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COGNITIVE FUNCTION IN EARLY CLINICAL PHASE HUNTINGTON DISEASE AFTER RIVASTIGMINE TREATMENT

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SUMMARY

Background: *In Huntington disease (HD) patients receiving rivastigmine treatment improvement of behavioral symptoms and of cognitive function (assessed with screening diagnostic instruments) has been reported. The aim of the present study was to verify such improvement in cognitive function by cognitive function assessment with a detailed neuropsychological battery covering all relevant cognitive systems expected to be impaired in early phase HD.*

Subjects and methods: *Eighteen (18) HD patients entered the study and were randomly allocated to the rivastigmine and placebo group. All subjects underwent neuropsychological assessment at baseline. Follow-up neuropsychological assessment was applied after 6 months of rivastigmine or placebo treatment. Eighteen (18) healthy controls entered the study to control for practice effect and underwent neuropsychological assessment at baseline and after 6 months, without treatment. The neuropsychological battery consisted of assessment tools that are sensitive to cognitive impairment seen in early phase HD: CTMT, SDMT, Stroop (attention and information control), RFFT, TOL, Verbal fluency (executive functioning), CVLT-II, RCFT (learning and memory). Effect of rivastigmine and possible effect of practice was assessed using the mixed ANOVA model.*

Results: *No statistically significant effect of rivastigmine treatment on cognitive function in HD patients was detected. There was no evidence for practice or placebo effect.*

Conclusions: *Detailed neuropsychological assessment did not confirm previously reported effect of rivastigmine treatment on cognitive function in HD patients. The limitations of our study are, in particular, small sample size and the lack of a single measure of relevant cognitive functioning in HD patients. Instead of focusing solely on statistical significance, a clinical relevance study is proposed to clarify the issue of rivastigmine effects in HD.*

Key words: *Huntington Disease – rivastigmine – neuropsychology - cognitive function*

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INTRODUCTION

Huntington disease (HD) is an autosomal dominantly inherited progressive neurodegenerative disorder, marked by changes in personality and abnormalities in motor and cognitive function. There is, as yet, no drug treatment to prevent or repair the HD neurodegenerative process (Van Raamsdonk et al. 2005). HD onset is usually between 30 and 50 years of age, while the juvenile form of HD is rare. Genetic and environmental factors add to HD onset variability (Spires & Hannan 2005, Josefson 1997).

HD can be diagnosed prenatally, and genetic testing allows for research in asymptomatic disease stages. Understanding gene mutation and molecular mediators of pathogenesis is key in development of new therapeutic methods for disorders such as HD (Spires & Hannan 2005), while functional imaging allows us to connect the neuroanatomical basis of the disease with its behavioral and cognitive symptoms (Montoya et al. 2006).

Beside motor symptoms and personality changes, cognitive deficits are the key characteric of HD. Neuropsychological studies (Lawrence et al. 1998, Montoya et al. 2006, Ho et al. 2003, Backman et al. 1997, Lawrence et al. 1996), some of them longitudinal (Ho et al. 2003, Bachoud-Levi et al. 2001), have demonstrated the heterogeneous nature of the cognitive deficit, but unfortunately uncomparable research designs were used. Thus, the cognitive impairment in HD is not yet well defined. HD is conceptualized as a subcortical dementia, due to the fact that primary HD pathology is found in subcortical brain structures and that its key characteristics are impairment of memory recall, information processing speed, cognitive flexibility and personality changes (Ross & Margolis 2001, Lawrence et al. 1998). According to anatomical and neuropathological data, expected cognitive deficits in HD are similar to those seen in focal lesions of the prefrontal cortex, which lead researchers to adopt the term frontostriatal dementia when discussing early phase HD (Montoya et al. 2006, Ho et al. 2003). Frontostriatal neuropathology was confirmed in functional imagining studies in early and moderate disease phases of HD. (Montoya et al. 2006, Backman et al. 1997). In early phase HD pathology is thought to begin in the dorsal caudate nucleus that forms part of the dorsolateral prefrontal circuit and extends over the whole frontostriatal system. Studies of brain tissue of deceased HD patients have shown an extensive decline of acetylcholine in striatum, caudate nucleus and the hippocampus (Spokes 1980, Kanazawa et al. 1985).

Acetylcholinesterase inhibitors, such as rivastigmine, positively affect cognitive functioning in Alzheimer's (Doraiswamy et al. 2002, Birks 2006, Roesler M et al. 1999) and Parkinson's disease (Schmitt et al. 2010, Emre et al. 2004, Reading et al. 2001) by raising acetylcholine levels in brain tissue, leading to improvement in cognitive and motor symptoms. However, responses to treatment are different with regard to type of dementia (Weintraub et al. 2011). Significant losses of acetylcholine and choline acetyltransferase activity have been observed in striatum, nucleus accumbens and hippocampus of HD patients. On the other hand, the activity of acetylcholinesterase is preserved, as are hippocampal postsynaptic muscarinic M1 receptors, suggesting a presynaptic cholinergic dysfunction, such as is also observed in AD. This finding led to the proposal that rivastigmine should improve motor, cognitive and behavioral functions in HD (Rot et al. 2002).

Cognitive changes are already present in the early phase HD and worsen in the following phases. Neuropsychological studies of HD and HD asymptomatic gene carriers (AGC) (Lemiere 2004, Lawrence et al. 1998, Kirkwood et al. 2000, Kirkwood et al. 2000, Hahn-Barma et al. 1998, Kirkwood et al. 1999, Witjes-Ane et al. 2003) have shown different patterns of cognitive impairment, including psychomotor, attention, memory, executive and visuospatial abilities. Longitudinal design studies have demonstrated the progression of cognitive decline (Bachoud-Levi et al. 2001, Lemiere 2004). The nature and extent of cognitive changes are not clearly defined (Paulsen 2010, Paulsen 2011). In later phase HD almost all cognitive functions are impaired; there is a global decline in cognitive functioning, with the cognitive impairment pattern becoming impossible to differentiate (Ho et al. 2003, Craufurd & Snowden 2002).

Changes of cognitive and behavioral symptoms after rivastigmine treatment are as yet poorly defined. An animal study (Kumar & Kumar 2009) confirmed rivastigmine as an effective therapeutic agent in reducing Huntington like symptoms in rats. In human studies (Rot et al. 2002, De Tommaso et al. 2004, De Tommaso et al. 2007) improvement of cognitive and behavioral symptoms has been reported, applying MMSE as an indicator of cognitive functioning. MMSE is widely used as an estimate of cognitive impairment (Woodford & George 2007) but has not been constructed as a diagnostic tool (Folstein et al. 2001). The following are the limitations of MMSE: the cutoff score has to consider factors such as age and education; only a limited number of cognitive domains are assessed, and it is insensitive to deficits in frontal lobe and the right hemisphere (Snyder & Nussbaum 2006). MMSE is used particularly as a dementia-screening test, i.e. as the first stage of cognitive assessment, leading to an extensive neuropsychological diagnostic process.

While MMSE offers a brief quantitative measure of cognitive status and can be used to follow the course of cognitive changes in the individual patient over time, as well as his response to treatment (Folstein et al. 2001), a thorough assessment of cognitive impairment requires a more extensive neuropsychological examination. Therefore, the present study was designed to further assess possible improvements in cognitive function in early stage HD patients receiving rivastigmine treatment using neuropsychological diagnostic instruments that cover a wider area of cognitive domains. The tools used in our study assess in depth cognitive functions that are usually impaired in early phase HD with focus on executive, memory and attention functions.

To our knowledge, this is the first follow-up study of rivastigmine treatment in HD using a comprehensive battery of neuropsychological tests. Our research should contribute to a better understanding of rivastigmine effect on cognitive functioning in HD patients.

METHOD

Participants

This was a prospective, randomized controlled, double-blind study. Male and female patients between 18 and 65 of age (outpatients at the Division of Neurology, University Clinical Center Ljubljana) were included in the study.

Patient enrolment was additionally based on clinical treatment relevance (rivastigmine potential to alleviate HD symptoms and if the therapy was justified).

Inclusion criteria were: clinically diagnosed and genetically confirmed HD with mild motor impairment, as measured by the Slovenian version of Unified Huntington's disease rating scale (UHDRS). Mild motor impairment on UHDRS was reflected in UHDRS score range of 5 - 25.

Exclusion criteria were: contraindication to rivastigmine (pregnant or lactating women, children, liver failure patients and carbamate sensitivity); history or presence of neurological disease other than HD; traumatic brain injury; brain surgery; psychiatric disease and all cognitive function affecting diseases, as well as all life-threatening states, such as heart rhythm disorder, heart failure, severe and uncontrolled hypertension, severe chronic obstructive pulmonary disease, liver or kidney failure, endocrine disorder and all other study-obstructive conditions (severe eyesight loss, language incompatibility, illiteracy).

Originally, 30 HD patients were considered, but 12 were excluded due to exclusion criteria. Patients were informed that the treatment given in the study is used in Alzheimer's disease patients, but is experimental in HD patients, and that there was a two-third chance of them receiving treatment, and one-third chance of receiving placebo. 18 patients were included into the study and were randomly allocated to two groups. For every placebo patient two patients were allocated to the treatments group. Thus, 6 patients were entered into the placebo group, and 12 patients into the rivastigmine treatment group. Group allocation was revealed to HD

patients after study conclusion. Concomitant treatment regimens remained unchanged. Research design is shown in Figure 1. Demographic data of HD patients are included in Table 1.

Eighteen (18) healthy volunteers, matched with patients in demographic characteristics (age, gender, education), with same exclusion criteria as the treatment group, have been included into control group.

The study was approved by The National Medical Ethics Committee of the Republic of Slovenia (NMEC), which conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). All patients gave informed consent and their anonymity was preserved.

Instruments

The neuropsychological battery consisted of standardized neuropsychological tests: Tests of attention, information processing and psychomotor speed (*Symbol Digit Modalities Test – SDMT* (Smith 2002)*; Stroop Color and Word Test – STROOP* (Golden 1978)*; Comprehensive Trail-Making Test – CTMT* (Reynolds 2002)*;* tests of executive functioning *(Verbal Fluency – VF* (Benton et. al 1994)*; Ruff Figural Fluency Test – RFFT* (Ruff 1996)*; Tower of London – TOL* (Culbertson & Zillmer 2005)); and tests of learning and memory (*Rey Complex Figure Test – RCFT* (Meyers & Meyers 1995); *California Verbal Learning Test – II – CVLT-II standard and alternate form.* All coefficients of reliability of the alternate form of CVLT-II are robust, ranging between r=0.64 and r=0.79 (r=0.79 for learning trials; r=0.73 for short delay recall; r=0.76 for long delay recall; r=0.64 for recognition hits) (Delis et al. 2000). At follow up, standard forms of all applies cognitive tests were used, with the exception of alternate version that was used for CVLT-II.

Procedure

All HD patients were measured on the UHDRS. Before allocation to treatment or placebo group, they underwent a battery of neuropsychological tests, as did the control group. The battery consisted of all instruments listed above, the CVLT-II standard form was used at this point. The treatment group was given rivastigmine at a 1.5 mg dose twice daily. The dose was increased to 3 mg twice daily after three months of treatment. The placebo group was given the inactive ingredient in alike capsules and at same time intervals as the treatment group. After six months of treatment/ placebo all patients underwent the same neuropsychological test battery, as did the control group. At follow up the parallel version of CVLT-II (alternate form) was applied.

In case of statistically relevant improvement of motor and/or cognitive functioning, the study was to become open label, with rivastigmine doses increased from 4.5 to 6 mg twice daily.

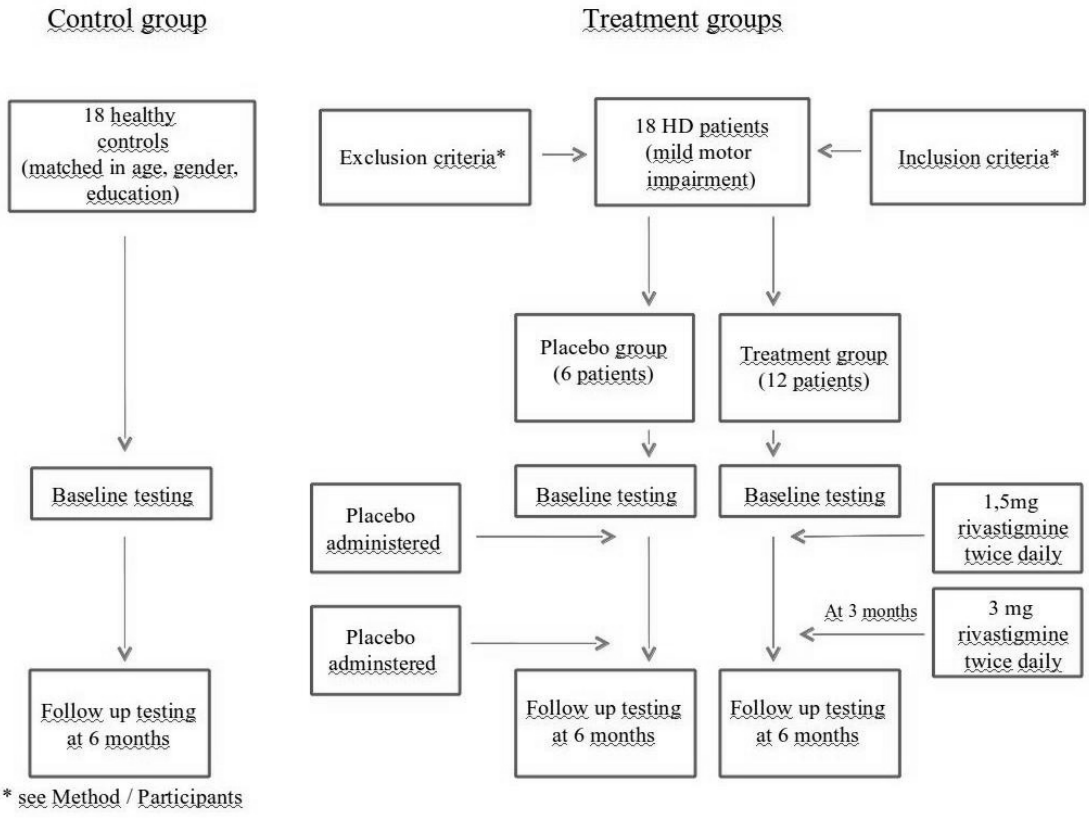

Figure 1. Research design of the current study

Table 1. Demographic and clinical characteristics of HD patients

Parameter	Rivastigmine	Placebo	p-values
Patient (N)	11	6	
Age (yrs)*	47.7±10.7 (27-62)	43.0±12.5 (22–59)	0.21[a]
Education (yrs)*	12.4±1.6 (11–16)	12.3±1.9 (11–16)	0.50[b]
Gender			
Female	7	5	
Male	4	1	
Drugs at admission			
3	1	-	
2	1	-	
1	-	1	
Type of drug			
Sertralin	1	-	
Olanzapine	2	-	
Citalopram	1	-	
Alprazolam	1	-	
Quetiapine	-	1	
Age at onset*	44.6±10.2 (25–59)	39.5±13.9 (17–57)	0.20[a]
Disease duration*	2.8±1.7 (1–7)	3.5±3.5 (1–10)	0.36[b]

Note: p-values denote the statistical significance of differences in demographic and clinical characteristics of the rivastigmine and placebo group. Independent-Samples T-test was used for the data meeting criteria for use of a parametric test and Kolmogorov-Smirnov Z test was used for other data. All values were above the 0.05 criteria., meaning there was so statistically significant differences between the rivastigmine and placebo groups. * Values are means ± standard deviations (ranges are in parentheses); [a] Independent-Samples T-test was used; [b] Kolmogorov-Smirnov Z test was used

Statistical analysis

Demographic and clinical characteristics were compared between rivastigmine and placebo groups using Independent-samples t-test and Kolmogorov-Smirnov Z test. Mean values and standard deviations were reported for the rivastigmine, placebo and healthy control groups. First and second neuropsychological assessments were compared in the healthy control group to screen for possible effect of practice. Baseline and follow-up neuropsychological assessment in the rivastigmine and placebo group were compared using the mixed 2 x 2 analysis of variance (ANOVA) model, with Drug (rivastigmine vs. placebo) as a between-subjects factor and Follow-up (baseline and follow-up assessment) as a within-subjects factor.

RESULTS

No statistical differences were found between the rivastigmine and placebo group regarding the demographic and clinical characteristics of the included 18 patients (Table 1).

One treatment patient was excluded in mid-study due to personal issues. His data and the data of his matched control was excluded from the statistical analysis.

Table 2 shows mean and standard deviations values of neuropsychological assessment variables across all groups. Some variables showed no cognitive improvement across rivastigmine and placebo groups and were thus excluded from further analysis (SDMT total, CTMT1, CTMT2&3, CTMT4&5).

Susceptability to practice effect emerges in normal as well as brain damaged patients (Lezak 2004), thus healthy controls were used to control for possible effect of practice. Practice effect in healthy controls was statistically significant in CVLT-II 1-5 Trials, possibly due to knowledge of the semantic clustering principle; the same trend was observed in HD patients, which is congruent with the observation that patients appears to approach tasks more effectively in repeated assessments (Lezak 2004). Additionally, statistically significant improved cognitive functioning in healthy controls at second condition was observed in VF, RCFT Immediate Recall, RCFT Delayed Recall and CVLT-II LD Recall.

Table 3 shows that there was a significant effect of Drug (between subjects - rivastigmine vs. placebo group) on TOL total moves, $F(1, 15)=6.154$, $p<0.05$ and TOL total time, $F(1, 15)=13.43$, $p<0.05$, meaning there was a significant difference between rivastigmine and placebo groups across repeated assessments.

There was a significant main effect of Follow-up on TOL rule violations, $F(1, 15)=4.765$, $p<0.05$ and CVLT-II Trials 1-5, $F(1, 15)=8.304$, $p<0.05$, meaning there was a significant difference between baseline and follow-up assessments. There was however no interaction effect of Follow up x Drug on TOL rule violations, $F(1, 15)=0.529$, $p=0.478$ and CVLT-II Trials 1-5, $F(1, 15)=0.403$, $p=0.535$, meaning the groups showed statistically significant improvement regardless of the type of treatment they received (rivastigmine or placebo). Additionally, a follow-up practice effect was observed in CVLT-II Trials 1-5 in healthy controls, meaning the improvement in both treatment groups could be attributed to practice effect.

Table 2. Neuropsychological assessment mean values and standard deviations of HD patients before (1) and after (2) rivastigmine / placebo treatment, healthy controls (HC), and practice effect with effect size for HC

Assessment	Time	Rivastigmine		Placebo		Healthy controls				
		M	SD	M	SD	M	SD	t/Ta	p	r
SDMT total	1	26.36	6.84	29.33	8.80	52.29	8.26	-1.09	0.146	0.26
	2	22.55	5.57	25.83	7.08	54.82	12.75			
Stroop word	1	62.00	18.08	64.50	11.45	98.88	11.31	-0.96	0.176	0.23
	2	62.36	14.34	69.83	15.46	100.88	10.92			
Stroop color	1	41.73	11.90	49.00	10.45	75.88	11.29	1.92	0.370	0.43
	2	42.00	11.62	50.33	13.69	79.24	12.15			
Stroop color word	1	29.91	4.70	29.17	14.72	45.47	6.78	-1.62	0.062	0.38
	2	27.00	8.26	30.00	10.88	48.92	7.99			
CTMT1	1	93.40	41.67	75.00	16.52	40.47	11.47	-3.34	0.000*	0.57
	2	106.64	58.06	78.17	33.68	34.29	11.37			
CTMT2&3	1	108.35	68.23	84.75	31.99	39.82	15.72	0.22	0.420	0.05
	2	120.59	71.80	96.25	51.82	39.06	14.85			
CTMT4&5	1	155.30	74.65	132.00	70.17	48.97	16.96	-0.22	0.820	0.05
	2	184.59	136.30	132.17	66.59	49.88	16.17			
VF	1	12.91	4.89	17.33	5.75	28.35	6.50	-2.60	0.010*	0.54
	2	17.18	6.57	15.17	5.74	31.94	8.33			
RFFT unique designs	1	48.00	20.70	56.17	21.79	93.53	21.88	-2.15	0.240	0.47
	2	55.80	25.69	58.83	29.61	102.53	19.04			
RFFT errors	1	0.22	0.21	0.36	0.51	0.07	0.06	-0.12	0.463	0.02
	2	0.22	0.16	0.16	0.18	0.07	0.07			
TOL total moves	1	80.00	27.04	48.83	12.38	32.24	17.27	-0.23	0.410	0.06
	2	70.18	21.78	50.00	34.84	33.53	21.38			
TOL total rule violations	1	3.36	4.01	1.50	1.87	0.12	0.48	-0.38	0.500	0.06
	2	1.36	1.96	0.50	0.84	0.18	0.39			
TOL total time	1	776.45	209.79	477.83	133.47	279.53	122.60	0.77	0.220	0.19
	2	712.64	177.66	444.17	133.24	260.59	107.30			
RFCT Immediate Recall	1	7.32	3.39	6.75	5.80	22.12	7.42	-2.73	0.010*	0.56
	2	8.23	6.81	12.00	8.85	24.88	7.40			
RFCT Delayed Recall	1	8.14	3.86	6.50	6.52	21.85	7.57	-2.65	0.010*	0.54
	2	8.55	7.05	11.41	8.59	24.56	7.65			
RFCT Recognition	1	16.45	3.21	18.83	0.98	20.12	2.69	-1.40	0.090	0.24
	2	17.73	3.26	18.83	2.14	21.06	2.14			
CVLT-II Trials 1 – 5	1	38.90	11.01	39.67	10.33	58.94	10.05	-4.55	0.000*	0.75
	2	42.64	9.02	45.50	7.7	66.58	8.37			
CVLT-II SD Recall	1	7.27	3.13	7.67	3.01	13.29	2.61	-1.47	0.100	0.25
	2	7.45	2.84	7.50	3.62	13.76	2.70			
CVLT-II LD Recall	1	7.45	3.11	8.33	2.65	13.41	3.02	-1.86	0.035*	0.32
	2	7.81	3.54	8.83	2.79	14.35	1.93			
CVLT-II Recognition Task	1	12.18	2.14	14.33	2.16	15.82	0.39	-1.00	0.266	0.17
	2	14.27	2.05	14.00	2.50	15.65	0.61			

Abbreviations: M = mean; SD = standard deviation; t/Ta = t stands for t-statistic of the dependent t-test, T stands for T-statistic of the Wilcoxon signed-rank test; p = statistical significance; r = effect size;
a Dependent t-test was used for and: SDMT, Stroop word, Stroop color, Stroop color word, CTMT2&3, CTMT4&5, VF, RFFT unique designs, TOL total move score, TOL total problem solving time, RCFT Immediate Recall, RCFT Delayed Recall, CVLT Trials 1 – 5; Wilcoxon signed-rank test was used for: CTMT1, RFFT errors, TOL total rule violations, RCFT Recognition, CVLT-II Short Delay, CVLT-II Long Delay, CVLT-II Recognition; *p<0.05

Table 3. Mixed 2x2 ANOVA model for effect of rivastigmine in follow-up neuropsychological assessment

Assessment	Source		SS	MS	df	F	p
Stroop word	Between Subjects	Drug	96.471	96.471	1	0.481	0.499
		B-S Error	3010.470	200.698	15		
	Within Subjects	Follow-up	63.002	63.002	1	0.819	0.380
		Follow-up x Drug	47.943	47.943	1	0.623	0.442
		W-S Error	1153.939	76.929	15		
Stroop color	Between Subjects	Drug	236.386	236.386	1	1.879	0.191
		B-S Error	1886.879	125.792	15		
	Within Subjects	Follow-up	5.007	5.007	1	0.157	0.697
		Follow-up x Drug	2.184	2.184	1	0.069	0.797
		W-S Error	477.758	31.851	15		
Stroop color word	Between Subjects	Drug	31.837	31.837	1	0.435	0.520
		B-S Error	1098.045	73.203	15		
	Within Subjects	Follow-up	0.144	144	1	0.007	0.937
		Follow-up x Drug	144	144	1	0.007	0.937
		W-S Error	330.091	22.006	15		
VF	Between Subjects	Drug	1.686	1.686	1	0.047	0.831
		B-S Error	539.284	35.952	15		
	Within Subjects	Follow-up	2.000	2.000	1	0.121	0.732
		Follow-up x Drug	55.530	55.530	1	3.369	0.086
		W-S Error	247.235	16.482	15		
RFFT unique	Between Subjects	Drug	97.538	97.538	1	0.174	0.683
		B-S Error	7843.400	560.243	14		
	Within Subjects	Follow-up	168.033	168.033	1	1.983	0.181
		Follow-up x Drug	32.033	32.033	1	0.378	0.549
		W-S Error	1186.467	84.748	14		
RFFT errors	Between Subjects	Drug	0.005	0.005	1	0.141	0.713
		B-S Error	0.509	0.036	14		
	Within Subjects	Follow-up	0.086	0.086	1	1.088	0.315
		Follow-up x Drug	0.062	0.062	1	0.790	0.389
		W-S Error	1.105	0.079	14		
TOL total moves	Between Subjects	Drug	2559.118	2559.118	1	6.154	0.025*
		B-S Error	6237.617	415.841	15		
	Within Subjects	Follow-up	145.295	145.295	1	0.340	0.569
		Follow-up x Drug	234.236	234.236	1	0.547	0.471
		W-S Error	6419.235	427.949	15		
TOL rule violations	Between Subjects	Drug	7.219	7.219	1	1.312	0.270
		B-S Error	82.545	5.503	15		
	Within Subjects	Follow-up	17.471	17.471	1	4.765	0.045*
		Follow-up x Drug	1.941	1.941	1	0.529	0.478
		W-S Error	55.000	3.667	15		
TOL total time	Between Subjects	Drug	312133.510	312.133	1	13.430	0.002*
		B-S Error	348508.700	348508.70	15		
	Within Subjects	Follow-up	18447.570	18447.570	1	1.170	0.297
		Follow-up x Drug	1764.750	1764.750	1	0.112	0.743
		W-S Error	236551.485	15770.100	15		
RFCT Immediate	Between Subjects	Drug	2.387	2.387	1	0.058	0.814
		B-S Error	622.628	41.509	15		
	Within Subjects	Follow-up	55.373	55.373	1	3.938	0.066
		Follow-up x Drug	51.667	51.667	1	3.675	0.074
		W-S Error	210.892	14.059	15		

Abbreviations: SS = Sum of squares; MS = mean square; df = degrees of freedom; F = F-ratio; p = statistical significance, * $p<0.05$

Table 3. (Continous)

Assessment	Source		SS	MS	df	F	p
RFCT Delayed	Between Subjects	Drug	0.461	0.461	1	0.012	0.916
		B-S Error	596.973	39.798	15		
	Within Subjects	Follow-up	44.358	44.358	1	4.477	0.051
		Follow-up x Drug	49.564	49.564	1	5.002	0.041*
		W-S Error	148.627	9.908	15		
RFCT Recognition	Between Subjects	Drug	40.816	40.816	1	4.259	0.057
		B-S Error	143.742	9.583	15		
	Within Subjects	Follow-up	0.144	0.144	1	0.005	0.943
		Follow-up x Drug	0.144	0.144	1	0.005	0.943
		W-S Error	415.091	27.673	15		
CVLT-II Trials 1 – 5	Between Subjects	Drug	12.727	12.727	1	0.150	0.704
		B-S Error	1269.890	84.659	15		
	Within Subjects	Follow-up	177.434	177.434	1	8.304	0.011*
		Follow-up x Drug	8.610	8.610	1	0.403	0.535
		W-S Error	320.508	21.367	15		
CVLT-II SD Recall	Between Subjects	Drug	0.187	0.187	1	0.022	0.884
		B-S Error	127.254	8.484	15		
	Within Subjects	Follow-up	0.000	0.000	1	0.000	0.989
		Follow-up x Drug	0.236	0.236	1	0.100	0.756
		W-S Error	35.235	2.349	15		
CVLT-II LD Recall	Between Subjects	Drug	3.482	3.482	1	0.410	0.531
		B-S Error	127.254	8.484	15		
	Within Subjects	Follow-up	1.448	1.448	1	0.517	0.483
		Follow-up x Drug	0.036	.036	1	0.013	0.911
		W-S Error	42.023	2.802	15		
CVLT-II Recognition Task	Between Subjects	Drug	3.426	3.426	1	1.117	0.307
		B-S Error	46.015	3.068	15		
	Within Subjects	Follow-up	5.996	5.996	1	1.831	0.196
		Follow-up x Drug	11.408	11.408	1	3.484	0.082
		W-S Error	49.121	3.275	15		

Abbreviations: SS = Sum of squares; MS = mean square; df = degrees of freedom; F = F-ratio; p = statistical significance, * p<0.05

There was a significant Follow-up x Drug interaction in RFCT Delayed Recall, $F(1, 15)=5.002$, $p<0.05$, but the observed improvement after treatment came from the placebo group, while the rivastigmine group only showed a slight increase in performance.

There was an observed trend of main effect of Follow up in RFCT Immediate, $F(1, 15)$, $F=3.938$, $p=0.066$, RFCT Delayed Recall, $F(1, 15)=4.477$, $p=0.051$, both due to an improvement in the placebo group. An observed trend of Follow-up x Drug interaction was seen in VF, $F(1, 15)=3.369$, $p=0.086$, but in light of the practice effect seen in healthy controls, $t(15)=-2.60$, $p=0.010$, $r=0.54$, the results could not be interpreted as solely the effect of rivastigmine treatment. An observed trend of Follow-up x Drug interaction was seen in RFCT Immediate Recall, $F(1, 15)=3.675$, $p=0.074$, again due to improvement in the placebo group. An observed trend of Follow-up x Drug interaction was seen in CVLT-II Hits, $F(1, 15)=3.484$, $p=0.082$, and while the result was not statistically significant according to our preset statistical significance criteria, the result was due to an effect of rivastigmine treatment (also see Figure 2).

There was no statistically significant effect detected across other neuropsychological assessment variables.

DISCUSSION

The purpose of our study was to examine the effect of rivastigmine treatment on cognitive functions in HD patients. Our hypothesis was based on findings of previous studies (Rot et al. 2002, De Tommaso et al. 2004, De Tommaso et al. 2007), which showed an improvement of cognitive and behavioral symptoms in HD patients receiving rivastigmine treatment. Our research expanded on previous studies by applying an extended neuropsychological assessment battery, covering all cognitive function systems (attention, memory and learning, executive functions) which are usually impaired in early phase HD.

Our study included multiple neuropsychological assesments, which have shown reliability in assessing early changes in cognitive functioning (especially executive, memory and attention functions) by previous studies (Lemiere 2004, Lawrence et al. 1998, Kirkwood et al. 2000, Kirkwood et al. 2000, Hahn-Barma et al.

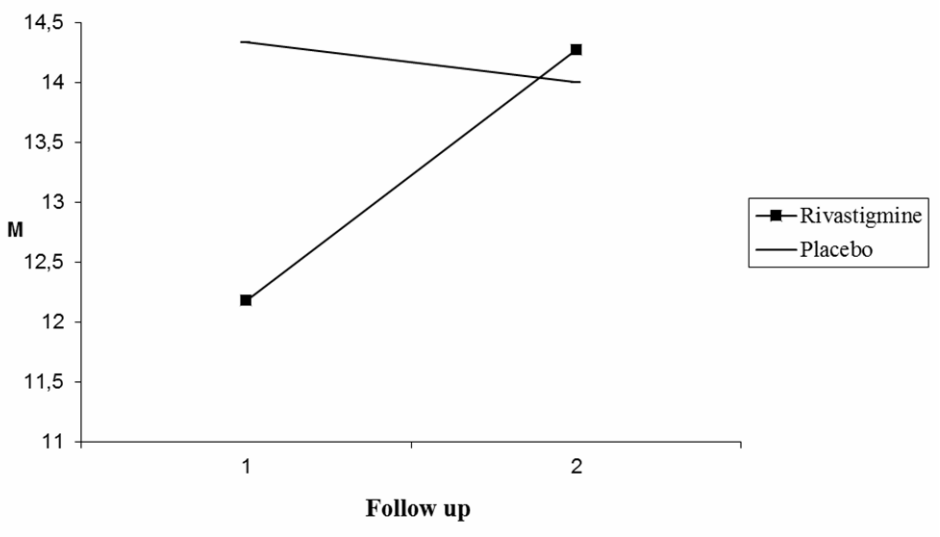

Figure 2. CVLT Recognition Task Interaction

1998, Kirkwood et al. 1999, Witjes-Ane et al. 2003, Paulsen 2010) on asymptomatic gene carriers (ACG). Multiple neuropsychological instruments were used for assessment of attention, information and psychomotor speed, executive functioning and learning and memory. Contrary to our hypothesis and previous findings (De Tommaso et al. 2004, Rot et al. 2002, De Tommaso et al. 2007), only several trends were detected, but overall, no statistically significant effect across neuropsychological assessment variables could be demonstrated.

A trend towards improvement was found in recognition of verbal information - on a yes/no recognition measure (CVLT-II Recognition Task). Subjects on rivastigmine treatments showed a more accurate discrimination between target and non-target words. As there was no practice effect found in the healthy controls in this measure, we can assign cognitive improvement in the recognition of verbal information to rivastigmine. The poor recognition performance on CVLT-II assessment can be discussed as a consequence of executive deficits in HD patients. A meta-analysis (Wheeler et al. 1995) determined that frontal pathology is clearly associated with deficits also in the performance of recognition tasks. At that time, it was generally agreed that the frontal lobe is involved in the memory processes, but its dysfunction does not cause a general memory impairment. Yet, the findings of the meta-analysis showed the importance of frontal lobe not only in free recall tasks, but the recognition tasks of episodic memory, which was impaired in patients with frontal lobe deficits. This is why we suggest impaired recognition performance in CVLT-II is a consequence of executive functions deficits in HD patients. Given that their performance on the recognition tasks improved after treatment with rivastigmine, it can be argued that rivastigmine treatment helped HD patients' to use more effective memorization strategies. This would be in line with the study done by Baldo et al (2002): their results showed that frontal lobe patients had trouble on the yes/no recognition task of CVLT-II assessment, as these patients made a significantly higher number of errors. This can be attributed to a deficit in executive functioning. Functional neuroimaging studies suggest that the prefrontal cortex plays a crucial role in target stimuli selection and inhibition of non-target stimuli (Shimamura 2000).

A trend toward statistical significance was found in assessments of executive planning abilities (TOL total rule violations variable); subjects on rivastigmine and placebo treatments showed improvement in capabilities of following and respecting symbolic rules. This improvement of cognitive functions in time cannot be assigned to rivastigmine treatment as improvement on this variable was also observed in the placebo group. HD patients, regardless of the treatment they received (rivastigmine and placebo), also improved their score in verbal learning assessments (CVLT-II Trials 1- 5) at follow-up assessment. This was a practice effect, as the same trend was noticed in healthy controls.

The MMSE used in previous studies on the effect of rivastigmine treatment in HD assesses a restricted set of cognitive functions in a simple and fast way (Lezak 2004). It is a good screening test, but it is not a definitive indicator of brain disease (Folstein et al. 2001). MMSE is most effective in discriminating patients with moderate and/or severe cognitive deficits from healthy individuals. It is less sensitive in discriminating mild cognitive deficits and/or early stages of dementia from healthy functioning; it also doesn't recognize cognitive differences between neurological patients and patients with lateralized or focal lesions (Folstein et al. 2001, Lezak 2004). MMSE is a less sensitive screening tool for subcortical dementia, where typically subcortical structures are damaged, including rostral brain stem, thalamus, basal ganglia and reciprocal connections between cortical and subcortical regions (Duke & Kaszniak 2000). Therefore, MMSE is not the most suitable choice for subcortical deficit assessments.

It has been reported that an average score on MMSE is not uncommon in patients with deficits in the right hemisphere, and even more frequent in patients with frontal subcortical dementia (Folstein et al. 2001). Deficits in motor functions (motor speed and gait stability) are a very important difference between cortical and subcortical dementia; motor functions are typically preserved in cortical dementia, but not in subcortical dementia. Early subcortical dementia typically manifests itself with prominent motor impairment (also gait disorder). The De Tommaso study reported a slight increase on MMSE assessment (2-years follow up), and furthermore suggested that chorea significantly improved in the rivastigmine group; reduction of disability in patients with rivastigmine therapy was positively related to improvements in motor scores (De Tommaso et al. 2007), which in turn confirms the role of cholinergic striated neurons in control of voluntary movements. It can be hypothesised that with motor improvement MMSE will show improvements in all tasks, which are influenced by improved motor skills (such as Comprehension, Writing and Drawing). Thus, improved motor function may have indirectly affected improvement of cognitive functions (eg. tasks which include many motor factors) in the studies on rivastigmine treatment of HD patients so far. It is not known in which area of cognitive functions the improvements have been made in previous studies applying MMSE, as said studies do not provide a detailed analysis of results on individual MMSE tasks.

CONCLUSION

Detailed neuropsychological assessment does not confirm an effect of rivastigmine on cognitive function which has been previously reported using the cognitive screening test MMSE. We suggest that improvement in cognitive functions in previous studies was not due to improvement of executive functions.

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