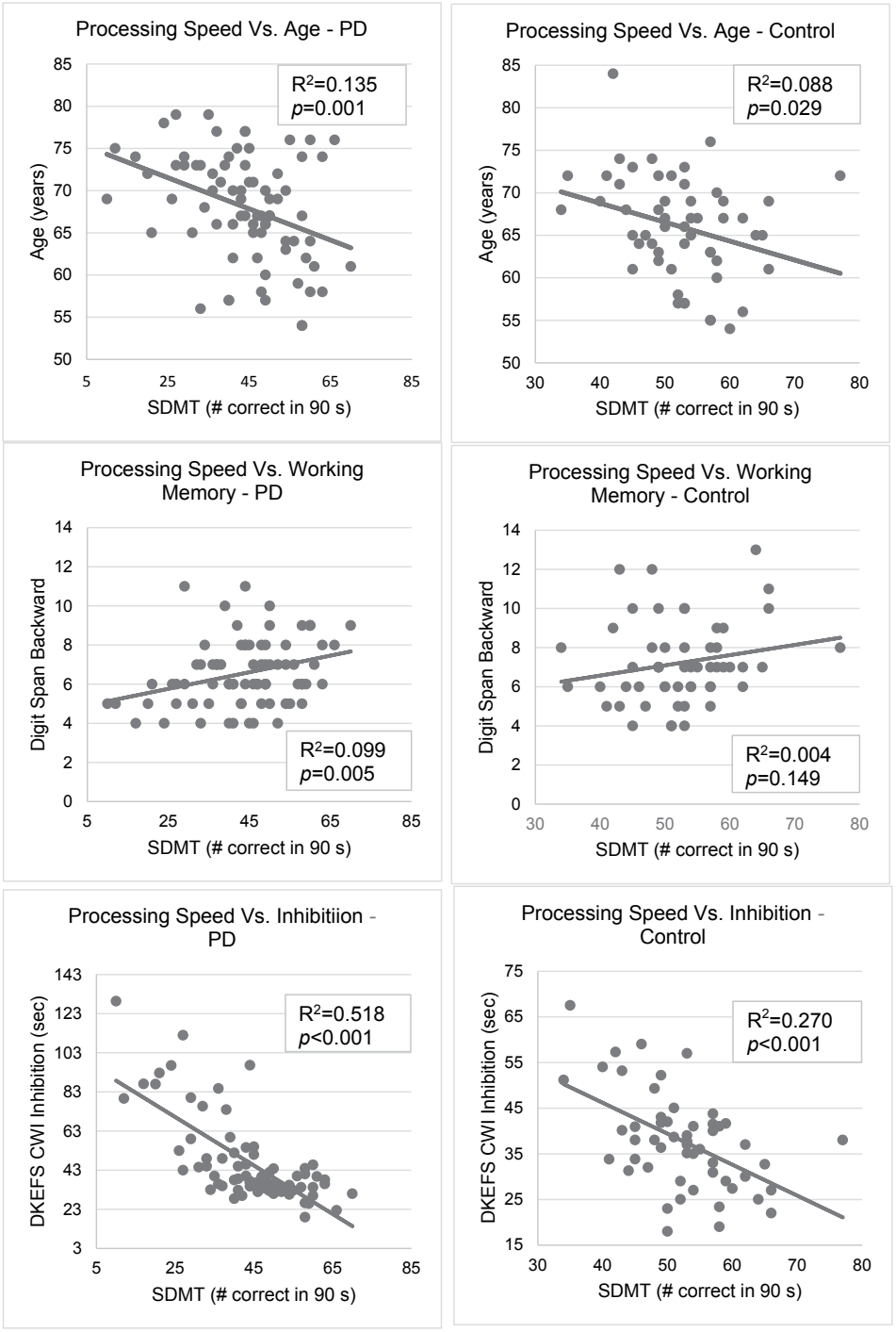

Figure 1: Processing speed scatterplots.

Processing speed (SDMT, total number correct in 90 seconds), working memory (Digit Span Backward) and DKEFS Inhibition is calculated from DKEFS CWI Condition 3: Inhibition minus DKEFS CWI Condition 2: Word Reading

poorer performance on measures of working memory and inhibition, increased age and increased reported symptoms of depression and apathy.

Linear regression analysis was used to investigate the hypothesis that processing speed and mood variables mediate the effect of age on executive function. For the outcome variable working memory, there was no significant relationship between age and working memory (r=0.054, p=0.64) in our sample (b=0.015, SE=0.031, p>0.05), thus the mediation evaluation criteria described in the data analysis section were not met. However, for the outcome measure inhibition, the evaluation criteria were met. First, results indicated that age was a significant predictor of processing speed (b=-0.731, SE=0.213, p<0.05). Second,

processing speed was a significant predictor of inhibition (b=-1.239, SE=0.138, p<0.05). Finally, age was no longer a significant predictor of inhibition after controlling for the mediator, processing speed (b=0.348, SE=0.294, p>0.05), which is consistent with full mediation. Approximately 53% of the variance in inhibition was accounted for by the predictor processing speed (R^2=0.527). The indirect effect was tested using a bootstrap estimation approach with 5000 samples [54]. These results indicate that the indirect coefficient was significant (b=0.859, SE=0.306, 95% CI=0.360-1.588). Greater age was associated with an approximately 0.86 s. longer time to complete the inhibition task in the PD group. While mood variables were correlated with inhibition, the criteria for mediation for depression (b=-0.106, SE=0.060, p>0.05) and apathy (b=0.028, SE=0.101, p>0.05) were not met because these variables were not correlated with age (GDS r=0.083, p=0.47; Apathy Scale r=0.095, p=0.41).

Similarly, for control subjects, there was no significant relationship between age and working memory in our sample (b=0.066, SE=0.047, p>0.05), thus the evaluation criteria for mediation were not met. However, as in the PD group, for the measure of inhibition the evaluation criteria were met for controls. First, results indicated that age was a significant predictor of processing speed (b=-0.395, SE=0.176, p<0.05). Second, processing speed was a significant predictor of inhibition (b=-0.691, SE=0.197, p<0.05), though again, depression (b=0.214, SE=0.527, p>0.05) and apathy (b=-0.090, SE=0.244, p>0.05) were not. Third, age was no longer a significant predictor of inhibition after controlling for the mediator processing speed (b=0.214, SE=0.276, P>0.05), consistent with full mediation. 20% of the variance in inhibition was accounted for by the predictor processing speed (R2=0.200). Testing the indirect effect using a bootstrap estimation approach with 5000 samples revealed that the indirect coefficient was significant (b=0.253, SE=0.161, 95% CI=0.021-0.627).Greater age was associated with approximately 0.25 s longer time to complete the inhibition task in the control group.

Discussion

We identified processing speed and inhibition deficits in relatively early stage, medicated PD participants. While the PD and control groups were similar for age, years of education, daytime sleepiness, premorbid IQ and global cognitive function (MMSE score), the majority (73%) of PD participants had reduced processing speed compared to controls, while about half the participants showed significantly decreased performance on the measure of inhibition. Participants in the PD group also reported more depression and apathy. As predicted by cognitive aging theory, the relationship between age and inhibition was mediated by processing speed, with a large portion of the variance in inhibition performance (57%) accounted for by processing speed. In contrast, decreased working memory performance in the PD group was a statistical trend and performance was not associated with age. While depression and apathy scores were correlated with processing speed, mood measures did not mediate the relationship between inhibition and age in PD. Furthermore, the pattern of mediation was similar in the PD and control groups.

Processing speed deficits in PD

Our findings on the prevalence of processing speed deficits in PD are in line with existing data. For example, Revonsuo et al. [36] showed that patients with PD were significantly slower than controls in tasks designed to measure processing speed [36]. They used computerized psychophysical measures of central controlled processing involving subtraction time and verification time tasks. They found that in their group of mildly impaired subjects, performance was slower compared to unimpaired PD and control subjects. A more recent study by Jokinen et al. [56] also showed slower processing speed in newly diagnosed, unmedicated PD patients using an experimental, 2-choice reaction time test, a 10-choice reaction time test, and a subtraction test. Pure cognitive processing speed was estimated by calculating the difference between the subtraction task and the 10-choice reaction time task, thus eliminating motor components. Their [18F]fluorodopa PET data revealed a relationship between slowing of processing speed and dopaminergic dysfunction in the basal ganglia-prefrontal cortex circuit. Similarly Yu et al. [57] used multiple psychophysical and experimental measures of processing speed as well as measures of executive functions, memory, visuospatial processing, attention and language in samples of people with PD MCI (mild cognitive impairment) and PDD (Parkinson's disease with dementia) [57]. The PD MCI participants showed impaired processing speed and executive functions. Interestingly, executive function, as measured using the modified Wisconsin Card Sort test was shown to be the most effective discriminator of PD from control participants. However, measures of processing speed also had large effect sizes ([57]; Table 3), indicating that, as in our study, processing speed was a significant component of cognitive dysfunction in PD.

The estimate of prevalence of processing speed deficits in PD MCI, was calculated using stringent criteria [57], and at 22.7% was much lower than the one reported here (77%). However, Yu et al. [57] required scores of 1.5 SD below the normative mean, while in the current study we used the control mean as our cut off for impaired classification. In our study, 35.6% of PD subjects were 1.5 SD below mean control group performance. Similarly, Muslimovic et al. [58] found that newly diagnosed patients performed significantly different from controls on four measures of processing speed including the SDMT [58]. While deficits in executive functions were most common, of participants with PD that exhibited MCI, 60% had a processing speed deficit. As in Yu et al. [57], a strict classification criterion was used (2 SD below norm mean). Interestingly, SDMT score was the primary discriminator between the PD and control groups in a logistic regression using all cognitive measures. Thus while prevalence estimates differ somewhat across studies, Parkinsonian processing speed deficits have been shown consistently across a variety of psychometric, experimental and psychophysical measures.

Processing speed deficits have been hypothesized to account for the majority of age-related variance for a large variety of cognitive tasks, including working memory and inhibition. These deficits may impact cognitive function in two ways [13]. First, cognitive performance declines with decreased speed of processing because relevant operations cannot be successfully completed in a timely manner, which is called the limited time mechanism. If early operations are not completed, then later processes will be less effective. Second, the simultaneity mechanism assumes that decreased processing speed results in reduced performance on complex tasks because the products of early processing are no longer available when later processing occurs, thus reducing the amount of simultaneously available information. Thus the synchronization required for many complex tasks is impaired when processing speed is reduced. A necessary assumption of this theory of cognitive aging is that processing speed is a fundamental part of the cognitive architecture that is common across cognitive domains [13,21-23]. However not all authors agree [59]. Our findings indicate that this process of cognitive decline is exacerbated in PD.

For example, people with PD showed reduced storage capacity and impaired ability to filter, or inhibit irrelevant stimuli. In addition,

impaired performance on the digit span backward test has been reported previously in medicated PD patients [57], which is consistent with our findings. Similarly, Warden et al. [60] found decreased digit span backward performance in cognitive subgroups of PD participants including dementia and mild cognitive impairment [60]. Furthermore, multiple aspects of memory ability, including recall, recognition, and story-free recall have been linked to processing speed (for review see [29]), supporting the hypothesis that processing speed accounts for a large portion of the variability in age-related cognitive decline on performance of a variety of cognitive measures [13]. Indeed, in our data set the measure of processing speed was strongly correlated with working memory performance, while processing speed did not mediate the relationship between working memory and age. However, the failure to meet mediation criteria was due to a lack of correlation between the working memory measure and age, rather than processing speed (Table 4).

Anatomy of processing speed, working memory and inhibition

In PD, the loss of dopamine producing neurons in the substantia nigra and of dopaminergic innervation of the caudate nucleus and consequent change in basal ganglia outflow, specifically in a basal ganglia-thalamocortical loop that includes the prefrontal cortex (PFC), is associated with cognitive decline in PD [61-64]. The correlation of cognitive aging with both processing speed and frontal lobe volume has been shown using high resolution magnetic resonance imaging in healthy subjects [65]. The PFC has also been shown to play a key role in healthy processing speed. For example, a human fMRI study revealed that the success of multitasking training hinged on the speed of processing in PFC [66]. Similarly, Woodward et al. [67] found that decreased processing speed was associated with impaired response selection and abnormal PFC activation in schizophrenia [67]. It is interesting to note that decreased processing speed has also been linked to global deterioration of white matter integrity [68,69].

Spatial working memory deficits in PD have also been associated with frontal lobe function, and patients with frontal lobe lesions have been shown to have specific memory deficits related to the temporal order of events [70] while item memory was unimpaired compared to controls. In PD, deficits in visuospatial working memory [4,5] have been described in participants who underwent medication withdrawal. In addition there is evidence that normal working memory performance in PD is maintained by compensatory mechanisms. Poston and colleagues [71] imaged brain activity during high and low load working memory tasks in controls and PD participants ON and OFF medication. In the OFF state they identified hyperactivation of bilateral putamen and posterior insula. This hyperactivation was decreased with dopamine replacement therapy and correlated with decreased task performance. Thus the relationship between working memory and age may be multifactorial in PD.

Finally, there is a wealth of data on the role of prefrontal cortex in response inhibition from monkey lesion work and more recently from human fMRI studies (see [72] for review). For example, Rubia et al. [73] were able to dissociate response inhibition form error detection using a very difficult no-go task which they were able to manipulate to produce an error rate of 50%. They found that response inhibition correlated with activity in right inferior frontal cortex while error performance correlated with mesial frontopolar and bilateral inferior frontal cortex. Furthermore, Cai et al. [74] compared brain activation during the stop signal task presented in both visual and auditory modalities in health

Edu.	ESS	NART-R	GDS	Apathy	MMSE	DA EQ	UPDRS	SDMT	Digit Span Backward	DKEFS Inhibition	Digit Span Forward		
0.038	0.011	0.069	0.083	0.095	-0.100	-0.056	0.095	-0.368**	0.054	0.353**	0.005	Correlation	Age
0.743	0.923	0.553	0.473	0.412	0.388	0.643	0.409	0.001	0.638	0.002	0.965	Sig.	
	-0.288*	0.425**	-0.152	-0.213	0.293**	-0.110	-0.084	0.187	0.372**	-0.318**	0.245*	Correlation	Edu.
	0.011	0.000	0.188	0.063	0.010	0.359	0.467	0.103	0.001	0.005	0.032	Sig.	
		-0.192	0.408**	0.296**	-0.153	0.186	0.247*	-0.315**	-0.184	0.330**	-0.146	Correlation	ESS
		0.094	0.000	0.009	0.183	0.121	0.031	0.005	0.109	0.003	0.204	Sig.	
			0.031	-0.128	0.228*	-0.016	-0.010	0.094	0.212	-0.227*	0.310**	Correlation	NART-R
			0.787	0.267	0.046	0.897	0.928	0.414	0.064	0.047	0.006	Sig.	
				0.438**	-0.098	0.353**	0.549**	-0.389**	-0.181	0.375**	-0.184	Correlation	GDS
				0.000	0.396	0.003	0.000	0.000	0.115	0.001	0.110	Sig.	
					-0.008	0.280*	0.459**	-0.250*	-0.231*	0.061	-0.224	Correlation	Apathy
					0.944	0.018	0.000	0.029	0.043	0.600	0.050	Sig.	
						-0.081	-0.143	0.403**	0.270*	-0.373**	0.225*	Correlation	MMSE
						0.500	0.215	0.000	0.018	0.001	0.049	Sig.	
							0.299*	-0.146	-0.056	0.061	-0.093	Correlation	DA EQ
							0.011	0.224	0.646	0.612	0.439	Sig.	
								-0.413**	-0.112	0.240*	-0.031	Correlation	UPDRS
								0.000	0.331	0.035	0.789	Sig.	
									0.314**	-0.720**	0.219	Correlation	SDMT
									0.005	0.000	0.056	Sig.	
										-0.192	0.622**	Correlation	Digit Span Backward
										0.095	0.000	Sig.	
											-0.144	Correlation	DKEFS Inhibition
											0.210	Sig.	

Edu: Education; DA EQ: Dopamine Equivalents; conventions as in previous tables; DKEFS Inhibition is calculated from DKEFS CWI Condition 3: Inhibition minus DKEFS CWI Condition 2: Word Reading

Table 4: Pearson correlations.

subjects. They found that activation in inferior frontal gyrus, middle frontal gyrus and basal ganglia was modality independent. In fact, mild cognitive impairment, including deficits in working memory and inhibition, has been linked to frontostriatal dopamine modulated function, while dementia in PD, characterized by impairments in verbal fluency, verbal and visual memory and visuospatial skills, is associated with more widespread, posterior degeneration [75-77].

Bradyphrenia and cognitive aging theory

The term bradyphrenia is frequently used to describe the slowed cognitive functioning [78] or slowness in mental processing that is associated with PD [79]. In 1922 Navile defined bradyphrenia as a chronic loss of initiative and intellectual activity [80]; however, the precise characterization of parkinsonian bradyphrenia has long been a point of debate [36]. For example, in a review of dementia in PD, Potagas and Papageorfiou [81] question the existence of parkinsonian bradyphrenia, suggesting that bradyphrenia has not been consistently differentiated from motor slowing, executive dysfunction or depression. They go on to say that several authors [82] have concluded that bradyphrenia has not been demonstrated in PD. In contrast, others acknowledge the existence of bradyphrenia in PD but debate the precise nature of the syndrome. For example, Rogers et al. [83] emphasize impairment of concentration and apathy as contributors to slowed cognitive processing; however, others cite attention deficits [84] or preserved attention and visuospatial processing [85]. A major stumbling block to the study of cognitive slowing in PD has been the lack of a concise definition of the term bradyphrenia. This problem is not new. In 1993 Revonsuo et al. reviewed the contradictory findings on cognitive slowing and concluded that the concept of bradyphrenia is too vague to be useful for research or cognitive neuropsychology [36]. They went on to suggest that cognitive dysfunction should be studied within a conceptual framework, in this case, using information processing concepts [36]. Our findings suggest that the processing speed theory of cognitive aging may be helpful in defining the term bradyphrenia.

The evaluation of parkinsonian cognitive slowing is confounded by motor slowing, memory and inhibition deficits, depression and apathy and our data confirm that measures of these variables are correlated (Table 4). However, considering some or all of these variables as a single concept such as bradyphrenia muddies our efforts to untangle this knot [86]. Instead, we used a conceptual framework, specifically the processing speed theory of cognitive aging [13], to interpret these relationships. We tested the hypothesis that, as in healthy aging, measures of processing speed underlie deficits in working memory and inhibition in PD. Processing speed and inhibition were clearly decreased in PD, while the results for working memory were somewhat more complicated. Using the processing speed theory of cognitive decline provides a framework for hypothesis testing about this complex concept. Our findings suggest that it may be useful to define bradyphrenia as decreased processing speed, a deficit which contributes to a variety of other cognitive and motor deficits in PD.

Limitations

Quantifying pure processing speed is difficult, as neuropsychological measures often involve memory and motor performance that may decline independently from aging [2,19,87]. This problem is particularly pronounced in PD, where motor deficits are a defining characteristic of the disease. We minimized motor requirements of the symbol digit substitution test by obtaining oral, rather than written responses. Nevertheless, it is difficult to distinguish between the cognitive and motor components of behavior. To that end, Sawamoto et al. [9] devised a mental-operation task that involved serial updating of a series of visual stimuli, with accuracy, rather than response time, over a variety of stimulus frequencies as the outcome variable [9]. Increasing stimulus frequency resulted in more errors in controls but this increase was larger in the group with PD. More recently Sanchez-Ferro et al. [88] used error rate on Part A of the Trail Making Test and found no significant difference in performance between PD and control groups [88]. This relatively simple task may be similar to the low frequency conditions from Sawamoto et al. [9] where control and PD groups showed similar performance. Sanchez-Ferro et al. [88] reported processing speed impairment in only 5.7% of their sample.

Conclusion

Dopamine replacement therapy clearly plays an important role in cognitive function in PD as well. PD is associated with a loss of dopamine producing neurons in the substantia nigra, and dopaminergic processes have been shown to be involved in cognitive functions such as processing speed. A study by Volkow et al. [89] linked deficits in processing speed and executive functions to a decrease in the binding of D2 receptors in the caudate and putamen in healthy subjects. In addition, D2 activity has been shown to be a strong predictor of performance on cognitive tasks that included processing speed in healthy subjects, indicating that changes in the striatal dopamine system are associated with loss in processing speed proficiency [90]. Similarly, Eckart and Bunzeck [91] reported that administering the drug levodopa (dopamine precursor) to healthy subjects accelerated the onset of the EEG novelty signal in the medial temporal lobe. When compared to placebo and the cholinesterase inhibitor galantamine, data indicated that levodopa regulates the speed of processing of new information. In PD, deficits in visuospatial working memory [4,5] have been described in participants who underwent medication withdrawal. Specifically, people with PD showed reduced storage capacity and impaired ability to filter, or inhibit irrelevant stimuli. Furthermore, recently Warden et al. [60] examined digit span backward scores in PD participants ON and OFF medication and found a significant improvement in performance ON medication. Dopamine also plays an important role in inhibition. Jacob et al. [92] antagonized dopamine D1 receptors while recording from neurons in prefrontal cortex of non-human primates during the performance of a delayed-match-to-numerosity task. They found that D1 neuromodulation was important for the encoding of relevant stimuli in the presence of task-irrelevant input. In PD, impairment of both response and cognitive inhibition have also been described (e.g. [93]). Thus the pathophysiology of PD has been linked to cognitive deficits in processing speed and executive functions. While we tested all subjects during their "best ON" period, clearly dopamine replacement status is an important and complex factor in the study of cognitive function.

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