Object decision and multiple sclerosis: a preliminary study

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Summary

The aim of this research was to study cognitive dysfunctions in multiple sclerosis (MS) by exploring subtle cognitive tasks, usually not included in the standard neuropsychological assessment. We wished to investigate whether it is possible to identify object decision deficits in MS patients without evident cognitive impairment; secondary objectives were to understand whether these deficits can be detected in the early stages of the disease and whether there are differences related to different phenotypes.
Participants were divided into four groups: (a) 12 patients with early relapsing-remitting MS [ERR]; (b) 14 with late relapsing-remitting MS [LRR]; (c) 10 with secondary progressive MS [SP]; (d) 36 healthy controls [HCs]. All participants performed a series of experimental tasks: an object decision task (recognition of chimeric and real figures) and naming and visual discrimination tasks. Our results suggest that object decision disorders are detectable in patients without overt cognitive impairments and that performances on these tasks are related to phenotypes. On the other hand, the Chimeric Figures task is not appropriate for identifying cognitive dysfunctions in early MS.

KEY WORDS: *cognitive disorders, multiple sclerosis, object decision, structural description system*

Introduction

Multiple sclerosis (MS) is a chronic progressive disease characterized by demyelination of the central nervous system and by several motor and cognitive consequences. Patients with MS may show impairment in many areas of cognition, including speed of information processing, attention, memory and executive functions (Rao et al., 1991a). Cognitive disorders, like physical impairments, can interfere significantly with working, social and relational activities (Rao et al., 1991b; Amato et al., 1995). Given the importance that neuropsychological assessment plays not only in detecting the severity and features of cognitive impairment, but also in the clinical assessment of disease evolution, the purpose of this research was to explore whether it is possible to identify object decision dysfunction in MS patients without overt cognitive impairments, and to investigate whether it is present in the early stages of the disease. This article sets out to present preliminary results; determination of the sensitivity, specificity and accuracy of the object decision task is beyond the scope of this study.
Cognitive impairment in MS is reported to occur in 40%-65% of patients (Bobholz and Rao, 2003) and despite the suggestion in the literature that cognitive deficits may already be present in the early stages of the disease (Amato et al., 2010), it continues to be largely under detected.
Object naming is a complex cognitive task characterized by three main stages: a) recognition of the structural description that encodes the shape and perceptual features of the object; b) semantic representation, where the perceptual features are compared with the functional and associative properties stored in the semantic memory; c) phonological representation, where they are compared with sounds and descriptions (Humphreys et al., 1988). There is a debate in the literature on whether a double dissociation exists between the structural description system, responsible for representing the global structure of an object and the relations between its components, and the identity-based system, which processes and stores semantic, functional and other non-structural distinctive features of an object (Cooper, 2013). The Hierarchical Interactive Theory (Humphreys and Riddoch, 2006) supports the idea that the two systems are distinct and that the structural description system is responsible for encoding representations of objects and storing the structural descriptions, while the semantic representations are stored in a different system.
The literature highlights that patients with a diagnosis of MS have deficits in processing shape (Vleugels et al., 2000), face-type stimuli (Ward et al., 1999), and visual-spatial stimuli (Rao et al., 1991).
Using an extensive visuoperceptual neuropsychological battery, Vleugels et al. (2001) showed that speed of information processing correlates with MS patients' visuoperceptual neuropsychological task performances and may be related to a magnocelluar pathway dysfunction.
Moreover, Laatu et al. (2001) investigated different stages of object identification: shape recognition, comparing objects with familiar representations in long-term memory, semantic categorization and naming. They compared the performances of MS patients with and

without cognitive impairment and healthy controls. The results showed that patients with cognitive impairment have difficulties in all the stages and that these visuoperceptual problems may be related to occipital-temporal dysfunction.
On the other hand, the literature also reports that patients with MS do not usually show impairments in language and in the semantic networks (Rao et al., 1991a). Thus, on the basis of the consideration that patients with MS may show visuoperceptual dysfunction while semantic knowledge is usually spared, our hypothesis was that MS patients may show dissociation between the structural description system and the identity-based system. The use of object decision tasks, which require higher cognitive effort that simple visual discrimination tasks, might constitute an opportunity to identify cognitive dysfunction in patients without overt cognitive deterioration, and might be useful in the early stages of the disease.
The complexity of MS symptoms requires a comprehensive neuropsychological evaluation approach, as well as the use of sensitive cognitive tools to assess cognitive disorders. The aim of this study was therefore to explore how MS patients perform on object decision tasks, and whether recognition of chimeric figures is impaired in the early stages of the disease.

Material and methods

Participants and data collection

The study included 72 participants aged 24 to 58 years, with an educational level greater than 8 years; all were native Italian speakers. The sample was divided into four groups: (a) 12 patients with a diagnosis of early relapsing-remitting MS [ERR group] (age: mean=37.00 years, SD=10.50 years; education: mean=14.16 years, SD=3.48; Expanded Disability Status Scale (EDSS) score: mean=0.95, SD=0.62; disease duration: mean=3.22 years, SD=2.49); (b) 14 with a diagnosis of late relapsing-remitting MS [LRR group] (age: mean=42.92, SD=8.42; education: mean=13.43 years, SD=3.80; EDSS score: mean=1.25, SD=0.80; disease duration: mean=11.71 years, SD=3.71); (c) 10 affected by secondary progressive SM [SP group] (age: mean=44.66 years, SD=7.44; education: mean=13.89 years, SD=2.63; EDSS score: mean=8.55, SD=5.63; disease duration: mean=15.6 years, SD=4.37); (d) 36 healthy controls [HCs], matched with the other groups for age, sex and educational level (age: mean=41.58, SD=9.62; education: mean=14.41, SD=3.86) (Tab. I).
Diagnoses were made according to revised McDonald criteria (Polman et al., 2011) by neurologists, who determined severity and MS phenotypes on the basis of clinical criteria.
Patients were recruited from the Neurological Clinic at the "San Salvatore" Hospital (L'Aquila, Italy) and from the Multiple Sclerosis Center at "Policlinico Umberto I" (Rome, Italy).
Only patients without a history of alcohol and/or drug abuse and without previous neurological and/or psychiatric diseases, and showing sufficient comprehension and good compliance with the testing procedure, were included in the study. Psychologists were blind to the research objectives when administering the tests; the assessment battery administration time was approximately 30 minutes. Informed consent was obtained from all the participants. The ethics committee of the University of L'Aquila approved the study.
All participants, both patients and HCs, were submitted to a neuropsychological evaluation. The assessment battery consisted of the following tests:
- Boston Naming Test (BNT) (Goodglass and Kaplan, 1983): the material for this naming test consists of 60 black and white figures representing living and non-living things. The participant's task was to name the figures.
- Wepman Visual Discrimination Test (WVDT) (Wepman et al., 1975): in this 20-item visual discrimination test the participant's task was to choose, among four alternatives, the stimulus corresponding, in terms of shape and orientation, to the target given.
- Chimeric Figures Task (Passafiume et al., 2015): this is an object decision task administered using a set of 48 stimuli, i.e. figures created using items taken from Snodgrass and Vanderwart's set of pictures (Snodgrass and Vanderwart, 1980). The stimuli comprised 24 chimeric figures and 24 real figures, both subsets evenly featuring objects and animals. Chimeric figures were composed of two figures, integrated with each other according to criteria of plausibility, outline, orientation and spatial relationship. The chimeric figures were chosen in a pilot study conducted among students to determine whether chimeric figures were clearly recognizable from real figures. The stimuli were chosen and administered in such a way as to avoid, as far as possible, the influence of other cognitive variables, such as memory, intelligence and abstract reasoning, and physical variables, such as quick motor and verbal responses. The figures were administered randomly varying the presentation of chimeric and real figures. The participant's task was to indicate whether each figure was real or unreal (Fig. 1).

Table I - Description of the groups.

Groups	Age (years)	Education (years)	Disease duration (years)	EDSS score
HCs (30 F, 6 M)	mean=41.58 SD=9.62	mean=14.41 SD=3.86		
ERR (11F, 1M)	mean=37.00 SD=10.50	mean=14.16 SD=3.48	mean=3.22 SD=2.49	mean=0.95 SD=0.62
LRR (11F, 3M)	mean=42.92 SD=8.42	mean=13.43 SD=3.80	mean=11.71 SD=3.71	mean=1.25 SD=0.80
SP (8 F, 2 M)	mean=44.66 SD=7.44	mean=13.89 SD=2.63	mean=15.6 SD=4.37	mean=8.55 SD=5.63

Abbreviations: HCs=healthy controls; ERR=patients with early relapsing-remitting MS; LRR=patients with late relapsing-remitting MS; SP=patients with secondary progressive MS; EDSS=Expanded Disability Status Scale; SD=standard deviation

The present battery was chosen to allow assessment of object decision as the primary outcome in neuropsychological evaluation and to verify whether naming and visual discrimination abilities significantly influence Chimeric Figures Task performance.
The patients were also administered the Brief Repeatable Battery (Rao et al., 1990), which confirmed that none of them had any substantial cognitive impairments. Indeed, all the scores were above the cut-offs (Tab. II), which were determined in reference to the standardized norms for the Italian population.

Statistical analysis

The data were evaluated using SPSS for Macintosh. Analyses of variance (ANOVAs) were used to compare performances on the Chimeric Figures Task.
The scores obtained on each of the experimental tasks were transformed into percentage of correct responses to allow comparison of tasks composed of different numbers of items.
Results were considered statistically significant at $p<05$.

Results

Naming and visual discrimination tasks

The four groups were first compared on the BNT and the WVDT, to verify whether these instruments were able to identify cognitive disorders at an early stage of the disease (see raw scores in Tab. III).
Multivariate analysis of variance showed that the groups gave significantly different performances on these tests [$F(2, 6)=5.37$, $p<001$].
Post-hoc analysis (Fisher's LSD) revealed that on the WVDT, the performances of the LRR (both $p<05$) and SP (both $p<001$) groups were significantly worse than those of the HCs and the ERR group (Tab. IV).
On the Boston Naming Test only the SP group performed significantly worse than the other three groups: HCs ($p<001$), ERR ($p<05$) and LRR ($p<005$) (Tab. V).

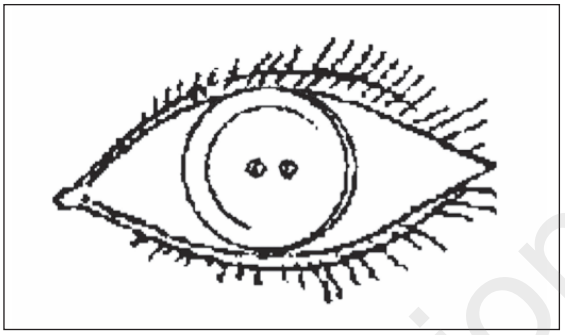

Figure 1 - An example of a Chimeric Figures Task stimulus.

Chimeric Figures Task

The performances of the groups were compared using a 4 (Groups) X 2 (Figures: chimeric and real) ANOVA for repeated measures (see raw scores in Tab. VI).
The results demonstrated a significant difference between Groups [$F(3,68)=7.56$, $p<.001$], a significant dif-

Table II - Patients' scores on the Brief Repeatable Battery.

	Brief Repeatable Battery	Scores		cut-off
		Mean	SD	
Verbal memory	SRT-LTS	45.15	9.3	23.3
	SRT-CLTR	34.47	5.98	15.5
	SRT-D	8.82	1.33	4.9
Visual memory	SPART	20.41	4.92	12.7
	SPART-D	7.35	1.61	3.6
Processing speed	SDMT	47.29	7.24	37.9
Auditory attention	PASAT 3	37.41	12.71	28.4
	PASAT 2	30.29	11.64	17.1
Verbal fluency	WLG	26.88	6.19	17.0

Abbreviations: SRT-LTS=Selective Reminding Test – Long-Term Storage; SRT-CLTR=Selective Reminding Test – Consistent Long-Term Retrieval; SRT-D=Selective Reminding Test – Delayed; SPART=10/36 Spatial Recall Test; SPART-D=Spatial Recall Test – Delayed; SDMT=Symbol Digit Modalities Test; PASAT 3 and PASAT 2=Paced Auditory Serial Addition Test 3 and 2; WLG=Word List Generation Test; SD=standard deviation.
The scores are corrected for age and level of education. The cut-offs are relative to the standardized norms for the Italian population.

Table III - Raw scores (means and standard deviations) of the four groups on the Wepman Visual Discrimination Test and the Boston Naming Test.

	HCs	ERR	LRR	SP
WVDT	20 (0)	20 (0)	19.14 (1.61)	18.4 (2.17)
BNT	55.47 (1.57)	53.5 (3.53)	54.21 (3.38)	49.7 (7.15)

Abbreviations: HCs=healthy controls; ERR=patients with early relapsing-remitting MS; LRR=patients with late relapsing-remitting MS; SP=patients with secondary progressive MS; WVDT=Wepman Visual Discrimination Test; BNT=Boston Naming Test

Table IV - Post-hoc analysis (Fisher's LSD) of the Wepman Visual Discrimination Test performances.

Wepman Visual Discrimination Test				
	HCs	ERR	LRR	SP
HCs		n.s.	p<05	p<001
ERR	n.s.		p<05	p<001
LRR	p<05	p<001		n.s.
SP	p<05	p<001	n.s.	

Abbreviations: HCs=healthy controls; ERR=patients with early relapsing-remitting MS; LRR=patients with late relapsing-remitting MS; SP=patients with secondary progressive MS; n.s.=not significant

Table V - Post-hoc analysis (Fisher's LSD) of the Boston Naming Test performances.

Boston Naming Test				
	HCs	ERR	LRR	SP
HCs		n.s.	n.s.	p<001
ERR	n.s.		n.s.	p<05
LRR	n.s.	n.s.		p<005
SP	p<001	p<05	p<005	

Abbreviations: HCs=healthy controls; ERR=patients with early relapsing-remitting MS; LRR=patients with late relapsing-remitting MS; SP=patients with secondary progressive MS; n.s.=not significant

Table VI - Raw scores (means and standard deviations) of the four groups on the Chimeric Figures Task

	HCs	ERR	LRR	SP
CFT - real	23.94 (0.23)	23.58 (0.67)	23.78 (0.42)	23.6 (0.70)
CFT - chimeric	23.08 (0.84)	23.17 (2.66)	21.57 (1.65)	19.4 (5.2)

Abbreviations: CFT=Chimeric Figures Task; HCs=healthy controls; ERR=patients with early relapsing-remitting MS; LRR=patients with late relapsing-remitting MS; SP=patients with secondary progressive MS.

ference between Figures [F(1,68)=46.72, p<001], and a Figures X Groups interaction [F(3,68)= 5.39, p<005].
Post-hoc analysis (Fisher's LSD), used to decompose the main effect on Groups, revealed that the LRR group (p<.05) and the SP group (p<001) performed worse than the HCs. Moreover, the performances of the ERR and LRR groups were significantly better than that of the SP group (both p<05).
Post-hoc analysis performed on Figures revealed that the groups performed significantly worse on chimeric figure recognition than on real figure recognition (p<001).
With regard to the interaction effect between Groups and Figures (Tab. VII), post-hoc analysis revealed that the HCs (p<001), the ERR group (p<001), and the LRR group (p <005) outperformed the SP group in recognizing chimeric figures, but the performances were similar in recognizing real ones (p>05).
Moreover, the LRR group performed worse than the HCs in recognizing chimeric figures (p<05) (Fig. 2).
To determine whether the interaction between Groups and Figures was due to the confounding influence of visual discrimination ability, we conducted an analysis of covariance with the WVDT as a covariate. This analysis showed a significant effect of visual discrimination [F(1,67)=29.97, p<001], and a significant interaction effect between visual discrimination and figure recognition [F(1,67)=19.20, p<001]. The main effect on Groups [F(3,67)=2.64, p>05] and the interaction effect between Groups and Figures [F(3,67)=1.27, p>05] were not significant.

Discussion

In the present study, we explored the structural description system as a possible means of identifying cognitive dysfunction in MS patients without overt cognitive impairments and in those who are in the early stages of the disease. We compared four groups of participants (patients with the relapsing-remitting phenotype at an early stage, patients with the relapsing-remitting phenotype at a late stage, patients with the secondary progressive phenotype and healthy adults for comparison) to determine whether it is possible to identify a prodromal symp-

Table VII – Interaction effect between groups and figures.

(Interaction Effect)	**F**	**DoF**	**p**
Groups*Figures	5.39	(3,68)	*<005*

Post-Hoc (Fisher's LSD)

	Real Figures	Chimeric Figures
HCs ERR LRR SP	mean=99.77 mean=98.26 mean=99.11 mean=98.33	mean=96.18 mean=92.36 mean=89.88 mean=80.83
Comparisons	n.s.	CG > LRR, SP ERR, LRR > SP
	CG, ERR, LRR, SP Real > Chimeric	

Abbreviations: DoF=Degrees of freedom; HCs=healthy controls; ERR=patients with early relapsing-remitting MS; LRR=patients with late relapsing-remitting MS; SP=patients with secondary progressive MS; n.s.=not significant

tom related to the structural description system and whether the pattern of deterioration differs according to phenotype.

Bearing in mind that visuoperceptual dysfunctions are well documented and that semantic knowledge is usually spared in MS, we hypothesized that patients could show a dissociation between the structural description system and the identity-based system. We therefore built an object decision task (chimeric figure recognition), which requires higher cognitive effort than simple visual discrimination tasks, in order to investigate a possible dysfunction in the structural description system.

The findings showed that ERR patients (those diagnosed with RR MS and still in an early stage of the disease) do not present dysfunctions either in simple visual discrimination or naming tasks. On the other hand, both late-stage relapsing-remitting (LRR) patients and those with the SP phenotype showed impairments in visual discrimination, while only patients with the SP phenotype were significantly impaired in naming.

The results also suggested that the Chimeric Figures Task is efficient in distinguishing the LRR phenotype and the SP phenotype. On the other hand, the task is not sensitive during the early stages of the disease. Our analyses revealed that difficulty in recognizing chimeric figures could be secondary to visual discrimination dysfunctions. Moreover, as hypothesized, patients could not be distinguished from HCs on the basis of discrimination of real figures. These results support the hypothesis that the structural description system and the identity-based system can be affected separately.

The performances of the RR phenotype patients with late-stage disease and of the patients with the SP phenotype, can be interpreted as reflecting impairment of the structural description system, which is used to access semantic information. Only in the SP phenotype did the impairment result in naming dysfunction.

These results are partially in line with the findings of a previous study (Laatu et al., 2001) in cognitively deteriorated MS patients, which revealed deficits in familiarity detection in a task that used real objects (coherent shapes) and unreal objects (non-coherent shapes). The findings of the present study suggest that deficits in familiarity detection can also be present in patients without cognitive dysfunctions. This discrepancy is probably due to the differences between our tasks, which considered only correct answers, and those of Laatu et al. (2001), which took into account both correct answers and reaction times. In the cited study (Laatu et al., 2001), as in the present one, patients without cognitive deficits were found to perform worse than healthy comparison adults if the comparison considered only correct answers.

The neuroanatomical hypothesis coherent with the findings of the present study is related to involvement of the fusiform gyri and the inferior gyri of the occipital lobes. Martin et al. (1996) found a bilateral activation of these areas in response to non-objects. Moreover, Bruffaerts et al. (2013) provided further support for a neurobiological distinction between the structural description system and the identity-based system and confirmed the role of the right mid-posterior fusiform gyrus in the structural description system.

The above hypothesis is also in line with our findings that performances on the Chimeric Figures Task are secondary to a deficit in visual discrimination of simple geometric lines. A qualitative analysis of patient errors showed that the majority were related to chimeric figures in which the objects were more integrated. Recognition of these objects thus requires the subject to pay attention to the contours inside the figures, and makes it difficult, through global perception, to identify figures as real or unreal.

It is also possible that patients with MS may fail because they have difficulties in generating mental images and comparing them with the real object.

Research in MS has shown that patients respond less accurately and more slowly that healthy comparison subjects when performing mental imagery tasks (Heremans et al., 2012). The literature shows that accuracy in

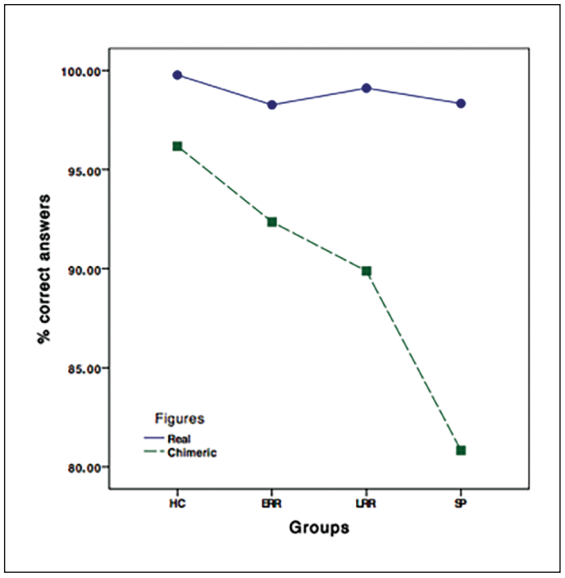

Figure 2 - Performances of the four Groups [healthy controls (HCs), early relapsing-remitting group (ERR), late relapsing-remitting group (LRR) and secondary progressive group (SP)] in recognizing real and chimeric figures.

motor imagery tasks is highly related to cognitive dysfunction, and in particular to global scores rather than to single cognitive function scores, indicating that multiple cognitive domains act simultaneously in motor imagery (Tabrizi et al., 2014).

Although our results are coherent with previous investigations, our conclusions are limited by the small number of participants included in our study. In addition, our study was cross-sectional; a longitudinal study would be needed to determine whether the object decision task is useful in detecting patients in the early stages of the disease and in following its course. Further research needs to be conducted to evaluate the sensitivity, specificity and accuracy of the object decision task in a larger sample and the possibility of inserting these types of task in basic neuropsychological assessment. Moreover, additional studies, using sensitive neuroimaging tools, are needed to explore the neural hypothesis.

Despite these limits, our results are important because they highlight the opportunity of identifying cognitive dysfunctions and starting cognitive rehabilitation while the patient is still in the early stages of the disease. An early intervention is in fact desirable for the benefits it can have on both clinical and neural outcomes, while delayed intervention can carry the risk of irreversible damage.

An early intervention can indeed slow the progression of the disease and have effects on the quality of life of both patients and families, considering that cognitive deficits, and particularly deficits of verbal memory, information processing speed and executive functions, can predict professional status (Benedict et al., 2006) and have a significant impact on complex tasks in the home and on driving (Shawaryn et al., 2002; Kotterba et al., 2003; Schultheis et al., 2002). Moreover, clinical investigations have indicated that early intervention with disease-modifying therapies may help to prevent permanent damage, and appears to reduce the frequency and severity of clinical attacks, slow the accumulation of disability, and reduce the development of new lesions.

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