OBJECTIVE COGNITIVE FATIGUE IN PARKINSON'S DISEASE

By

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To my parents and all of the amazing mentors who encouraged me to pursue my dreams.

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LIST OF ABBREVIATIONS

5-HT	Serotonin
CFS	Chronic Fatigue Syndrome
CNS	Central Nervous System
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
FSS	Fatigue Severity Scale
MEG	Magnetoencephalography
MFI	Multidimensional Fatigue Index
MS	Multiple Sclerosis
PD	Parkinson’s Disease
TMS	Transcranial Magnetic Stimulation

Abstract of Thesis Presented to the Graduate School
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Non-motor symptoms in Parkinson's disease (PD) are increasingly recognized as a significant source of suffering and disability. Fatigue in particular affects 33-58% of PD patients and is reported by one third to be their most disabling symptom. Unfortunately, the pathogenesis of fatigue in PD remains unknown and we have no effective treatments. Progress in this area is hampered in part because studies of fatigue in PD rely almost exclusively on subjective questionnaires. While these questionnaires provide valuable epidemiologic information, they are limited in their ability to probe deeper questions regarding pathophysiology. Prior research has demonstrated objective motor fatigue in PD patients but did not find a correlation between this objective fatigue and subjective complaints. While PD patients have deficits in cognitive function, no study to date has used an objective test of mental fatigue to understand the basis of subjective fatigue complaints in PD. The objective of this study was to develop objective tests of cognitive fatigue and to utilize these tests to determine whether PD patients have objective cognitive fatigue. A secondary objective was to determine the relationship between subjective and objective measures of fatigue.

We recruited seven healthy subjects and six PD patients. Subjects completed two three hour sessions on separate days of continuous performance tasks. One session involved a

continuous Stroop performance task to test executive function and the other session involved a visual search attention task. Reaction times and accuracy were recorded on a trial by trial basis. Fatigue was quantified as the percent change in performance from the first to the last block of trials.

There was no evidence of significant differences between PD subjects and control subjects in their performance at baseline. PD patients demonstrated significant slowing across all aspects of the Stroop task as well as a significant increase in total errors over the three hour period. PD subjects also demonstrated a significant increase in errors of omission on the attentional task. Healthy controls only demonstrated significant changes in their speed of performance on incongruous color trials of the Stroop and false positive errors on the working memory trials of the attentional task. Several objective performance measures correlated with subjective fatigue measures.

PD subjects showed greater cognitive fatigue than healthy controls. While this may be a source of disability in this patient population, further studies are needed to determine how this fatigue correlates with quality of life and disability.

CHAPTER 1
INTRODUCTION

Significance of Fatigue in Parkinson's Disease

PD is the second most common neurodegenerative disease, with over 4.1million affected individuals worldwide, and an expected doubling of this figure in the next 20 years due to the aging of our population (Dorsey, 2007). Although PD is traditionally thought of as an extra-pyramidal motor disorder, more recent research highlights the prevalence and impact of non-motor symptoms, including cognitive dysfunction, depression and fatigue (Chaudhuri et al., 2006). Fatigue was noted by James Parkinson (1817) in his original description of the disorder but it was not until 1993 that studies began describing its prevalence, progression and impact (Freidman and Friedman, 1993). All studies reported to date demonstrate a higher prevalence of fatigue in PD patients versus age-matched controls with a prevalence of around 40% (range 33 to 58%) compared to the general population prevalence of 10 to 25% (Freidman et al., 2007). Studies assessing the impact of fatigue in PD further report that over half of PD patients feel that fatigue is one of their most severe and disabling symptoms (van Hilten et al., 1993, Friedman and Friedman, 1993). Despite the clear impact of fatigue in PD, we do not understand its pathophysiology and do not have any adequate treatments (Ferrari et al., 2006).

Defining Fatigue

Fatigue is a normal phenomenon that we have all experienced and includes both subjective sensations and an objective deterioration in performance. While many authors use their own definition of fatigue, these definitions frequently confound fatigue with other related phenomena (particularly sleepiness) or are too vague to allow practical measurement. Ryan (1947) defines two distinct components of fatigue:

1. Feelings of tiredness, weariness, or exhaustion (subjective fatigue).
2. A reduction in the capacity to perform a task as a result of continuous performance on the same task (objective fatigue).

Objective fatigue, by definition, always affects performance on the task used to induce fatigue and may affect performance on other tasks, particularly if both tasks stress shared physiological substrates. Alternatively, fatiguing performance on one task may have no impact, or even enhance performance, on a subsequent unrelated task (Davranche and Audiffren, 2004). Like many complex constructs, studies of the phenomenology and physiology of fatigue in healthy adults and animal models reveal the utility of focusing our research efforts on understanding the components of fatigue rather than treating fatigue as a single entity.

Components of Fatigue

Although many branches of science have approached the problem of fatigue, few authors have attempted to bring these findings together in a single model. The model proposed in Figure 1-1 presents a general framework for organizing the fatigue literature and applying it to clinical populations. These components are not meant to be mutually exclusive. In fact, they may all be present at one time in an individual and may interact with each other. However, under certain task conditions and/or pathological states a specific component of fatigue can dominate a subject's perceptions and/or performance. Once identified, our understanding of this component can direct further investigations into the pathophysiology underlying task failure and perceived fatigue in patient populations. Similarly, by isolating specific components we may be able to develop better directed treatments.

Homeostatic Subjective Fatigue

Homeostatic subjective fatigue serves a regulative function in protecting the organism from the damaging effects of prolonged activity and energetic catastrophe. Several lines of research

have suggested that structures within the CNS act as a “central governor” to prevent total energy depletion (Noakes et al., 2004). While the signaling mechanisms and CNS targets are incompletely known, several potential pathways have been identified including inflammatory (IL-6), metabolic (cerebral glycogen depletion) and neuronal (increases of serotonin and decreases of dopamine) (Davis and Bailey, 1997). Animal models have suggested that the hypothalamus is at least one of the CNS structures responsible for homeostatic fatigue that is mediated by 5-HT (Soares, 2007). While fatigue has been noted with lesions of the hypothalamus, it is difficult to attribute fatigue directly to these lesions as these patients frequently have additional CNS lesions and often have associated hypersomnolence, circadian rhythm disturbances and endocrine disturbances (Chaudhuri and Behan, 2004). While PD may affect the hypothalamus (Braak and Braak, 2000), it is unknown if these lesions are associated with fatigue in this population.

Psychological Subjective Fatigue

Psychological subjective fatigue is not directly related to homeostatic mechanisms but rather reflects psychological factors including performance expectations, motivation, arousal and mood. The strong association of depression and fatigue in PD supports the role of mood as a contributor to subjective fatigue (Alves et al., 2004). Experiments in healthy subjects have also shown that performance and sensations of effort may be altered by giving false feedback regarding temporal duration or force output (Wells et al., 1993). Since PD subjects have disturbances of temporal estimation (Pastor et al., 1993) and magnitude estimation, these misperceptions may create a heightened sense of effort, similar to normal subjects under false feedback.

Peripheral Fatigue

Peripheral fatigue refers to decrements of task performance on the basis of dysfunction at the level of muscle or peripheral nerves. This fatigue is typically brought on by physically demanding motor tasks involving frequent or prolonged muscle contractions. Peripheral fatigue is the predominant form of fatigue in many diseases of the peripheral nervous system and muscle including myasthenia gravis and glycogen storage disorders (Chaudhuri and Behan, 2004). Many physiological and cellular mechanisms of peripheral fatigue have been proposed on the basis of direct electrical stimulations of nerve and muscle (Westerblad and Allen, 2004). However, the task of distinguishing peripheral from central fatigue can be quite challenging in a living organism under physiologic conditions (Gandevia, 2001). Although decrements in cognitive tasks are almost always due to central causes, decrements in motor tasks are rarely due to isolated peripheral dysfunction. For instance, Hunter et al. (2005) demonstrated that subjects maintaining a static arm contraction had different rates of fatigue depending on whether they were given feedback based on their force output or arm position, despite having identical physical loads. Although PD patients demonstrate objective motor fatigue, these deficits are presumed to arise from central causes (Lou et al., 2003a).

Central Fatigue

Central fatigue refers to objective decrements in either cognitive or motor task performance due to changes within the central nervous system. The choice of task is a critical tool in understanding fatigue as subtle changes in task demands can have large effects on performance (Barry and Enoka, 2007). These effects must be mediated by differences in the demands placed on specific CNS networks necessary for maintaining optimal performance. Neurological lesions within these networks may increase the vulnerability of these systems to fatigue induced stress. For example, aging's effects on cognitive function appear to lead to accelerated rates of

performance decline in tasks demanding divided attention but not on tasks demanding only sustained attention (Kallus et al., 2005). This may be due to the selective effects of aging on the central nervous system which affect the cognitive systems that mediate executive control (Gazzaley and D'Esposito, 2007). Studies of cognitive fatigue in MS have also suggested that central fatigue may be domain specific (Krupp and Elkins, 2000). No studies to date have examined central fatigue in PD using cognitive tasks. Unlike peripheral fatigue, the mechanisms underlying central fatigue are unknown but may generally be divided into neurophysiological and energetic explanations (Dalsgaard and Secher, 2007). These explanations are not mutually exclusive, and may in fact be complementary, as energetic deficits can affect neuronal function (Takata and Okada, 1995). Whether central fatigue in PD is caused by alterations of global energy expenditure (Levi et al., 1990) or mitochondrial dysfunction (Martin, 2006) is unknown but plausible given the high rates of chronic fatigue in patients with mitochondrial disorders (Fattal et al., 2007).

Pathological Fatigue

In healthy adults, fatigue is a transient phenomenon brought about by prolonged exertion which diminishes with rest and does not typically interfere with daily functioning. This is in contradistinction to pathological fatigue which is frequently chronic, brought on by minimal exertion, does not fully improve with rest and causes significant disability (Fukuda et al., 1994). While pathological fatigue may arise in otherwise healthy individuals, pathological fatigue is frequently associated with disease states, particularly neurological disorders (Chaudhuri and Behan, 2004). Fatigue associated with diseases may arise from a secondary cause. For example, fatigue in cancer patients is frequently secondary to anemia and responds to anemia treatment (Harper and Littlewood, 2005). Alternatively, fatigue may be a primary manifestation of a disease, such as the classical motor decrements seen with prolonged exertion in myasthenia

gravis (Keesey, 2004). This fatigue is due to pathological changes at the neuromuscular junction and responds to treatment of the primary disease process.

Possible secondary causes of fatigue in individuals with PD include sleep disorders, medications and depression (Yoshii, 2006). However, population based studies in PD demonstrate that sleep disorders (Shulman et al., 2001) and daytime somnolence (van Hilten et al., 2006) do not account for fatigue in the majority of PD subjects. This highlights the importance of distinguishing between sleepiness and fatigue in subjective ratings (Shen et al., 2006). Similarly, studies of the most common medications used in PD show no effect or even slight improvements in fatigue (Abe et al., 2001), despite reports of excessive daytime somnolence associated with these same medications (Razmy et al., 2004). While several studies demonstrate a correlation between measures of depression and fatigue (Alves et al., 2004), this may in part be due to methodological issues in the overlap of symptoms on fatigue and depression inventories including the DSM-IV. Even in studies demonstrating this correlation, nearly half of PD patients without depression still report fatigue (Alves et al. 2004). Similarly, up to a one half of patients with major depression still experience fatigue after their depression is successfully treated (Fava et al., 1994). In addition, fatigue appears to be independent of motor symptoms (Shulman et al., 2001) and disease severity (Friedman and Friedman, 1993). Longitudinal studies also suggest that PD patients with fatigue continue to have fatigue, while those without fatigue rarely develop fatigue (Friedman and Friedman, 2001). Taken as a whole, these studies show that the majority of PD patients must have either primary fatigue or fatigue secondary to an as yet unidentified factor.

Limitations of Self-Report Measures of Subjective Fatigue

Although many self-reported symptoms, including depression, pain and fatigue, are undoubtedly real sources of suffering and disability for patients they present a challenge to study

through the scientific method. While some advances have been made possible through improvements of subjective scales, there is a great scientific need for the development of objective correlates of these symptoms. This includes physiological markers, biological models, neuropsychological tests and procedures for reproducing patient's symptoms. This proposal will address this need in the domain of PD fatigue by determining the objective neuropsychological correlates of subjective fatigue, assessing the use of prolonged cognitive performance as an objective measure and procedure for inducing fatigue, and utilizing electrophysiological techniques to determine physiological markers and possible mechanisms of PD fatigue.

Our knowledge of PD fatigue comes almost exclusively from studies based on subjective scales (Friedman et al., 2007). While the data generated by these scales raises interesting epidemiological questions, one must be cautious in interpreting the results of these studies. A related limitation is the effect that cognitive deficits, mood and personality may have on the manner in which subjects interpret and score test items independently of the underlying constructs these scales are purporting to measure. Literature in several domains demonstrate that self-report data may be prone to bias, including memories of specific incidences (Kuiken, 1991), symptom frequency (Burton and Blair, 1991) and reports of actual deficits (Stone et al., 2000). For instance, self-reports of cognitive dysfunction in subjects taking antiepileptic drugs correlate more with indices of anxiety and depression than they do with the objective neuropsychological test scores (Elixhauser et al., 1999). In MS patients, subjective ratings of fatigue correlated with self-reports of neuropsychological impairments but did not correlate with objective decrements in cognitive performance (Beatty et al., 2003).

A further issue is the lack of external validation of these scales. As discussed above, subjective fatigue may reflect objective fatigue, but it may also exist independently of objective

findings due to psychological factors or changes in the generation or perception of homeostatic feedback. Determining the relation of subjective complaints to objective measures of fatigue is thus critical to understanding the origin of these complaints. A strong correlation with objective measures would imply that subjective fatigue complaints are secondary to objective components. Conversely, a lack of correlation would imply that other factors are more important in determining subjective complaints. Lou et al. (2003a) found that while PD patients had evidence of increased objective motor fatigue this objective fatigue did not correlate with subjective ratings, including subjective ratings of physical fatigue. Moreover, while levodopa treatment improved this objective motor fatigue it had no effect on subjective ratings. This study is consistent with data from studies in MS and fatigue which have also failed to find a correlation between objective motor fatigue and subjective ratings (Scwid et al., 1999). While there is some evidence to suggest that cognitive fatigue may be related to subjective fatigue in MS (Greim et al., 2007), no study to date has assessed objective cognitive fatigue in PD.

Objective Neuropsychological Testing

A well designed battery of neuropsychological tests can provide a great deal of information regarding the mechanisms, localization and impact of both anatomical and functional brain lesions (Lezak et al., 2004). Studies of patients with chronic fatigue syndrome (CFS) and MS have revealed distinctive neuropsychological profiles which specifically demonstrate deficits of attention, concentration and executive function (Busichio et al., 2004, Krupp and Elkins, 2000). In CFS these cognitive deficits have been shown to significantly correlate with disability and are thus a critical factor to consider in the management of this disorder (Christodoulou et al., 1998). The impact of fatigue on cognition in PD is currently unknown but potentially significant given the prevalence of both cognitive deficits and subjective fatigue in this population. Neuropsychological testing also has the potential to elucidate some of the functional CNS

mechanisms underlying subjective fatigue. For instance, Krupp et al. (1994) administered a neuropsychological battery to both MS and CFS patients and found correlations between depression and cognitive function only in the CFS group. This study highlights the ability of neuropsychological testing to separate the contributions of mood and brain pathology to subjective fatigue across patient groups. We hypothesize that subjective fatigue in PD will be strongly correlated with mood as well as specific domains of cognitive function.

PD is known to affect cognitive functioning, particularly in the domains of executive function and attention (Zgaljardic et al., 2003). In fact, a dysexecutive syndrome reflecting both cortical and subcortical pathology is one of the hallmarks of both cognitive dysfunction and dementia in PD patients (Bosboom et al., 2004). Several studies suggest that cognitive deficits may be associated with fatigue. Abe et al. (2000) demonstrated a significant correlation between frontal hypometabolism and fatigue ratings as well as a trend for correlation with a frontally mediated neuropsychological test (the Wisconsin Card Sort test). MMSE scores have also been shown to correlate with fatigue ratings (Alves et al., 2004). Deluca (*unpublished data*) has also demonstrated both decreased frontal and caudate activation to be associated with fatigue in an fMRI experiment. We hypothesize that objective fatigue on prolonged tasks demanding executive control will be associated with subjective fatigue complaints in PD patients.

A second hallmark of cognitive deficits in PD is disturbances of attention (Grande et al., 2006). These attentional deficits are seen early and prominently in tasks requiring divided attention (Sharpe, 1996). This deficit probably reflects an inability of PD subjects to efficiently allocate top-down attentional resources, although deficits in bottom-up attention have also been reported (Lieb et al., 1999). Although the role of attention deficits has not been studied in PD fatigue, a recent study in traumatic brain injury demonstrated that attentional deficits may be

predictive of fatigue in pathological states (Ziino and Ponsford, 2006). Similarly, studies of objective cognitive fatigue in multiple sclerosis have demonstrated a correlation between sustained attention tasks (Greim et al., 2007) but not working memory tasks (Bailey et al., 2007). We hypothesize that objective fatigue on prolonged tasks demanding top-down attention will be associated with subjective fatigue complaints in PD patients.

Objectives of this Study

We have four major objectives for this research project:

1) To develop objective tests of cognitive fatigue testing executive and attentional functions.

2) To determine the pattern of objective cognitive performance changes seen in healthy older adults and PD patients.

3) To determine if there are significant differences in objective cognitive fatigue between PD patient's and healthy older adults.

4) To determine whether there is a correlation between objective and subjective measures of fatigue in PD patients.

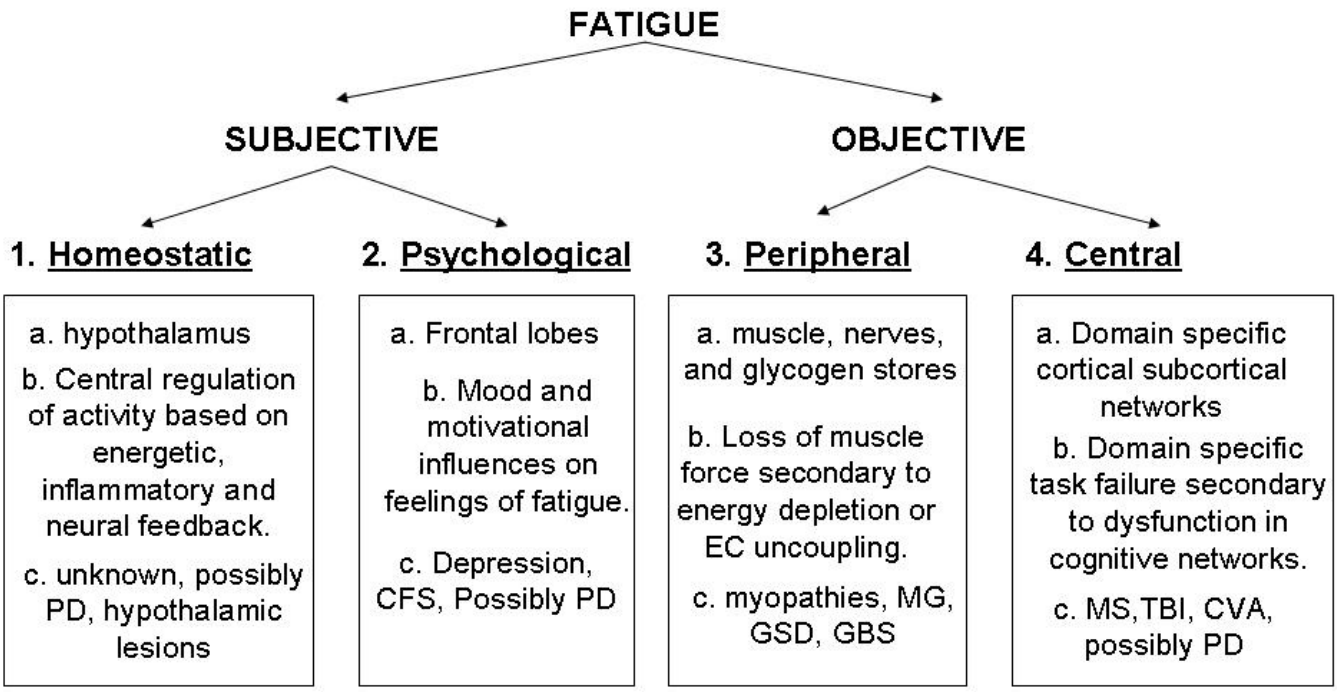


Figure 1-1. Components of fatigue. Letters in boxes refer to: a) known neuroanatomic cites mediating this component of fatigue; b) Normal function of this component of fatigue; c) Pathological states involving this component. CFS – chronic fatigue syndrome; EC – excitation/contraction; MG – myasthenia gravis; GSD – glycogen storage diseases; GBS – Guillain-Barre syndrome; TBI – traumatic brain injury; CVA – cerebrovascular accident.

CHAPTER 2
METHODS

Participants

This investigational protocol was approved by the University of Florida Institutional Review Board. All participants gave written informed consent. Six patients with PD (mean age +/- SD; 56 +/- 12 years, 4 men) and seven healthy dextral volunteers (61 +/- 14 years, 5 men) were enrolled. All subjects were screened for illnesses other than PD associated with fatigue including depression. All PD patients were diagnosed by a fellowship trained Movement Disorders neurologist using UK Brain Bank criteria (Hughes et al., 1992). PD patients were non-demented and in a mild to moderate stage of the disease (Hoehn and Yahr Stage of 3 or less). PD patients were tested in their best on state while taking their usual medications. Handedness was determined by the Edinburgh Handedness Inventory (Oldfield, 1971). All participants were asked to abstain from caffeine on the day of testing.

Subjective Fatigue Questionnaires

To measure subjective fatigue we used two previously standardized scales. The Multidimensional Fatigue Inventory (Smets et al., 1995) measures five independent dimensions of fatigue; general fatigue, physical fatigue, reduced motivation, reduced activity and mental fatigue. While this scale covers a wide range of symptoms, it is not particularly sensitive to overall fatigue severity and it does not have clear cut points. The Fatigue Severity Scale (Krupps et al., 1989) is a seven item questionnaire which queries fatigue generally, but is sensitive to severity and has clear scoring (a score of 4 or greater signifies moderate to severe fatigue).

Objective Fatigue of Executive Function

Participants performed a computerized single-trial, cued version of the Stroop task (Cohen et al., 1999) displayed on a PC using the Experimental Run Time System (Berisoft Corporation,

Frankfurt, Germany). In this task subjects are presented with an instructional cue on each trial ("word" or "color"). This is followed by a 1,3 or 5 second interstimulus interval (ISI) followed by an imperative color word stimulus ("red", "blue" or "green") written in colored letters. For the "word" task subjects were instructed to read the word, while in the "color" task subjects are instructed to name the color of the letters. On 60% of the trials the color of letters and the word were congruent (e.g. "red" written in red letters), but on the other 40% the letters and word were incongruent (e.g. "red" written in green letters). Reaction times were determined by a microphone and voice activation software and responses were manually recorded in real time by a research assistant. After receiving a brief practice session (30 trials), subjects are fitted with EEG electrodes (data not presented here) and were asked to perform the task for a single three hour session. Breaks for any purpose were taken only if requested, and the times of breaks noted. If a subject was unable to complete the task for any reason, the time of discontinuation was recorded.

Objective Attentional Fatigue

Participants performed a computerized target detection task. All presentations and response recordings were displayed on a PC using the Experimental Run Time System (Berisoft Corporation, Frankfurt, Germany). Participants were instructed to maintain fixation on a central cross throughout the experiment to minimize eye movements. After learning two targets, subjects performed a visual search task in which they responded with one of two buttons depending on whether the target is present or absent. Targets were presented in one of three conditions (Figure 2-1):

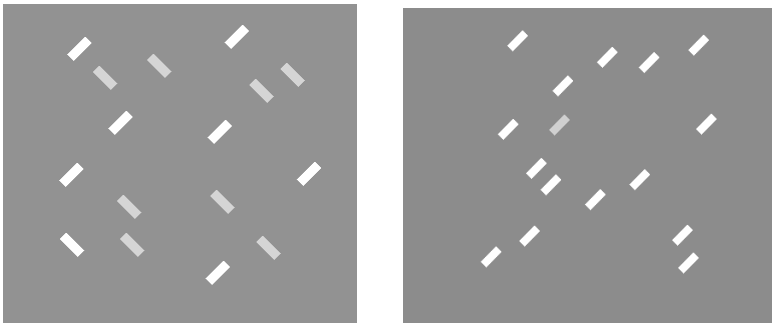
a) a visual search condition in which targets share two visual features with distracters (top-down attention); b) a pop-out condition in which distracters differ in a single visual feature (bottom-up attention) and; c) a working memory condition in which only one stimuli was present on the screen. Trials may be further divided into those with 1, 7 or 15 distracting items. Stimuli were

presented in a continuous fashion to subjects in balanced blocks of 60 trials (24 visual search, 24 pop-out and 12 working memory, including 50% target absent trials and 8 of each distracter number in the visual search and pop-out conditions). After receiving a brief practice session (40 trials or until competency is demonstrated), subjects were fitted with EEG electrodes and asked to perform the task for a single three hour session. Breaks for any purpose were taken only if requested, and the times of breaks noted. If a subject is unable to complete the task for any reason, the time of discontinuation was recorded.

Statistical Analyses

Summary statistics were computed, summarized and graphed (e.g. box and whisker plots) to identify outliers and/or impossible or implausible values and to check for distributional forms. For each block of 390 trials, error rates were calculated as the mean error and speed was calculated as the median reaction time to minimize the effect of outliers. To determine objective fatigue of our outcome measures we calculated the percent change from the first 390 trials (following a training trial) to the last 390 trials completed by each subject. Group comparisons were made using the Wilcoxon rank sum test and correlations were made using Spearman correlation. A two-sided alpha=0.05 was the level of significance used for all tests. SAS version 9.1 (SAS Institute, Cary, NC) was used for all data management and statistical analyses.

a) b)



c)

Figure 2-1. Sample visual displays of attention fatigue trials with target present:
a) visual search (white "\" is target) b) pop-out (grey "/" is target) c) working memory (white "\" is target)

CHAPTER 3
RESULTS

Executive and Attentional Function at Baseline

There were no significant differences between the two groups in any of our performance measures at baseline (all $p > 0.10$). Table 3-1 and Table 3-2 summarize these results. Figures 3-1 and 3-2 demonstrate these results graphically for the two groups over different task types.

Objective Fatigue of Executive and Attentional Function

For this study, we defined objective fatigue as a statistically significant difference between a performance measure recorded at baseline and during the last two blocks of testing. For the Stroop task, PD subjects showed significant changes in speed across all task types, and in total errors (see Table 3-3). Healthy controls showed significant decrements only in their reaction time for the incongruous color condition. By doubling the reaction times on error trials we calculated a total performance metric. Figure 3-3 demonstrates these results graphically. There were no significant group differences across any outcomes.

On the attentional task, PD patients demonstrated a significant increase in their errors of omission for both the pop-out and visual search condition, as well as a trend for false positive errors on the pop-out condition. For control subjects, a significant increase in false positive errors was noted only for the working memory condition. There were no significant changes in reaction times nor where there significant group differences across any outcome measure. These results are summarized in Table 3-4 and Figure 3-4.

Correlation of Objective and Subjective Measures of Fatigue

We performed an explorative analysis using Spearman's correlation to determine if the FSS, the MFI or any subscale of the MFI was correlated with our objective measures of executive function fatigue. The only significant correlations were between the percent change in Stroop

performance and the General Fatigue Score of the MFI (r^2=0.27, p=0.001) and the Reduced Activity Score (r^2=0.17, p=0.045).

For our attentional outcomes, we found a significant negative correlation between the total FSS score and changes in errors on all task types. Within the MFI, positive correlations were found between the General Fatigue factor and errors of omission on the pop-out task and between the Reduced Activity factor and errors of omission on working memory and false positive errors on the pop-out task. These results are summarized in Table 3-5.

Table 3-1. Stroop Performance at Baseline; Mean (SD)

	Congruous Word	**Congruous Color**	**Incongruous Word**	**Incongruous Color**	**Combined**
PD					
RT (msec)	1332 (340)	1336 (365)	1661 (510)	1753 (418)	1462 (374)
Error (%)	0.1 (0.4)	0.1 (0.3)	10.9 (10)	15.6 (13)	5.3 (4.2)
Controls					
RT (msec)	1236 (223)	1250 (220)	1456 (297)	1533 (288)	1343 (241)
Error (%)	0.1 (3)	0.4 (0.4)	3.2 (3)	11 (14)	3.1 (3)

Table 3-2. Attentional Performance at Baseline (Mean (SD) divided by task type and target present (+) or absent (-).

	Pop-out		**Working Memory**		**Visual Search**	
	+	**-**	**+**	**-**	**+**	**-**
PD						
RT (msec)	2416 (1400)	2516 (1270)	3013 (2900)	2709 (1900)	3506 (831)	5687 (3580)
Error (%)	11.9 (22)	8.8 (18)	14.7 (21)	10.9 (16)	16.7 (15)	11.3 (23)
Controls						
RT (msec)	1614 (640)	1397 (550)	2397 (2030)	1599 (790)	2480 (890)	4265 (1970)
Error (%)	9.4 (22)	9.8 (22)	12.3 (22)	5.2 (11)	19.0 (14)	8.4 (19)

Table 3-3. Objective Executive Performance Fatigue (Percent change (SD)

	Congruous Word	**Congruous Color**	**Incongruous Word**	**Incongruous Color**	**Combined**
PD					
RT	16.6 (11)*	22.4 (27)*	13.5 (17)*	20.0 (20)*	18.0 (13)*
Error	0.0 (0.5)	0.0 (0.4)	4.3 (10)	4.3 (7)	1.8 (2)*
Controls					
RT	11.8 (23)	8.9 (20)	11.7 (20)	18.5 (12)*	10.8 (19)
Error	0.0 (0.5)	0.0 (0.5)	1.1 (3)	1.1 (8)	0.2 (2)

* significant change from baseline ($p \leq 0.05$)

Table 3-4. Objective Change in Attentional Performance

	Pop-out		**Working Memory**		**Visual Search**	
	+	-	+	-	+	-
PD						
RT	23.8 (48)	51.8 (107)	3.5 (15)	7.1 (23)	15.1 (28)	8.7 (18)
Error	7.3 (10)*	7.1 (10) **	5.1 (10)	-1.0 (1.7)	7.0 (8) *	0.3 (8)
Controls						
RT	3.9 (17)	8.5 (16)	9.4 (19)	17.5 (24)	1.0 (12)	8.9 (23)
Error	-0.9 (5)	0.3 (1)	0.5 (4)	2.4 (3) *	2.4 (6)	-0.3 (1)

* significant change from baseline ($p \leq 0.05$)

** trend for change from baseline ($p \leq 0.1$)

Table 3-5. Correlations between Subjective Outcomes and Objective Attentional Fatigue. **FSS** = Fatigue Severity Scale; **GF**= General Fatigue; **MF**= Mental Fatigue; **PF**= Physical Fatigue; **PO**= Pop-out; **RA**= Reduced Activity; **RM**= Reduced Motivation; **VS**=Visual Search; **WM**= Working Memory.

	PO (+)	**PO (-)**	**WM (+)**	**WM (-)**	**VS (+)**	**VS (-)**
FSS	-0.44 *	-0.47 *	-0.37 *	-0.57 *	-0.34 *	-0.29 *
GF	0.18 *	0.11	0.11	0.03	0.14	0.07
RA	0.09	0.25 *	0.30 *	0.03	-0.24 *	0.16
MF	0.04	-0.08	-0.07	-0.06	.11	-0.07
PF	0.00	-0.03	0.00	-0.13	-0.07	-0.05
RM	-0.12	-0.07	0.05	-0.22	-0.32 *	-0.14
* significant $p < 0.05$						

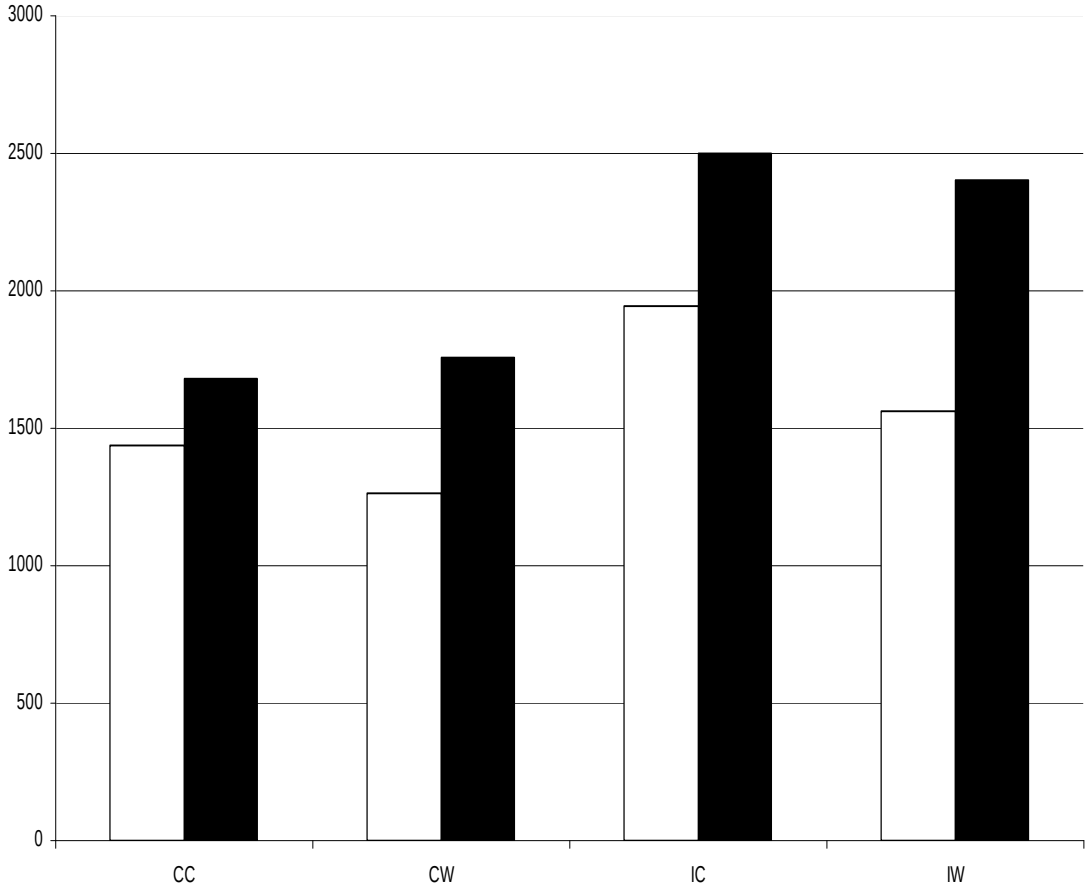
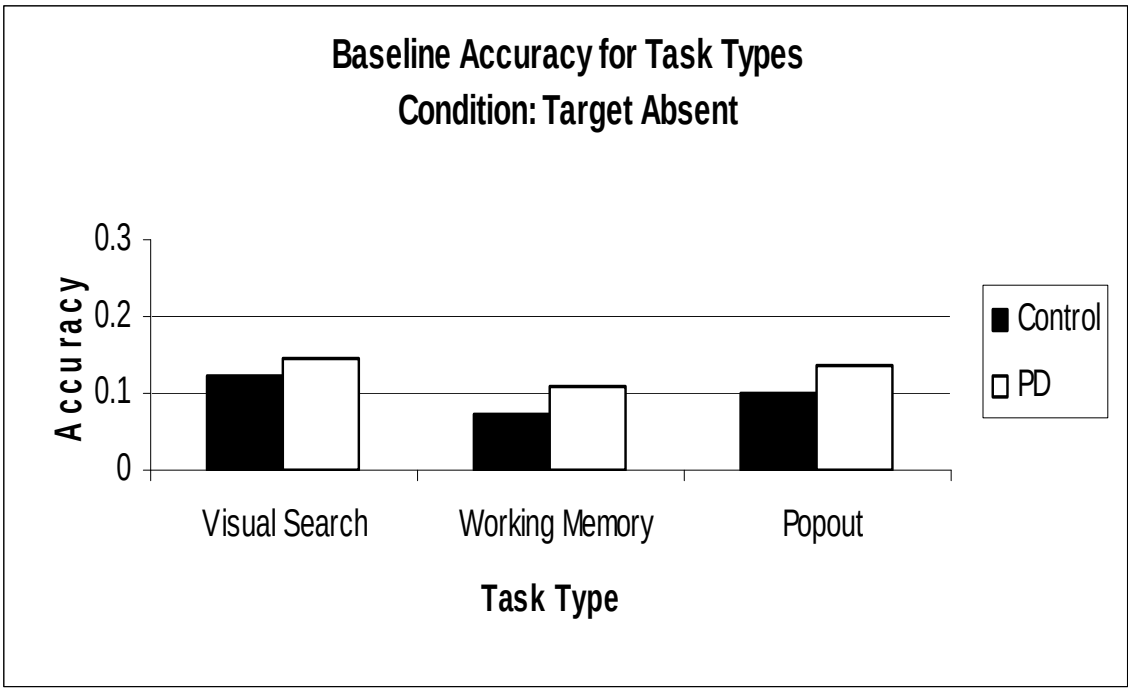


Figure 3-1. Baseline performance on Stroop task. White is controls, black is PD. Tasks are (from left to right): congruous color naming, color word reading, incongruous color naming and incongruous word reading.



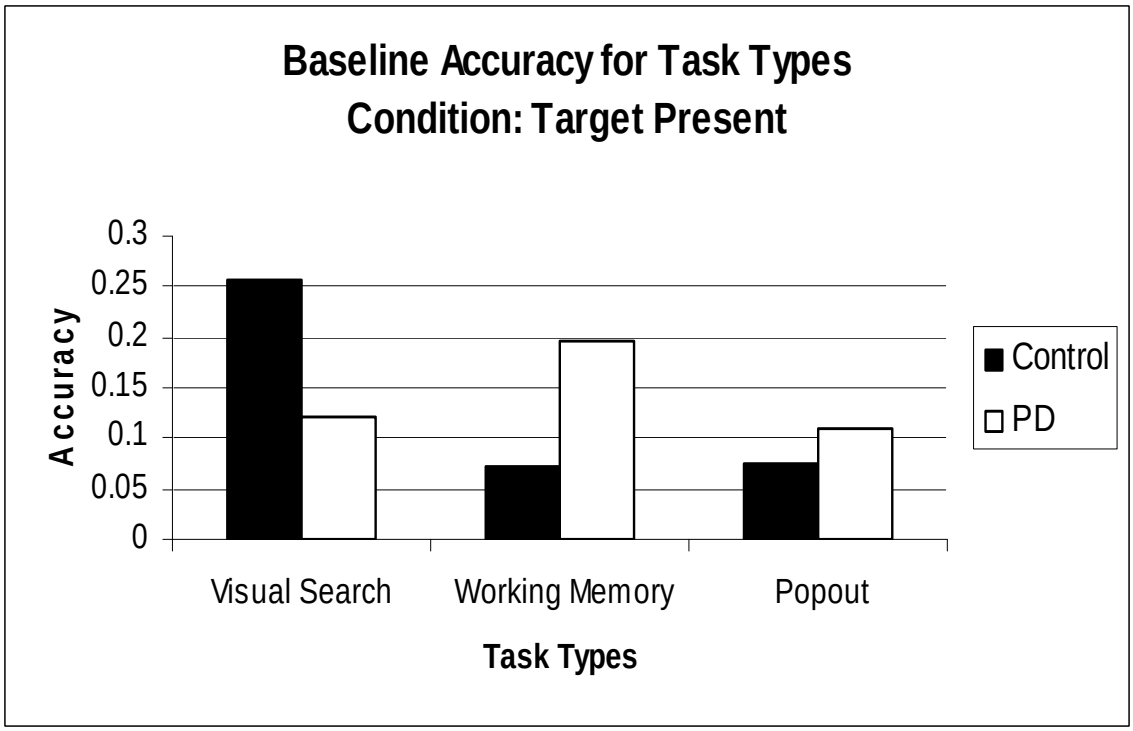


Figure 3-2. Attentional performance at baseline.

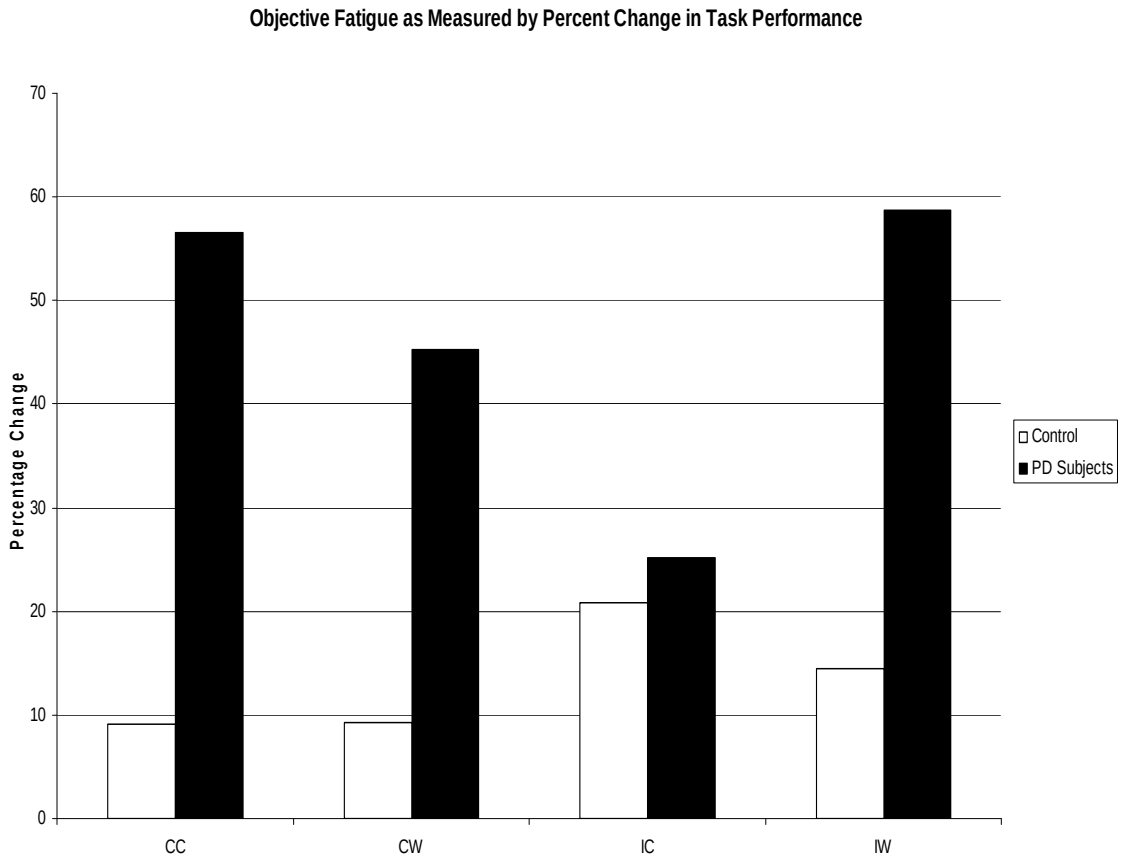


Figure 3-3. Fatigue in overall performance on Stroop task. White is controls, black is PD. Tasks are (from left to right): congruous color naming, color word reading, incongruous color naming and incongruous word reading.

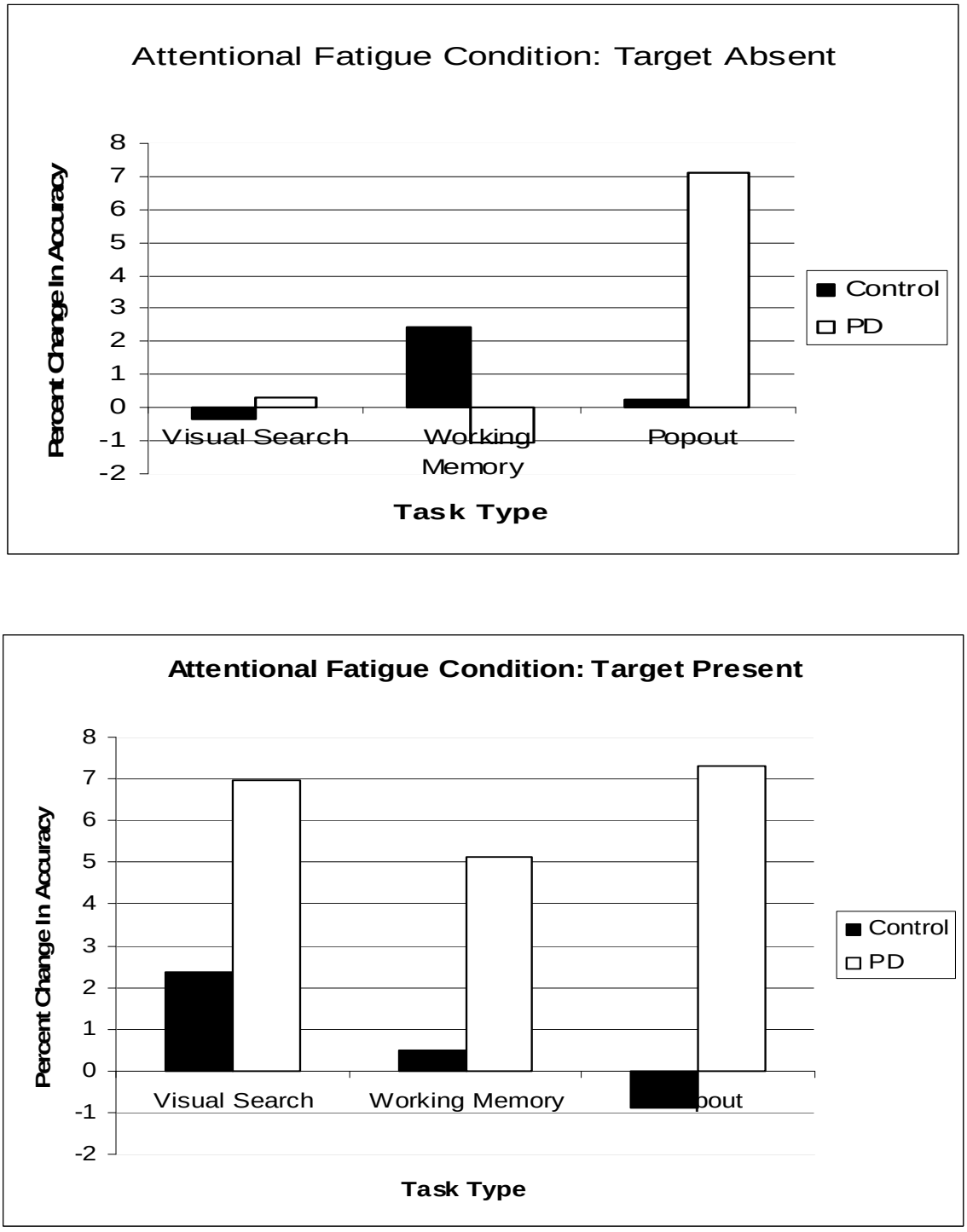


Figure 3-4. Change in accuracy on attentional task with fatigue.

CHAPTER 4
DISCUSSION

Objective Cognitive Fatigue in Healthy Older Adults

Our experimental tasks were designed to have internal control conditions to allow us to distinguish focal fatigue of cerebral networks from either general fatigue or other general factors such as boredom, loss of motivation and sleepiness. The prolonged Stroop task was chosen as its continued performance would be expected to place specific demands on frontal-executive networks. Consistent with our predictions, older adults demonstrated a disproportionate decrease in performance on the incongrous color naming task which demands the most executive control compared to other task types. Our visual search task was chosen to distinguish effortful top-down attention from pre-attentive bottom-up attention. We predicted that older adults would demonstrate a disproportionate increase in errors with fatigue on top-down visual search items. The finding of increased errors on the working memory item may reflect a susceptibility to working memory deficits with fatigue, a finding reported in CFS (Dobbs et al., 2001). Alternatively, both the visual search and pop-out tasks can be correctly answered without relying on internal resources by searching for a stimuli which differs from the others. The working memory task, on the other hand, requires internal resources as there are no external cues and this dependence on internal resources may be more susceptible to fatigue. Studies demonstrating involvement of medial frontal structures with fatigue are consistent with this hypothesis as these structures are associated with internally generated actions (Boksem et al., 2006).

Performance strategies are known to effect variables such as speed and accuracy (Pfefferbaum et al., 1983). It is not surprising that they would also effect changes in these variables with fatigue. On the Stroop task, it appears that subjects sacrifice time to maximize

their accuracy. This may be expected in that subjects are typically aware of the correct response. In fact when subjects make errors they will often spontaneously correct their response or change their response mid-word. In contrast, subjects had almost no change in speed over time while performing the attentional task but had a significant increase in errors of omission. It is likely that subjects were unaware of these errors, although a second source of data such as event related potentials or eye tracking would be needed to prove this postulate.

Objective Cognitive Fatigue in Parkinson's Disease

In contrast to healthy older adults, PD subjects demonstrated more global impairments in function with the onset of fatigue. Contrary to our expectations on the prolonged Stroop task, PD subjects showed significant slowing across all tasks, with the smallest relative difference found for the congruous color naming task. This may be due to several factors. First, PD subjects had impairments in the incongruous color task at baseline and may not change as significantly with fatigue due to a floor effect. Secondly, PD subjects have objective motor fatigue (Lou et al., 2003a) and may be expected to develop oromotor slowing as well. This would lead to a general slowing across tasks due to the time of speech generation. This slowing may in fact surpass cognitive control as a rate limiting step and even allow subjects additional time to compute their response prior to speaking. Finally, cues for difficult tasks are known to induce greater preparatory activity and attention compared to easier tasks (Perlstein et al., 2006). As PD subjects are more dependent than control subjects on external versus internal cueing (Jenkins et al., 2000), they may have a relative advantage in the face of strong as opposed to weak cues.

PD subjects showed similar broad deficits across tasks types with our attentional experiment. This seems to be unlikely due to a simple general effect such as sleepiness or boredom in that PD subjects made increasing errors of omission, but did not have alterations of false positives or reaction time. The most parsimonious explanation for these findings would be

that PD subjects have impairments in early pre-attentive processes that worsen over time. Alternatively, PD subjects may have deficits in both attentive and pre-attentive processes that independently impair function on the various tasks. As discussed in the introduction there is evidence that PD affects both pre-attentive and attentive processes (Lieb et al., 1999). A particularly rich way of exploring this question would be the use of event related potentials to determine the timing of differences in the processing of stimuli presented at baseline and after fatigue.

Subjective Fatigue Complaints

Although significant correlation was found between the scores of General Fatigue and Reduced Activity on the MFI and Stroop performance, it is possible that this is a spurious association. With only six subjects, it is equally difficult to conclude that there is truly no association between objective and subjective variables. A larger study is needed to more definitively answer this question. It is similarly difficult to draw conclusions on the handful of positive correlations between elements of the MFI and attentional outcomes. The consistent negative correlations between the FSS and all attentional variables were an unexpected finding. This may also reflect a spurious association, as there were no significant correlations when this analysis was re-run using Pearson's r. Alternatively, this may reflect an anosognosia for fatigue in those with greater attentional deficits.

While it is possible associations may be demonstrated in larger samples, the lack of significant correlations between subjective and objective measures of fatigue is consistent with data from numerous other studies comparing objective tests to self-report data. As discussed in the introduction, numerous authors have found that subjective complaints of cognitive deficits correlate with mood and other subjective estimates but are not correlated with objective neuropsychological testing (Beaty et al., 2003; Elixhauser et al., 1999). This may indicate that

subjective fatigue in PD subjects is a perceptual or psychological disturbance that is unrelated to objective function. Alternatively, it may indicate that we have not yet utilized an appropriate test of objective fatigue. Further studies are needed to determine if either motor fatigue (Lou et al., 2003a), cognitive or attentional fatigue are associated with either quality of life or objective disability.

CHAPTER 5
FUTURE DIRECTIONS

Measurement of Fatigue in Clinical Populations

As discussed in the Introduction, fatigue is a multidimensional phenomenon that encompasses many distinct components. While subjective fatigue is clearly problematic for many patient populations, further research is needed to determine whether this symptom is a reflection of an objective deficit, a disturbance of homeostatic energy regulation, a perceptual disturbance or related to mood disorders. Determining an underlying etiology of subjective is important as these distinct causes would be hypothesized to respond to different treatments and arise from different regions of the neuraxis.

The development of a standardized fatigue battery which contains both subjective questions as well as objective assessments of peripheral and cognitive fatigue would greatly improve our ability to measure fatigue in clinical populations. Given the limitations of self-assessments, it should provide a more consistent and reliable measure to study fatigue epidemiology as well as assess potential fatigue treatments. As fatigue treatments develop, it would also help direct specific treatments to appropriate individuals or populations on the basis of their fatigue profile. Finally, although subjective fatigue is clearly related to self-reported quality of life measures, a battery would allow for a better assessment of the true causes of disability.

Neurophysiology

While the physiological basis of fatigue in PD is unknown, several research hypotheses may be made from data obtained in other populations affected by fatigue, functional imaging studies in PD and basic science studies of neuronal function and networks. First, studies using EEG in healthy controls have shown that Event Related Potentials (ERPs) generated by medial frontal

areas decrease over time as fatigue develops (Boksem et al., 2006). This represents an attractive potential neuroanatomical correlate for PD fatigue as these areas are known to be affected in PD (Mattay et al., 2002) and are hypothesized to underlie difficulties in internally generated action. Second, a large body of literature has implicated the involvement of the basal ganglia in fatigue across many populations, including PD (Chaudhuri and Behan, 2000). Third, neurocomputational models have shown that the accumulation of noise in a cortical network over time could explain many of the behavioral effects seen as subjects fatigue (Li and Sikstrom, 2002). As dopamine and norepinephrine are related to neuronal signal to noise ratios and are affected by PD this may represent a pharmacological marker for fatigue. Finally, studies using transcranial magnetic stimulation (TMS) have demonstrated that PD patients have abnormal cortical excitability, possibly mediated through basal ganglia dysfunction (Lefaucher, 2005). Recent research has demonstrated the importance of inhibitory activity in maintaining normal local oscillatory activity as well long range communication between brain areas in cortical networks, both of which may be disrupted with fatigue in normal subjects (Gevins et al., 1987) and have been hypothesized to underlie many PD deficits (Schnitzler and Gross, 2005). Moreover, Lou et al. (2003b) found subjective fatigue to be associated with resting motor threshold in PD subjects.

To begin to address the neurophysiologic basis of PD fatigue we propose to analyze EEG data recorded while our subjects were completing our objective fatigue testing. We will utilize the Variable Signal Plus Ongoing Activity (VSPOA) model (Truccolo et al., 2002). Traditional ERP research averages many EEG traces which are time locked to a stimulus of interest to eliminate background noise and accentuate time locked activity. There are many well characterized ERPs which have been used for decades to assess for changes in specific cortical

activity across conditions or patient groups and may be used to address neuroanatomical questions regarding the potential role of medial frontal structures in PD fatigue. However, this procedure loses or distorts activity which is not precisely time locked to stimulus onset. The VSPOA model maximizes the information obtained through EEG by separating activity into stimulus related signal (single trial ERPs) and ongoing oscillatory activity on a trial by trial basis. As detailed below, the VSPOA model enables EEG data to be analyzed for aspects of basal ganglia function (such as coherence among network components), internal noise (by quantifying variability in the amplitude and timing of signal related processes) and cortical excitability (by examining the phases of gamma oscillations). As these hypotheses are not mutually exclusive, we can maximally utilize this rich data set to simultaneously address multiple aspects of neurophysiological functions potentially relevant to the pathophysiology and eventual treatment of PD fatigue.

Fatigue Treatment

Our ultimate goal is of course to develop treatments for PD fatigue. As we begin to answer critical questions regarding the causes and neurophysiology of fatigue, we can utilize our knowledge of normal physiology to develop interventions. This would include pharmacological interventions based on our understanding of neural networks and circuitry. Other interventions may include the potential of deep-brain stimulation to novel targets (or alterations of DBS parameters to known targets), cortical stimulation (via transcranial magnetic stimulation) or non-pharmacological interventions, including cognitive training.

CHAPTER 6
CONCLUSIONS

Fatigue is an important contributor to disability and quality of life in PD patients. In this study we have demonstrated that PD patients develop attentional fatigue and fatigue of executive control at an accelerated rate compared to healthy control subjects. Although this fatigue may be expected to impact daily function it is not definitively correlated with patient's subjective complaints. Further research is needed to determine the cause of subjective fatigue complaints in PD subjects and to determine the components of fatigue most predictive of disability.

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BIOGRAPHICAL SKETCH

As a psychology undergraduate, I became deeply fascinated with clinical neuroscience and began my pursuit of a career in academic medicine. My experience in clinical research began in 1996 when I was awarded a University of Colorado Cancer Center Summer Student Fellowship focusing on the association between chronic obstructive pulmonary disease and lung cancer. After only three years at the University of Colorado, Boulder, I earned a B.A. in psychology and was one of the first recipients of the University of Colorado's certificate in Neuroscience and Behavior for my exceptional performance in physiological and experimental course work. Upon graduating in 1997, I was awarded a second Summer Fellowship to investigate pediatric zinc metabolism at the University of Colorado Center for Human Nutrition. My contributions to this laboratory were recognized by the American Society for Clinical Nutrition's C. Everett Koop Award (given to the top selected research intern) and by the Western Medical Student Research Forum for Best Abstract in the area of clinical nutrition.

At the age of 19, I was the youngest person accepted into the University of Colorado's School of Medicine Class of 2001. During my first two years of medical school, I continued to perform research with the Center for Human Nutrition. During this time I contributed to a manuscript on zinc homeostasis (Krebbs et al., 2000) and helped to inititiate a study of calcium homeostasis. I was also the University of Colorado's representative to the Western Medical Student Research Forum. In this role, I promoted research opportunities for medical students and reviewed research as a judge for their annual meetings. During my fourth year of medical school, I dedicated the majority of my elective time to clinical neurology and research. I helped to initiate a pilot study investigating the role of mitochondrial dysfunction in Alzheimer's Disease

and played a key role in developing a novel method to extract mitochondrial DNA from brain tissue.

I chose to pursue neurology residency at the University of Colorado for their excellent clinical training program and their support of resident research. During my residency, I became further interested in behavioral neurology, particularly its intersection with movement disorders. I was fascinated by the basic science and clinical research which suggested that similar physiological mechanisms may be responsible for the generation of both movements and cognition. In my elective time, I pursued this interest further by designing and perfoming a research study under the mentorship of Dr. Donald Rojas, Ph.D. This study investigated the localization and timing of the neuroanatomic networks involved in generating volitional actions by using a novel go/nogo task and magnetoencephalography (MEG). I was the principal investigator for this study and thus responsible for all aspects of the investigation from inception through analysis. My work on this project was recognized with the American Neuropsychiatric Association's 2005 Young Investigator Award. This study also convinced me that further training in neuropsychology and neurophysiology would improve my ability to answer clinically relevant questions regarding the physiology of behavior.

After completing residency in June 2005, I began a three year Behavioral Neurology Fellowship at the University of Florida under the mentorship of Dr. Kenneth Heilman, M.D. This program is internationally recognized for its research contributions to neuropsychology and its record for training successful clinical investigators in this field. During this fellowship, I successfully applied for an NIH Loan Repayment Program grant and an American Academy of Neurology Foundation Clinical Research Training Fellowship to extend my research training. These highly competitive grants gave me an extra year of research support to further develop and

refine my own line of programmatic research into the objective measurement and pathophysiology of clinical fatigue. Through this fellowship and associated collaborative projects I have received in depth training in clinical behavioral neurology, neuropscyhological testing, transcranial magnetic stimulation, and functional imaging with a particular emphasis on electroencephalography and event related potentials. Also during this time, I successfully applied to the University of Florida's Advanced Postgraduate Program in Clinical Investigation (APPCI), an NIH K-30 program. As an APPCI fellow, I am completing a master's degree in clinical investigation.

During the last six months of my Behavioral Neurology Fellowship, I chose to focus my research in patients with Parkinson's disease (PD) due to the high burden of fatigue in this population. To further my understanding of PD and other movement disorders, I began a Movement Disorders Research Fellowship at UF in July of 2007 under the mentorship of Drs. Michael Okun and Hubert Fernandez. In addition to my neurophysiologic research, I have been actively collaborating with members of the Movement Disorders Center to utilize their database to understand the neuropsychological and clinical characteristics most associated with PD fatigue.

I have recently secured a joint appointment as an Assistant Professor in the Departments of Neurology and Psychiatry at the University of Colorado at Denver and Health Sciences Center to start August 1, 2008. In many ways, this appointment is the culmination of the past 14 years of my dedication to clinical neuroscience. The Departments of Neurology, Psychiatry and the Colorado Neuromagnetic Imaging Center are commited to helping me start my own TMS laboratory as well as utilize their MEG facilities to continue my line of programmatic research.