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Impaired Performances in a Stimulus for Relapsing-remitting Multiple Sclerosis Patients versus Controls

Sandra Vanotti*

Universidad de Buenos Aires y Centro Neurológico, Hospital Ramos Mejía, Buenos Aires, Argentina

Ángel Tabullo,

Universidad de Buenos Aires, Argentina

Evangelina E. Cores, Leticia Fiorentini

Universidad de Buenos Aires y Centro Neurológico, Hospital Ramos Mejía, Buenos Aires, Argentina

Orlando Garcea, Alberto A. Yorio

Universidad de Buenos Aires, Argentina

Abstract

The objectives of this study were to determine whether patients with Multiple Sclerosis (MS) have difficulties in a stimulus equivalence task, and to assess the potential relationship between their difficulties and cognitive impairment. A total of 12 MS patients and matched controls completed the stimulus equivalence task. Patients with MS also completed measures of a neuropsychological evaluation that included the Brief Repeatable Battery in Multiple Sclerosis, Trail Making A and B, the Wechsler Adult Intelligence (Digit Span), the Wisconsin Card Sorting Test, the California Verbal Learning Test, the Wechsler Memory Scale (Logic Memory), and the Boston Naming Test. The stimulus equivalence task showed that MS patients had poorer performance and slower response times as compared with controls in the stimulus equivalence task. There was a significant correlation among stimulus equivalence task parameters and indexes of executive function and memory from the neuropsychological evaluation.

Key words: stimulus equivalence, category learning, multiple sclerosis, cognitive impairment.

Novelty and Significance

What is already known about the topic?

- Has been extensively studied the usefulness of equivalence relations paradigm for the study of generative behavior in healthy subjects.
- The paradigm has the advantage of controlling the subjects' familiarity with the classes of stimuli trained.

What this paper adds?

- This paper shows its application in the assessment of patients with cognitive impairment and the association of the performance in equivalence relations tasks and other conventional tasks that assess cognitive skills.

As it has been documented, the stimulus equivalence (SE) procedure has been widely used in human subjects (Catania, 1984; Sidman, 1994, 2000). The SE procedure is established by a matching to-sample task. During the training stage, a series of conditional discriminations among arbitrary stimuli are trained. The stimuli have neither perceptual similarity nor previous semantic relation. In the testing stage, new untrained relations between the stimuli are tested without feedback. The emergent relations are analogous to the equivalence properties in logic and mathematics: a) reflexivity, or the relation of each stimulus with itself (e.g. A-A), b) symmetry, or the bidirectional relations between directly trained stimuli (e.g. B-A if A-B was trained), and c) transitivity, that is

* Correspondence concerning this article: Sandra Vanotti, Universidad de Buenos Aires, Escuela de Psicología, Centro Neurológico, Hospital Ramos Mejía, Holmberg 1785 (1430) Buenos Aires, Argentina. Email: svanotti@psi.uba.ar

the transference of the relation between trained stimuli (e.g. A-C if A-B and B-C were trained). The demonstration of all three relations is considered to be the definition of an equivalence class (Catania, 1984). The SE procedure was thought to provide a tool for studying symbolic processes relevant to categorization (Zentall, Galizio, & Critchfield, 2002). Recent evidence has suggested the existence of certain differences in the way people learn new categories and a variety of different strategies that may lead to success in category-learning tasks. It has also been shown that neuro-imaging studies, cognitive models, and neuropsychological data obtained with different types of category-learning tasks are also qualitatively different (Keri, 2002).

Functional Magnetic Resonance Imaging (fMRI) studies of healthy subjects during the SE task have shown a bilateral activation of dorsolateral prefrontal and posterior parietal cortexes, as well as other subcortical regions such as thalamus, caudate nucleus and putamen (Dickins, Singh, Roberts, *et al.,* 2001; Schlund, Hoehn-Saric, & Cataldo, 2007). Furthermore, the SE paradigm has been formalized in computational neuroscience using neural network models that involve the prefrontal cortex and its connections with other brain structures (Barnes & Hampson, 1997; Lew, 2007). These brain regions are considered critical for categorization processes (Miller, Nieder, Freedman, & Wallis, 2003). The study of neurologically and cognitively impaired patients using appropriate experimental categorization paradigms constitutes a relatively novel approach, which has only been applied to a few brain diseases (Keri, 2002). PET studies show reduced metabolism of frontal and parietal cortex in MS (Bakshi, Miletich, Kinkel, Emmet & Kinkel, 1998), Also, MRI studies in MS patients have found that declined performance in attention, processing speed and verbal memory was associated with the presence of white matter lesions in frontal and parietal regions (Blinkenberg, Jensen, Holm, Paulson, & Sorensen, 1999). Therefore, the brain regions engaged in SE tasks are the ones that suffer the greatest damage during the course of MS.

Cognitive impairment in multiple sclerosis (MS) has been widely documented in the past decades with a prevalence of around 50% (McIntosh-Michaelis, Roberts, Wilkinson, *et al.* 1991; Benedict, Cookfair, Gavett *et al.* 2006). In Argentina, the RECOMEN study (National Survey of Cognitive Impairment in Multiple Sclerosis in Spanish) confirmed a 46% prevalence of cognitive impairment in MS patients (Cáceres, Vanotti, Rao, & Reconem Workgroup, 2011).

The most common neuropsychological deficits were observed in: long-term and working memory, attention, processing speed, executive function and visuospatial abilities (Bobholz & Rao, 2003; Benedict, Wahlig, Bakshi *et al.,* 2005, Sepulcre, Vanotti, Hernández *et al.,* 2006). Cognitive disorders resulted in functional upheavals that are independent of the associated sensory-motor signs (Amato, Ponziani, Siracusa, & Sorbi, 2001). Also, studies performed in MS patients have shown performance deficits in classic categorization tests such as the Wisconsin Card Sorting Test (WCST) that evaluates early learned categories (Heaton, Chelone, Talley, Kay, & Curtiss, 1985). The acquisition of new categories with the stimulus equivalence paradigm has not been studied in MS patients.

The objectives of this study were 1) to determine if relapsing-remitting MS patients have difficulties in the formation of stimulus equivalence classes, and 2) to examine the potential links between difficulties in the formation of stimulus equivalence classes and MS-related neuropsychological deficits.

Method

Participants

We selected 12 patients with a diagnosis of relapsing-remitting MS (Polman, Reingold, Edan *et al.,* 2005) and 12 healthy controls matched for age and education (Table 1). Participants were excluded if they a) were younger than 18 or older than 60 years, b) had a history of alcohol or drug abuse or a Nervous System Disorder other than MS, c) had a major psychiatric disorder, d) had a severe motor or visual impairment that could interfere with cognitive testing, e) were experiencing an exacerbation of symptoms, and/or f) had received corticosteroid treatment four weeks before testing.

We obtained approval from the local ethics committee and written informed consent from patients in accordance with the Ethics Committee (Internal Review Boards) from the Hospital Ramos Mejia. All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

The level of disability of subjects was quantified using the Expanded Disability Status Scale (EDSS), (Kurtzke, 1983). Depression was assessed with the Beck Depression Inventory (BDI), (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and cognitive status was evaluated with the Spanish adapted version (Cáceres, Vanotti, Rao, & Reconem Workgroup, 2011) of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N see below). Cognitive impairment criteria for MS patients were based on the fifth percentiles of BRB-N, calculated for a larger control group according to specifications published elsewhere (Rao, Leo, Bernardin, & Unverszagt, 1991). An MS patient was considered cognitively impaired if at least two of his or her BRB-N tests scores were below the fifth percentile of the controls. Thus, the fifth percentile was used as a cut off to determine the number of cognitively impaired MS patients. This was done in order to examine the SE task performance between subgroups of cognitively "impaired" and "unimpaired" MS patients. Healthy controls with no history of neurological disease and Folstein MMSE scores >26 were also recruited (Folstein, 1975) and completed the Stimulus equivalence task.

Table 1. Demographic characteristics of the study sample.

	Patients	Control group
Number	12	12
Gender (male/female in percentages)	42 / 58	39 / 61
Mean age (years)	40.97 ± 11.20	34.2 ± 9.7
Mean education level (years)	13.7 ± 3.1	14.2 ± 3.9
Mean disease course (years)	7.15 ± 6.53	NA
Mean Expanded Disability Status Scale (EDSS):	1.3 ± 1.15	NA
Mini-mental State Examination (MMSE)	NA	28.8 ± 0.9

Notes: Values are mean ± standard deviation or percentage; NA: not applied.

Procedures and Measures

Training and test stages of the SE task were performed in individual sessions. The number of classes of the SE task was reduced as much as possible in order to minimize the effect of fatigue in the results. The interval between trials was slightly longer than usual for the same reason (see below). The time required to complete the task was approximately 30 minutes both in MS patients and in control subjects. After the SE task, patients and controls were administered a questionnaire that assessed their knowledge of the directly trained relations. The questionnaire consisted of a sheet of paper with the four possible sample combinations of sample and the comparison stimuli of the trained relations (A-B and B-C). Patients received a written instruction sheet to mark with a cross below the figures, which of the comparison stimuli was selected in the presence of each sample stimulus. This was followed by the written question: "Are you sure?" and the options "yes - no". The purpose of the questionnaire was to evaluate the explicit recall of the baseline conditional relations. The level of disability and depression was also evaluated in the same session.

The neuropsychological measures were administered in another two separate sessions (not more than two weeks between both sessions), that lasted about 3 hours each. The neuropsychological evaluation was conducted by a professional expert in neuropsychological assessment following the guidelines for neuropsychological research in MS (Peyser, Rao, LaRocca, & Kaplan, 1990).

MS patients completed the following evaluation tools for neuropsychological measures:

The *Brief Repeatable Battery in Multiple Sclerosis* (BRB-MS) (Rao, 1991) translated into Spanish and culturally adapted to this Latin American population (Cáceres, Vanotti, Rao, & Reconem Work Group, 2011). The BRB-MS consists of the following tests:

1. The Selective Reminding Test (SRT), from which measures of learning (long-term storage or LTS) and consistency of recall (consistent long-term retrieval or CLTR) are derived (Buschke & Fuld, 1974).
2. The 7/24 Spatial Recall Test (7/24 SRT), that assesses visual learning and recall by recreating the pattern of 7 checkers on a 6 x 6 checkerboard viewed for 10 seconds (Rao, 1991).
3. The Paced Auditory Serial Addition task (PASAT), that evaluates sustained attention and information processing speed, and is measured by asking the patient to add each number to the one immediately preceding it while numbers are presented every three seconds and every two seconds (Gronwall, 1977).
4 The Word List Generation (WLG) that measures verbal fluency thus evaluating the spontaneous production of words beginning with a particular letter during 60 seconds (Benton & Hamsher, 1976).

- Trail Making A and B (TM A-B), (Spreen & Strauss 1991); Wechsler Adult Intelligence Scale-III – Digit Span (WAIS - DS), (Wechsler 1997); Wisconsin Card Sorting Test (WCST), (Heaton et al. 1993); California Verbal Learning Test (CVLT), (Delis, Kramer, Kaplan, & Ober et al. 2000); Wechsler Memory Scale-Revised-Logic Memory (WMSR-LM), (Wechsler, 1987); and Boston Naming Test (BNT), (Kaplan, Goodglass, & Weinntraub, 1983) to assess attention, executive function, verbal memory, and language.

Sessions of Stimulus equivalence task were conducted in an experimental room of approximately 3mx2m containing a table and a chair. The SE task consisted in a series of matching to sample tasks that were programmed with DMDX software (Forster, 2002). The sample stimulus was presented in the center of the screen while the comparison stimuli were presented at the left and right sides of the center. Stimuli were white figures on a black background. These included Greek letters and geometrical figures (Yorio, Tabullo, Wainselboim, Barttfeld, & Segura, 2008). The size of the stimuli was 1.5 by 1 inches. Participants were seated in front of a 14 inch PC monitor (distance 50 cm). Subject's right and left index fingers were in contact with the corresponding right and left keys of a response device connected to the PC. Task's instructions and stimuli were presented in the monitor and subject's responses were recorded by the keys pressed. Each trial started with the sample stimulus in the center of the screen (duration 500 milliseconds) followed by a short delay (100 milliseconds), after which the comparison stimuli were presented. Comparison stimuli persisted until the participant provided a response. The delay between the display of the sample and the comparison stimuli was included in order to avoid the simultaneous presentation of both stimuli. This was done only to guarantee that the matching stimuli could be well distinguished from the sample´s presentation. The inter-trial interval lasted 3000 milliseconds. Subjects could decide when they would begin with each block of trails in both the training and the test stages. Response time was defined as the time elapsed between the appearance on the screen of the comparison stimuli and the occurrence of a contact of the key pressed on the response device. Only those trials in which the subjects matched correctly were considered. The arithmetic means of response times in the different blocks of trials were computed for each participant.

During the training stage, arbitrary relations between stimuli A1, 2 - B1, 2 and B1, 2 - C1, 2 were trained in successive blocks of trials, each consisting of 32 randomly-presented consecutive trials. Participants responded by pressing the key of the response box that corresponded to the side of the chosen stimulus. Feedback messages ("correct" or "error") were presented immediately after the response for 1000 milliseconds. Learning criterion was 9 consecutive correct responses, with a maximum of 32 trials per block presented. During the test stage, comparison stimuli were presented following the sample stimulus in three different types of trials according to the relation between sample and comparison stimuli: reflexivity, symmetry and transitivity. These tests were done in a random sequence. During this stage no feedback messages were presented. Test criterion was the same as learning criterion.

Data analysis

SE task's dependent variables were: number of trials until reaching learning and test criteria, percentage of correct responses, and response time (Green & Saunders, 1998). Separate 2×3 repeated measures ANOVA was used for each dependent variable in the training and test stages, with group (MS patients, control) as the between-subjects factor and trial type (relation AB, BC, AB-BC in training; reflexivity, symmetry and transitivity in test) as the within-subjects factor. We applied the Greenhouse-Geisser correction to *F*-values for non-spherical data. We used Tukey's HSD test for between-subjects post hoc comparisons, and Bonferroni adjustment for within-subjects post hoc analysis. Statistical analysis with parametric techniques was performed both with the raw and the normalized data. MS patients were divided in two subgroups: cognitively impaired and unimpaired, according to the previously defined cognitive impairment criterion. Comparisons between subgroups of MS patients were made with the non-parametric Kruskal-Wallis test. On the other hand, the proportion of subjects who reached learning and test criteria was calculated for control subjects, and cognitive impaired and unimpaired MS patients group, and compared by a chi-squared test. In order to identify associations between SE task performance and neuropsychological test scores, non-parametric correlations (Spearman's Rho) were computed.

RESULTS

MS patients obtained abnormal scores in several neuropsychological tests. The tests with the higher frequency of low scores were: Trail Making "B", PASAT 3", WCST, CVLT (Immediate delay recall, Long delay recall), SRT (Long Term Storage, Consistent Long Term Retrieval), 7/24 Spatial Memory (Trial 1-5, Immediate Recall). Descriptive statistics of MS patients neuropsychological test (raw scores), are shown in table 2.

According to the previously defined cognitive impairment criterion, 5 of 12 patients were cognitively impaired. Cognitively impaired patients had significantly different

Table 2. Neuropsychological Test Performance for MS patients.

			Mean ± *SD*	Range
Attention and Executive function	TMT - Version A		45.83 ± 14.80	28 - 73
	TMT - Version B		108.17 ± 42.68	73 - 195
	WAIS-III DS		43.18 ± 8.26	30 - 54
	Forward		8.75 ± 2.63	4 - 13
	Back		6.33 ± 1.87	4 - 10
	PASAT 3"		38.33 ± 13.73	16 - 56
	PASAT 2"		33.00 ± 15.23	5 - 54
	WCST Categories		3.67 ± 2.53	0 - 6
	WLG	Phonological fluency	30.67 ± 9.36	13 - 42
		Semantic fluency	17.92 ± 4.34	10 - 24
Verbal Memory	SRT		34.92 ± 16.86	2 - 57
	LTS		23.25 ± 15.92	0 - 44
	CLTR		6.33 ± 3.26	1 - 10
	Delayed retrieval	CVLT	46.09 ± 15.04	20 - 72
		Trail 1-5	8.36 ± 5.24	0 - 16
		Immediate delay recall	9.00 ± 3.29	4 - 16
		Long delay recall	14.00 2.93	7 - 16
		Recognition	34.92 ± 16.86	2 - 57
Visual Memory	7/24 SRT	Trail 1-5	25.92 ± 5.16	20 - 33
		Immediate Recall	4.58 ± 2.39	0 - 7
		Delay Recall	5.00 ± 1.59	2 - 7
	WMS-R-Logic Memory	Immediate Recall	24.33 ± 7.47	11 - 36
		Delay Recall	17.89 ± 7.54	4 - 25
Language	Boston Naming Test	Vocabulary	54.00 ± 2.65	49 - 58

Notes: TMT= Trail Making Test; WAIS-III= Weschsler Adult Inteligence Scales; PASAT= Paced Auditory Serial Addition Task; DS= Digit Span; WCST= Wisconsin Card Sorting Test; WLG= Word list generation; SRT= Selective Reminding Test; LTS= Long-term storage; CLTR= Consistent long-term retrieval; CVLT= California Verbal Learning Test; 7/24 SRT= Spatial Recall Test; WMS-R= Wechsler Memory Scale Revised.

scores as compared to unimpaired patients in the following tests: PASAT, WCST, WLG phonological fluency, SRT, CVLT and 7/24-SRT. Table 3 shows neuropsychological tests scores for MS patients with and without cognitive impairment.

Performance was lower in MS patients at both stages of the task, as they had fewer percentages of correct responses. (Training: $F(1,22)= 4.882$, $p= .038$, Test: $F(1,21)= 15.172$, $p= .001$), required more trials to reach criterion (Training: $F(1,22)= 6.408$, p= .019; Test: $F(1,21)= 8.184$, $p= .009$) and had slower response time (Training: $F(1,22)= 13.547$, $p= .001$, Test: $F(1,21)= 4.555$, $p= .045$). MS patients were divided in two groups: cognitively impaired and unimpaired, according to the previously defined cognitive impairment criterion. To identify differences in SE task performance associated with cognitive impairment, we compared the behavioural data on the stimulus equivalence task between impaired and unimpaired

The proportion of subjects who reached learning criterion in the training and the test stages was lower for the cognitively impaired MS patients. All controls and unimpaired MS patients, but only 40% of impaired MS patients successfully completed the training stage ($\chi^2= 13.029$, $p= .005$). All controls (100%) and 71.4% cognitively

Table 3. Neuropsychological data of MS patients with and without cognitive impairment (CI).

	With CI	Without CI	*t* - test	*p*
TMT – Version A (seconds)	44.00 ± 17.93	47.14 ± 13.51	-0.35	.74
TMT – Version B (seconds)	130.80 ± 55.48	92.00 ± 23.57	1.68	.13
WAIS- III / forward	7.40 ± 3.13	9.71 ± 1.89	-1.61	.14
WAIS-III / back	5.40 ± 2.07	7.00 ± 1.53	-1.55	.15
PASAT 3"- successes	25.80 ± 7.22	47.29 ± 9.30	-4.30	.00**
PASAT 3"- successes 1º phase	13.60 ± 5.37	23.71 ± 8.12	-2.42	.04
PASAT 3"- successes 2º phase	12.20 ± 2.68	23.57 ± 4.16	-5.33	.00**
PASAT 2" – successes	18.60 ± 7.89	43.29 ± 9.34	-4.80	.00**
PASAT 2"- successes 1º phase	11.40 ± 4.51	22.14 ± 4.10	-4.30	.00**
PASAT 2"- successes 2º phase	7.20 ± 4.71	21.00 ± 6.19	-4.17	.00**
WCST – Categories completed	2.00 ± 2.35	4.86 ± 2.04	-2.25	.05*
WCST - perseverations	53.75 ± 36.98	10.50 ± 12.53	2.71	.03*
WCST – Failure to maintain set	52.25 ± 54.78	11.33 ± 0.52	1.89	.10
WCST - % perseverative errors	43.02 ± 27.18	10.58 ± 8.63	2.79	.02*
WCST – Total completed categories	114.25 ± 27.50	84.50 ± 22.43	1.88	.10
WLG-Phonological fluency	24.00 ± 10.00	35.43 ± 5.53	-2.55	.03*
WLG-Semantic fluency	16.60 ± 5.55	18.86 ± 3.39	-0.88	.40
SRT- LTS	26.80 ± 22.47	40.71 ± 9.52	-1.48	.17
SRT - CLTR	11.8 0± 16.92	31.43 ± 9.31	-2.60	.03*
SRT intrusions	0.80 ± 1.10	0.43 ± 0.79	0.69	.51
SRT recognition	4.20 ± 2.86	7.86 ± 2.73	-2.24	.05*
CVLT – Trail 1-5	32.00 ± 11.34	54.14 ± 10.24	-3.33	.01*
CVLT - Immediate delay recall	6.50 ± 5.92	9.43 ± 4.96	-0.88	.40
CVLT - Long delay recall	7.00 ± 3.16	10.14 ± 2.97	-1.65	.13
CVLT – Recognition	12.25 ± 3.86	15.00 ± 1.91	-1.61	.14
CVLT - false positives	4.75 ± 2.63	2.43 ± 3.87	1.06	.32
CVLT – intrusions	0.75 ± 1.50	1.43 ± 2.51	-0.49	.64
7/24 SRT Total correct responses	21.00 ± 1.73	29.43 ± 3.51	-4.92	.00**
7/24 SRT Immediate recall	2.40 ± 2.07	6.14 ± 0.90	-4.30	.00**
7/24 SRT Delay recall	4.20 ± 1.92	5.57 ± 1.13	-1.56	.15
WMS-R LM Immediate recall	22.50 ± 8.74	25.80 ± 6.94	-0.63	.55
WMS-R LM Delay Recall	14.75 ± 10.31	20.40 ± 4.04	-1.14	.29
BNT- Naming	53.50 ± 3.32	54.29 ± 2.43	-0.45	.66

Notes: See Table 2 for key abbreviations; *= p <.05, **= p <.01.

unimpaired MS patients but only 40% of impaired MS patients completed the test stage (χ^2= 8.063, *p*= .012). The number of trials to reach criterion, the percentage of correct responses, and response times in the training and test stages were compared between control subjects, cognitive impaired and unimpaired MS patients using a Kruskal-Wallis test. In the training stage, significant differences were found between groups in number of trials to criterion (H(2)= 7.913, *p*= .014), and percentage of correct responses (H(2)= 8.559, *p*= .009). During the training stage, impaired patients required more trials to reach criterion vs. controls (*U*= 6, p= .009) and unimpaired patients (*U*=4, *p*= .030). Furthermore, they had fewer hits than controls (U= 3, *p*= .002) and unimpaired patients (*U*= 5, *p*= .048). In the test stage, significant differences were also found in the number of trials to criterion and percentage of correct responses (H(2)= 10.440, *p*= .003). Impaired MS patients required more trials to reach criterion (*U*= 6.5, *p*= .03) and had fewer hits (*U*= 6.5, *p*= .03). No significant differences were found between impaired and unimpaired patients in this stage. On the other hand, performance was not significantly different between unimpaired patients and controls during the training and test stages.

Thus, results suggest that cognitively impaired MS patients required more training to learn conditional relations and to form the stimulus equivalence classes. The performance of cognitively unimpaired MS patients was better but did not match results obtained in healthy controls during the test stage.

The proportion of MS patients that correctly evoked the trained relations (AB, BC) after the test stage was significantly lower than controls (58.30 vs. 89.7%, χ^2= 6.230; *p*= .024). Moreover, 85.7% of patients who recalled the trained relations were successful in the equivalence tests, while only 14.3% of those who did not remember them, had reached criterion in the SE tests (χ^2= 5.182, *p*= .045). This association between the explicit memory of trained relations and success in equivalence tests was not found in controls.

MS patients that successfully completed the SE test stage obtained higher scores in the following neuropsychological tests: TMT-B (*t*= -2.509, *p*= .038), WAIS direct digit span (*t*=2.573, *p*= .028), PASAT 3” (*t*= 3.882, *p*= .003) y 2” (*t*= 3.129, *p*= .011), 7/24 (*t*= 4.796, *p*= .001). This effect was observed in other tests, but it was not statistically significant: WCST completed categories (*t*= 1.982, *p*= .077) and Boston naming test (*t*= 2.246, *p*= .051).

We obtained several correlations between the dependent variables of the SE task and the neuropsychological test scores of the MS patients. We found correlations between performance in both the training and the test stage and between the following tests: PASAT (3” and 2”), direct and inverse span (WAIS), CVLT, Buchke SRT, WMS-R ML. Correlations with the training stage were only obtained in the following tests: symbol-digit (WAIS), phonological fluency (WLG), 7/24 (SRT). Correlations with test stage were only obtained in the following tests: TMT-B, categories (WCST) and vocabulary (BNT). No significant correlations were observed between neuropsychological scores and age, education, duration of symptoms, BID or EDSS scale scores. The most significant correlations are shown in Table 4.

Table 4. Correlations among neuropsychological test performance and indices of the Stimulus Equivalence Task.

		Training phase			Test phase		
		TN	%C	TR	TN	%C	TR
TMT – Version A		--	--	--	--	--	--
TMT – Version B		--	--	--	--	--	.685
WAIS-III	DS	--	--	-.711*	--	--	--
	Forward	-.771**	.772**	-.636*	-.969**	.907**	-.661*
	Back	-.644*	.649*	--	-.635*	--	--
PASAT 3”		.890**	.705*	--	-.684*	--	-.700*
	First phase (1-30)	--	--	-.681*	-.691*	--	-.728*
	Second phase (31-60)	-.862**	.854**	--	--	--	--
PASAT 2”		-.915**	.925**	--	--	.669*	--
	First phase (1-30)	-.864**	.887**	--	-.752*	.717*	--
	Second phase (31-60)	-.864**	.856**	--	--	--	--
WCST Categories		--	--	--	-.839**	.877**	--
WLG Phonological fluency		-.732*	.760*	--	--	--	--
Buschke SRT	Long Term Storage	--	--	-.612*	--	--	--
	Long Term Retrieval	--	--	-.799**	-.676*	.783**	-.640*
CVLT	Trail 1-5	--	--	-.667*	--	.670*	--
	Immediate delay recall	--	--	-.790*	--	--	--
	Long delay recall	--	--	-.854**	--	--	--
	Recognition	--	--	-.805*	--	--	--
7/24 SRT	Trial 1-5	-.820**	.797**	--	--	--	--
	Immediate Recall	-.781**	.682*	--	--	--	--
	Delay Recall	--	--	--	--	--	--
WMSR-LM		--	--	--	--	--	--
	Immediate Recall	--	--	-.720*	--	--	--
	Delay Recall	--	--	-.879**	--	.787*	--
BNT Vocabulary		--	--	--	-.836**	.890**	-.706*

Notes: See Table 2 for key abbreviations; TN= trial number until reaching learning criterion, %C= percent correct, RT: reaction time; --= non significant. *= $p < .05$, **= $p < .01$.

Discussion

Our results show that there were clear differences between the sample of MS patients and controls in the ability to learn the baseline relations and to exhibit the derived relations of reflexivity, symmetry and transitivity. As the percentage of correct responses in MS patients was lower than controls in the baseline relations test, it is possible that the observed differences in SE tests of the MS patients are likely to be associated to a worst learning outcome of baseline relations in these subjects. Performance in both baseline and emergent relations in cognitively impaired MS patients was lower than that of unimpaired patients, who did not differ significantly from controls. This suggests that the deficit in SE performance in the MS group was due to the cognitive impairment of some of the patients. Nevertheless, it should be noted that performance of unimpaired MS patients did not match that of healthy controls, as they had slower response times during training and committed more errors during the test.

Successful explicit recall of the trained conditional relations (AB and BC) was less frequent in MS patients versus controls. Additionally, those MS patients who evoked the trained relations reached testing criterion of the equivalence relations. This could indicate that MS patients relied on explicit reasoning processes to solve the SE task. If this was the case, the decline in SE performance in MS patients could be due to a lack of consolidation of the explicit memory of the baseline relations.

MS patients showed deficits in a wide range of cognitive abilities, mainly including executive function, verbal and visual memory. The SE task was shown to be sensitive to cognitive impairment in MS, as the proportion of MS patients who succeeded in the task was lower in the cognitive impaired subgroup, and several performance indexes were significantly different among groups.

Our results show significant correlations between SE parameters and several neuropsychological test scores. Some of these correlations were obtained in both training and test stages of the task, while others were limited to one of the stages. Correlations suggest that learning of conditional relations (training stage) is associated with visual memory and processing speed, while the formation of equivalence relations depends on executive functioning, verbal memory and language. Tests assessing attention show correlation with both stages of the task. This suggests that both processes imply attention demands. The correlations found for the MS group does not necessarily indicate disease, but associations between SE performance and the cognitive skills that are examined through the neuropsychological tests. The pattern of correlations observed in MS patients could be matched with that of normal controls. Future studies should examine this issue.

In this study a delayed MTS procedure was used. When a delay is inserted between the sample and comparison stimuli, matching accuracy may vary as a function of the duration of the delay. The resulting function can provide suggestive evidence for the nature of the underlying retention process (Zentall, Wasserman, Lazareva, Thompson, Rattermann et al. 2008). However, the relatively short delay used (100 milliseconds), may not have be involved in any kind of memory. Moreover, the low percentage of MS patients who explicitly recalled the trained conditional relations may be related to the deterioration of the episodic memory observed in MS patients (Thornton, Raz, & Tucker, 2002).

One limitation of our study may its small sample size. For this reason the results should be interpreted with caution and should be confirmed with larger sample studies. However, to our understanding, our results are useful as a first exploratory approach of the MS population in our country. Another limitation is the absence of matched controls for the neuropsychological evaluation. Further investigations should be conducted to extend and deepen the findings that we have observed. On the other hand, fatigue has been shown to play a significant role in cognitive functioning in MS patients, and no measures of fatigue were taken during the SE task. However, MS patients and controls subjects were allowed to decide when to begin each block of trails in both the training and test stages of the SE task, and the duration of the task were not different between groups.

In conclusion, our results show that equivalence relation learning was compromised in our sample of MS patients, particularly in those who were cognitively impaired. The correlations found between SE task performance and a wide range of neuropsychological tests suggest that SE learning is a complex cognitive process, which integrates diverse cognitive domains. This impairment is congruent with the MS-related damage in frontal and parietal regions, which connect with most brain structures and are critical for this kind of learning.

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