Published in final edited form as:
J Clin Exp Neuropsychol. 2010 June ; 32(5): 474–480. doi:10.1080/13803390903201769.

MODAFINIL EFFECTS ON COGNITIVE FUNCTION IN HIV+ PATIENTS TREATED FOR FATIGUE: A PLACEBO CONTROLLED STUDY

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Abstract

Both mild cognitive impairment and fatigue are common among people with HIV/AIDS. This study examined the efficacy of modafinil for HIV+ patients who sought treatment for fatigue in a placebo-controlled double blind 4-week trial. A battery of standard neuropsychological tests was administered at study entry and Week 4, and change in performance was compared for 59 patients receiving modafinil vs. 44 patients receiving placebo. A significant effect on fatigue was observed. In addition, cognitive performance, as measured by a global change score, improved more in the modafinil than placebo group although the effect was not specific to any cognitive domain.

Introduction

Both fatigue and mild cognitive impairment are often found among people with HIV/AIDS. Estimates of fatigue prevalence across studies cluster around 50% (Breitbart, McDonald, Rosenfeld, Norman, Monkman & Passik, 1998; Leserman, Barrosso, Pence, Salhuddin, & Harmon, 2008; 2008; Henderson, Safa, Easterbrook, & Hotopf, 2005); fatigue often is associated with considerable functional impairment (Justice, 1999). A common ancillary complaint concerns difficulties with cognitive function. Patients with fatigue often report that they have trouble concentrating, remembering things, and focusing (Millikin, Rourke, Halman, & Power 2003), and formal testing has shown that mild cognitive impairment is prevalent among HIV+ individuals even in the absence of fatigue (Durvasula, Norman, & Malow 2009; Norman, Basso, Kumar & Malow, 2009). There are no established treatments either for fatigue or for cognitive problems, although the modest available data suggest that methylphenidate and dextroamphetamine may modify cognitive decline in HIV+ patients (Hinkin, Castellon, Hardy, Farinpour, Newton, & Singer, 2001; Brown, 1995). More recently, modafinil has been marketed for the treatment of sleep disorders including narcolepsy, obstructive sleep apnea, and shift work related sleep disorders. In off-label use, trials have addressed its effects on fatigue in clinical populations including multiple sclerosis (Rammohan, Rosenberg, Lynn, Blumenfield, Pollak, & Nagaraja, 2002), Parkinsons Disease (Adler, Cavinoss, Hentz, Lind, & Tiede, 2003), amyotrophic lateral sclerosis (Rabkin, Gordon, McElhiney, Rabkin, Chew, & Mitsumoto, 2009), and cancer (Cooper, Bird, & Steinberg, 2009).

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The authors report no financial affiliations or other relationships relevant to the subject of this article.

Modafinil is a wake-promoting agent that is classified as a Schedule IV drug by the FDA. It differs from methylphenidate and amphetamine in its lower liability of abuse (at least in non-drug abusing individuals [Volkow, Fowler, Logan, Alexoff, Zhu, Telang et al. 2009]), lower risk of adverse cardiac effects, and different mechanisms of action (Ballon & Feifel, 2006). Investigators have evaluated its effects on cognitive function in patients with sleep disorders as well as healthy volunteers, sleep-deprived volunteers, and those with psychiatric disorders including major depression and schizophrenia. Positive results have been reported quite consistently for patients with sleep disorders (e.g. Dinges & Weaver 2003; Hirshkowitz & Black, 2007), but otherwise the findings are variable. In their comprehensive review of this literature, Minzenberg & Carter (2008) concluded that modafinil "improves function in several cognitive domains, including working memory and episodic memory…in healthy adults and across several psychiatric disorders." (p. 1477). This finding was not uniform either across studies or between neuropsychological tests, however. For example, Randall, Shneerson, Plaha & File (2002) did not find change in cognitive function in 30 healthy young volunteers tested 3 hours after receiving placebo or 100 mg. or 200 mg. of modafinil. Among patients with major depressive disorder and residual fatigue treated adjunctively with modafinil for 4 weeks, DeBattista, Lembke, Solvason, Ghebremicael, & Poirer (2004) found improvements on Stroop interference, but not on letter-number sequencing, Digit Span, or Trails A,B. A recent review of modafinil effects on sedation and cognition in schizophrenia (Saavedra-Velez, Yusim, Anbarasan, & Lindenmayer, 2009) concluded that while modafinil "may have some efficacy in the treatment of antipsychotic-induced sedation and cognitive domains, the small samples, contradictory results and methodological differences between trials, especially with respect to cognitive testing, make it difficult to draw firm conclusions" (p. 104). This critique applies to much of the literature on modafinil effects on cognition in clinical populations.

We conducted a placebo controlled clinical trial of modafinil for the treatment of fatigue among HIV+ patients, and administered a one-hour battery of neuropsychological tests before and after the 4-week trial. Baseline and Week 4 measures also included scales to assess fatigue, depressive symptoms, and perceived cognitive problems. We addressed the following questions: 1) Do patients randomized to modafinil show greater improvement on neuropsychological tests than patients randomized to placebo? Are there particular domains (executive function, memory, verbal fluency, reaction time) that show differential change? 2) Are baseline fatigue severity, depressive symptoms or level of cognitive performance related to amount of change, if any? 3) Do perceived cognitive problems preferentially diminish in the group randomized to modafinil vs. placebo?

Methods

Research Participants

Eligible patients were HIV+, aged 21–75 years, had clinically significant fatigue, defined as interference with at least two daily activities on a Role Function Scale, and a score of at least 41 on the Fatigue Severity Scale (described below). Patients with untreated major depression, unstable medical conditions, untreated conditions associated with fatigue such as anemia or hypothyroidism, change in antiretroviral medications in the past month or initiation of antidepressant medications in the past 2 months were excluded.

Measures—(Note: all were administered at baseline and Week 4, and higher scores indicate more of the condition assessed, unless otherwise noted.)

Fatigue measures: The 9-item self-rated Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) is a unidimensional measure of the impact of fatigue on everyday functioning, with scores ranging from 9 to 63; the conventional cut-off for clinically significant

fatigue is 41+. We adapted a 10-item Role Function Scale using items from the MOS-36 Health Survey (Albert & Rabkin, 2008) to determine whether fatigue, if present, interfered with daily activities, and at least 2 activities had to be rated as substantially impeded

Psychiatric measures: The SCID (Koback, Skodol, & Bender, 2008) psychotic screen and depression modules were used at baseline only to determine eligibility criteria. We used the structured version of the Hamilton Depression Rating Scale for Depression (HAM-D) (Yonkers & Samson, 2008), a clinician-rated scale, with scores combining frequency and severity of depressive symptoms. The 21-item Beck Depression Inventory (2^{nd} edition) is a self-report scale providing a subjective estimate of depressive severity (Yonkers & Samson, 2008) The Clinical Global Impressions-Severity of Illness Scale (Williams, 2008) used to assess depression at baseline, and the 7-point Clinical Global Impressions-Improvement Scale was used at Week 4.

Medical measures: CD4 and HIV plasma RNA viral load were measured at baseline and Week 4. Patients also received a urine toxicology screen for acute or recent use of drugs.

Neuropsychological measures: A battery of 10 neuropsychological (NP) tests was administered to assess memory, attention, language function, executive functions, and motor/psychomotor speed. The following tests were administered: UCLA-WHO Verbal Learning Test IMaj, D'Elia, Satz, Janssen, Zaudig, Uchiyama, et al; 1993); WAIS subscales including Digit Symbol, Digit Span, Number-Letter Sequencing and Symbol Search (Wechsler, 1997); Color Trails (D'Elia, Satz, Uchiyama, & White, 1996); Stroop Color Interference Test (Golden, 1978) California Computerized Assessment Package (CalCAP: Miller, 1990), Controlled Oral Word Association Test (Benton, Lezak, Howieson & Loring, 2004) and Grooved Pegboard (Matthews & Klove, 1964).

Fatigue Outcome Measure: The primary endpoint defining fatigue responder vs. non-responder was the Clinical Global Impressions- Improvement Scale (CGI: Guy, 2008). Scores range from 1 = very much improved to 7 = very much worse. Scores of 1 or 2 defined treatment response; non-responders had scores of 3 (minimally improved) or worse. This global assessment by the blinded study psychiatrist is based on all available data including clinician judgment, patient self-reports and ratings.

Procedures—This was a 4-week randomized double-blind placebo-controlled study. Patients were randomized in blocks of 4 according to a computer-generated list provided by the Research Pharmacy, which also packaged the identical appearing modafinil and placebo tablets. Neuropsychological tests were administered at baseline and Week 4. Responders to modafinil were offered an additional 8 weeks of open label medication, and placebo non-responders or placebo responders who relapsed were offered open label modafinil for 12 weeks. The protocol was approved by the New York State Psychiatric Institute Institutional Review Board, and all participants gave written informed consent after being informed of the procedures, risks, and alternatives to study participation. Data were collected between December 2004 and December 2008. The study was registered with clinical Trials.gov, identifier: NCT00614926.

Statistical Analyses—First, repeated measures analysis (using covariates of age, education and gender) was performed for each neuropsychological test and subtest, comparing patients randomized to modafinil vs. placebo. Next, in order to examine the overall effect of modafinil on NP performance, a global difference score for all subtests was calculated as follows: First, timed tests (Grooved Pegboard, Trails, Calcap) were converted from "elapsed time" to "speed" using reciprocal transformations ((1/x) * 100). One subtest from each measure was chosen to

contribute to the global score (WHO total score, Stroop Color-Word, Color Trails 2, Grooved Pegboard non-dominant hand, Verbal Fluency FAS total, CalCap-Sequential Reaction Time 2). The difference score for each of the 10 measures was calculated subtracting the baseline score from the Week 4 score. The resulting difference was transformed into a Z-Score and the 10 subscales summed into a global change score. ANCOVA analyses were then performed, controlling for variables with significant univariate correlations to the global change score.

These analyses were repeated for patients for whom English is a second language, and for responders vs. non-responders, and then the subset of patients who were NP "outliers" at study entry, across treatments groups. First we defined "outlier" as scoring 1 SDs on 2+ non-redundant tests, or 2+ SDs on 1+ test. We also used a more stringent definition of "outlier" as 1+ SD on 4+ non-redundant tests or 2+ SDs on 2+ non-redundant tests.

Scores on the Cognitive Failures Questionnaire (CFQ) were then subjected to comparable analyses, using total scores at Baseline and Week 4. and then controlling for baseline fatigue and depressive symptoms. All tests were 2-tailed, alpha = .05.

Results

Sample

One hundred fifteen patients were randomized, and 105 completed the 4-week trial. Eight of the 10 dropouts were randomized to placebo. Of the 105 study completers, 103 patients had complete neuropsychological test data and constitute the sample of interest. Mean age was 46 (SD=9; range = 28–70); 85% were male; 40% were Black, 34% were non-Hispanic white, 24% were Hispanic and 2%, other. Most had at least some college, although 20% had not finished high school. Half had a significant history of substance use, and 72% were men who had sex with men. For the entire sample, mean BDI score was 19.6 (SD=9.7) and mean Fatigue Severity Scale score was 51.1 (SD = 6.1) at baseline.

At baseline, mean CD4 cell count was 474 (SD=253) and 64% had an AIDS diagnosis according to CDC criteria, usually based on past rather than current illnesses and CD4 count. 88% were taking antiretroviral medications, 20% had hepatitis C, and 40% had a current (past month) depressive disorder including dysthymia, minor depression or major depression in partial remission. Twenty-nine percent were taking antidepressants. As shown on Table 1, the modafinil and placebo treatment groups did not differ on any baseline demographic, psychiatric or medical variables.

Treatment effects of modafinil vs. placebo

In an intention to treat analysis (N= 115), 73% (45/62) of patients randomized to modafinil were responders, compared to 28% (15/53) of placebo patients ($X^2 = 22.45$, 1df, $p<.0001$). Fatigue measures showed superiority of modafinil over placebo in reducing fatigue, although fatigue improved in both groups.

Responders did not differ from non-responders on any demographic variable, and response rate for the 21 patients with HCV was similar to that of patients without HCV in the total sample: 64% of HCV patients and 50% of HCV- patients were responders (p = NS).

Neuropsychological Test Performance

Modafinil vs. placebo groups—Repeated measures analysis of the 22 subtests from the 10 tests was used to compare treatment groups; results are shown on Table 2. Only 2 of the 22 subtests showed statistically significant superiority for the modafinil group (Digit Symbol and Grooved Pegboard Non-dominant Hand). This may be attributable to chance with alpha set at .

05. Performance by modafinil patients showed non-significantly greater improvement on 15 of the remaining 20 comparisons, although patients in both treatment groups showed improvement on nearly all tests.

We next examined the univariate correlations between the outcome variable of global change score and demographic variables such as age and education, and baseline and Week 4 measures of fatigue and depression (FSS and BDI). The only significant correlate was age, with younger age associated with greater global change (improvement) ($r = -2.25$, $p = .023$). The baseline BDI score showed a trend association: more depressive symptoms at study entry were associated with greater NP improvement at Week 4. Using the global change score as the outcome variable, an ANCOVA controlling for age and baseline BDI score produced a significant treatment group effect favoring modafinil ($F = 6.451$, 1df, $p = .013$).

Secondary Analyses

English as a Second Language—Patients for whom English was the second language were equally represented in both treatment groups: 7 (16%) in the placebo group and 11 (19%) in the modafinil group ($X^2 = .131$, 1 df, $p = .718$). Based on inspection, their performance at baseline was worse on 5 of the 22 subtests and better on two. However, their mean global change score did not differ from native English speakers in an ANCOVA controlling for baseline BDI and age, [.79 (4.5) vs. −.08 (4.0),$t = .855$, $df = 101$, $p = .394$).

Responders vs. Non-responders—Results of this comparison are essentially similar to those comparing treatment groups, which is not surprising since 43 of the 56 responders (77%) had been randomized to modafinil. Repeated measures analyses of the 22 subtests (from 10 tests) again showed 2 significant differences favoring Responders: Digit Symbol remained significantly superior for responders, and in this analysis WAIS Letter-Number Sequence was also superior for responders vs. non-responders.

Using the global change score as the outcome measure, an ANCOVA controlling for age and baseline depression (BDI) produced a trend response group effect favoring responders ($F = 2.989$, $p = .087$). Age was the only significant covariate ($F = 4.527$, $p = .036$).

Patients with Cognitive Impairment at Baseline—Of the 103 participants, only 6 patients (6%) were not outliers on any of the 22 tests when “outlier” was defined as 1+ standard deviation from the age and education-adjusted means. When we used the criterion of 1 SD on at least 2+ non-redundant tests or 2+SDs on 1+ test, 83 (81%) patients met this definition of “outlier.” We then defined “outlier” more rigorously as 1 SD on 4+ tests or 2 SD’s on 2+ tests, so that the “impaired” subgroup consists of 48 patients (47% of the total sample).

Using the first definition of “outlier,” the group means on the NP global change score did not differ significantly (the 83 patients in the impaired group mean = 0.1 [SD= 4.0]; 20 patients in the unimpaired group mean = 0.4 [SD = 4.6], 101 df, $t = .063$, $p = .95$). Using the more rigorous definition, the “impaired” group (N= 48) again did not differ from the “unimpaired” group (N=55) in terms of global mean score (means of .17 [SD = 4.2] vs. .02 [SD = 4.0, 101 df, $t = .188$, $p = .85$).

Neither time since HIV test nor history of substance use disorders were related to cognitive impairment, using the more rigorous definition of impairment. Severity of HIV illness was also unrelated: mean CD4 cell count did not differ between “impaired” (N = 48) and “unimpaired” (N = 55) groups (means of 449 (SD= 241) and 496 (SD=262) respectively; $t = .938$, 101 df, $p = .35$). nor did HIV RNA $\log_{10}$ viral load (means of 2.4 (SD=1.1) and 2.5 (SD=1.2) respectively, $t = .081$, 100df, $p = .935$).

Subjective Perception of Cognitive Function: The CFQ

For the group as a whole, mean CFQ score at study entry was 47 (SD=17) and at Week 4 was 37 (SD = 17). This decline reflects less perceived impairment at Week 4 compared to baseline (paired t = 6.27, 99 df, p = <.001). Each treatment group showed significant decline in CFQ scores (paired t for modafinil group: mean at baseline =47.6, Week 4 mean = 35.2, 57 df, p < . 001; for placebo group baseline mean = 45.5, at Week 4 = 40, 42 df, t = 2.72, p = .009). Comparing treatment groups using ANCOVA, controlling for CFQ baseline scores, the difference was significant with greater decline in perceived cognitive difficulties in the modafinil group (F = 5.43, p = .022).

CFQ scores were correlated with measures of depression (r with BDI = +0.45, p <.01) and fatigue (r with FSS = +0.28, p = .005). At Week 4, these remained significant correlates. However, CFQ and NP global mean change scores were not correlated significantly either at baseline (r = +0.03) or at Week 4 (r = −0.05). Similarly, the CFQ change score and the NP mean global change score were not significantly correlated (r = −0.10, p = .34).

DISCUSSION

Cognitive function improved more in the modafinil treatment group compared to placebo, although it is not a major effect and is not specific to any cognitive domain. Comparisons of performance on the 22 tests and subtests identified only two statistically significant differences between treatment groups, but the global change score did show superiority of modafinil. This overall effect for drug vs. placebo on the global NP score may be of more than academic interest; Heaton, Marcotte, White, Ross, Meredith, Taylor et al. (1996) have reported that this kind of global NP finding, even when slight, has been related to employment status in HIV+ individuals.

When we examined potential correlates of improvement in cognitive function for the total sample and also for the modafinil group analyzed separately, we found that improvement was associated with greater severity of depressive symptoms at study baseline, but was not correlated with baseline fatigue severity, time since HIV test, history of substance use, or HIV RNA viral load. However, lower baseline CD4 cell count was inversely related to global cognitive change scores: those with greater immunosuppression showed more improvement. Observed changes were not related to whether patients were native English speakers or spoke English as a second language. Similarly, the presence of some cognitive impairment at study baseline was not related to change in mean global score. Perhaps this may be explained by the inconclusive evidence of a connection between neuropsychological tests in a clinical setting and how individuals function in everyday life (Heaton et al, 1996).

Subjectively perceived cognitive problems (CFQ) improved for the entire sample at Week 4, but more so in the modafinil than placebo group. The CFQ scores were correlated with measures of both depression and fatigue, but neither the baseline nor Week 4 CFQ scores were correlated with NP global change scores. Other investigators (Wilkins, Robertson, Snyder, Robertson, van der Horst & Hall, 1991 and Moore, van Gorp, Hinkin, Stern, Swales & Satz, 1997) similarly found in their HIV+ respondents that subjective complaints of cognitive problems were common, but were not related to actual cognitive deficits on NP test performance.

Several study limitation should be considered. First, the 1-hour NP battery was somewhat limited, and more extensive tests may have revealed additional differences between treatment groups. Second, we did d not control for time between last medication dose and NP testing. Importantly, we did not have a measure of “real world” behavioral difficulties attributable to cognitive impairment.

Finally, in this sample the range of cognitive impairment was restricted; all participants were able to give informed consent (and travel alone by subway to the medical center).

Despite these shortcomings, our findings show a positive effect of 4 weeks of modafinil treatment on overall cognitive function among HIV+ adults with fatigue, both in terms of performance on NP tests and subjective perception of cognitive problems. Future research would usefully examine the effect of modafinil on patients with the primary presenting problem of cognitive impairment.

Acknowledgments

This work was partially supported by NIMH grant R01 MH072383 (JGR).

During the 3rd and 4th years of this study, modafinil and matching placebo were provided by Cephalon, Inc.

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Table 1

Baseline Demographic, Psychiatric and Medical Characteristics of Study Patients (N = 103)

	All Patients N = 103	Modafinil Group N = 59	Placebo Group N = 44	t or X^2	*p*
Demographic					
Age, mean (SD)	46 (9)	46 (9)	46 (8)	.165	.869
Ethnicity, number (%)					
Black	41 (40%)	22 (37%)	19 (43%)		
White (non-Hispanic)	35 (34%)	21 (36%)	14 (32%)		
				.444	.931
Hispanic	25 (24%)	15 (25%)	10 (23%)		
Other	2 (2%)	1 (2%)	1 (2%)		
Gender, number (%)					
Men	88 (85%)	51 (86%)	37 (84%)		
				.112	.738
Women	15 (15%)	8 (14%)	7 (16%)		
Years Education, mean (SD)	14 (3)	14 (3)	14 (3)	−.092	.927
Work Status, number (%)					
Full time	14 (14%)	10 (17%)	4 (9%)		
Part time	16 (16%)	12 (20%)	4 (9%)	4.496	.106
Unemployed	73 (71%)	37 (63%)	36 (82%)		
Psychiatric					
DSM-IV depression diagnosis[1], number, (%)	41 (40%)	26 (44%)	15 (34%)	1.047	.306
Taking antidepressant medication, number (%)	30 (29%)	15 (25%)	15 (34%)	.917	.338
Past drug use history, number, (%)	52 (51%)	31 (53%)	21 (48%)	.234	.629
		21.1		-	.079
Beck Depression Inventory-II, mean (SD)	19.6 (9.7)	(10.1)	17.7 (8.9)	1.776	
Fatigue Severity Scale, mean (SD)	51.5 (6.1)	51.7 (5.9)	51.2 (6.4)	−.403	.688
Cognitive Failures Questionnaire	47 (17)	48 (18)	45 (15)	−.633	.528
Neuropsychological Test Battery Outlier[2],					.319
number (%)	48 (47%)	25 (42%)	23 (52%)	.993	

J Clin Exp Neuropsychol. Author manuscript; available in PMC 2011 June 1.

	All Patients N = 103	Modafinil Group N = 59	Placebo Group N = 44	t or X^2	*p*
Medical					
Months since testing HIV+, mean (SD)	145 (69)	136 (70)	157 (65)	1.540	.127
AIDS Diagnosis, number, (%)	6 (64%)	39 (66%)	27 (61%)	.246	.620
Taking antiretroviral therapy, number, (%)	93 (90%)	53 (90%)	40 (91%)	.033	.855
Hepatitis C, number, (%)	21 (20%)	10 (17%)	11 (25%)	1.006	.316
CD4 cell count, mean (SD)	474 (253)	486 (250)	458 (258)	−.560	.577
		2.51	2.35		.438
Log_{10} Viral Load, mean (SD)	2.44(1.14)	(1.16)	(1.13)	−.704	

[1] DSM-IV depression diagnosis of major depressive disorder in partial remission, minor depression, or dysthymia

[2] Neuropsychological test battery outlier defined as 1 SD below average on 4+ tests or 2 SD's on 2+ tests

Table 2

Neuropsychological Test Comparisons by Treatment Group Using Repeated Measure ANCOVAs with Gender, Age and Years of Education as Covariates.

	Modafinil Group N = 59		Placebo Group N = 44			
TEST	**Baseline**	**Week 4**	**Baseline**	**Week 4**	**Interaction Term: Time by Group F**	***p***
WHO AVLT: Trial 1–5 Total	47 (10)	53 (10)	47 (10)	51 (11)	1.383	.243
Delay 1	9.6 (2.8)	11.2 (2.7)	9.4 (2.5)	10.3 (2.8)	1.211	.274
Delay 2	9.7 (2.9)	11.5 (2.6)	9.5 (2.8)	10.7 (2.9)	1.920	.169
Recognition	13.5 (1.8)	14.2 (1.3)	13.5 (1.8)	13.9 (1.2)	.748	.389
WAIS: Digit Symbol	66 (14.6)	74 (16.6)	69 (14.4)	72 (15.4)	8.583	.004 *
Digit Span	16 (4.5)	17 (4.3)	16 (3.9)	17 (3.8)	.007	.933
Symbol Search	31 (9)	32 (9)	29 (7)	31 (9)	.489	.486
Letter-Number Sequence	9.6 (2.5)	10.0 (2.8)	9.3 (2.6)	9.5 (3.0)	.658	.419
Stroop: Words	95 (18)	99 (18)	98 (14)	99 (13)	1.531	.219
Colors	68 (13)	71 (14)	67 (13)	67(12)	3.384	.069
C-W	40 (9)	43 (9)	38 (8)	40 (8)	2.081	.152
Interference	0.57 (7.03)	2.46 (6.56)	−1.91 (6.15)	−0.02 (6.79)	.001	.972
Color Trails: 1	41 (17)	35 (15)	47 (21)	42 (21)	.053	.819
2	90 (39)	83 (33)	95 (35)	88 (29)	.001	.976
Grooved Peg: Dominant Hand	71 (14)	67 (12)	72 (17)	70 (14)	.834	.363
Non-Dominant	79 (19)	73 (15)	79 (19)	78 (20)	3.963	.049 *
Verbal Fluency: FAS Letters						
Total	36 (12)	40 (11)	41 (13)	44 (14)	1.866	.175