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Original Research Paper

Impairment of decision-making in multiple sclerosis: A neuroeconomic approach

Maria Sepúlveda, Begoña Fernández-Diez, Elena H Martínez-Lapiscina, Sara Llufriu, Nuria Sola-Valls, Irati Zubizarreta, Yolanda Blanco, Albert Saiz, Dino Levy, Paul Glimcher and Pablo Villoslada

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Abstract

Objective: To assess the decision-making impairment in patients with multiple sclerosis (MS) and how they relate to other cognitive domains.

Methods: We performed a cross-sectional analysis in 84 patients with MS, and 21 matched healthy controls using four tasks taken from behavioral economics: (1) risk preferences, (2) choice consistency, (3) delay of gratification, and (4) rate of learning. All tasks were conducted using real-world reward outcomes (food or money) in different real-life conditions. Participants underwent cognitive examination using the Brief Repeatable Battery-Neuropsychology.

Results: Patients showed higher risk aversion (general propensity to choose the lottery was 0.51 vs 0.64, $p=0.009$), a trend to choose more immediate rewards over larger but delayed rewards ($p=0.108$), and had longer reactions times ($p=0.033$). Choice consistency and learning rates were not different between groups. Progressive patients chose slower than relapsing patients. In relation to general cognitive impairments, we found correlations between impaired decision-making and impaired verbal memory ($r=0.29$, $p=0.009$), visual memory ($r=-0.37$, $p=0.001$), and reduced processing speed ($r=-0.32$, $p=0.001$). Normalized gray matter volume correlated with deliberation time ($r=-0.32$, $p=0.005$).

Conclusion: Patients with MS suffer significant decision-making impairments, even at the early stages of the disease, and may affect patients' quality and social life.

Keywords: Multiple sclerosis, cognitive impairment, decision-making, neuroeconomics

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Correspondence to:
P Villoslada
Center of Neuroimmunology, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Department of Neurology, Hospital Clinic of Barcelona, Centre Cellex 3A, Casanova 145, 08036 Barcelona, Spain.
pvilloslada@clinic.ub.es

Maria Sepúlveda
Begoña Fernández-Diez
Elena H Martínez-Lapiscina
Sara Llufriu
Nuria Sola-Valls
Irati Zubizarreta
Yolanda Blanco
Albert Saiz
Center of Neuroimmunology, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Department of Neurology, Hospital Clinic of Barcelona, Barcelona, Spain

Dino Levy
Recanati Business School and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

Paul Glimcher
Center for Neural Science, New York University, New York, NY, USA

Pablo Villoslada
Center of Neuroimmunology, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Department of Neurology, Hospital Clinic of Barcelona, Barcelona, Spain/Department of Neurology, University of California—San Francisco (UCSF), San Francisco, CA, USA

Introduction

Decision-making process involves an evaluation of the possible options and their outcomes, comparing between the utilities of those options and then choosing the option with the highest utility. Decision-making is a process that involves multiple brain areas, occurs on various time scales and ranges in complexity.[1] Impairment of decision-making processes was evident in patients with focal or diffuse damage in prefrontal networks from traumatic brain injury, Parkinson's disease, or frontotemporal dementia.[2–4]

It is well known that patients with multiple sclerosis (MS) frequently suffer mild-to-moderate cognitive impairment, even from the early stages of the disease.[5–7] Importantly, previous studies found abnormal decision-making-related behaviors in MS patients.[8–17] However, it is unclear if and to what extent do these abnormal behaviors contribute to the deterioration in the quality of life of MS patients and how are they related to other dimensions of the disease such as disability, cognition, or social aspects.

Therefore, we evaluated a set of well-defined decision-making processes of MS patients compared to healthy controls using a comprehensive set of tasks developed in the field of behavioral economics. Our aim was to systematically and rigorously evaluate several decision-making components that are very important in our day-to-day lives and are basic components of any decision-making theory. We evaluated individuals' preferences toward risk and delay of gratification, their rate of learning from experience and their choice consistency. Importantly, in all tasks, we

used real monetary and primary (food) rewards and we used different real-life conditions for improving ecological validity.[18] We evaluated subjects' performance in all these tasks and its relationship with cognitive ability, physical disability, social impact, and with global measures of brain damage.

Methods

Study population

The study was proposed to consecutive patients with MS attending the Center of Neuroimmunology at the Hospital Clinic of Barcelona from May 2013 to May 2014. We included a total of 84 patients with different MS subtypes (75 patients with relapsing–remitting MS, 4 with secondary-progressive MS, and 5 with primary-progressive MS) and 21 gender- and age-matched healthy controls. We excluded patients with severe anxiety or depression using the validated Spanish version[19] of the Hospital Anxiety and Depression Scale (HADS) and the Beck Depression Inventory (>10 points). These tests were conducted before we started to run the cognitive batteries. In addition, we excluded from the study patients who were taking steroids at the time of the test or had experienced a clinical relapse within the previous 3 months. All participants underwent neurological examination, including the Expanded Disability Status Scale (EDSS) and a cognitive examination using the Brief Repeatable Battery-Neuropsychology (BRB-N) conducted on the same day as the decision-making tests. All participants gave informed consent, and all procedures were approved by the Ethics Committee of the Hospital Clínic of Barcelona, Spain.

Cognitive evaluation

The BRB-N includes the Selective Reminding Test (SRT), the Spatial Recall Test (SPART), the Paced Auditory Serial Addition Task (PASAT), the Symbol Digit Modalities Test (SDMT), and the Word List Generation (WLG). The results of the cognitive tests were transformed to *z*-scores, derived from a normalized data obtained from a cohort of healthy controls matched for age and educational level as previously described.[5] Patients were classified as cognitively impaired if they scored 1.5 standard deviations (SDs) below the average value of the healthy controls in at least two of the tests corresponding to different domains.

Decision-making tasks

We analyzed the decision-making-related behaviors using a battery of four tasks that examine several basic economic aspects of decision-making (Figure 1) (see supplementary material for detailed description of the tasks): (1) risk preferences: the risk task was previously described in detail in Levy and Glimcher[20]; (2) consistency in choices: the economic rational behavior (generalized axiom of revealed preference (GARP) task) was previously used and described in detail in Burghart et al.[21]; (3) delay of gratification: the temporal discounting task was previously used and described in Kable and Glimcher[22]; and (4) rate of learning from experience. The design of the crab game is based on the design reported in Rutledge et al.[23] All tasks were administered using the E-prime software (Psychology Software Tools). In addition to analyzing the choice data, we also measured the reaction time for each choice and implemented it in our analysis. Subjects were classified as being impaired on a given decision-making task if they scored >1.96 SDs below the mean score of the control group.

Magnetic resonance imaging

We performed a magnetic resonance imaging (MRI) study within 1 month of the neurological and cognitive assessment with a 3T Magnetom Trio (Siemens, Erlangen, Germany) scanner, using a 32-channel phased-array head coil as previously described.[24] We obtained a three-dimensional (3D) structural T1-weighted MPRAGE sequence. T1-lesion masks were created manually from T1-MPRAGE using ITK-SNAP software. Normalized brain parenchymal volume (NBPV), normalized gray matter volume (NGMV), normalized white matter volume (NWMV), and lesion volume (LV) were evaluated with SIENAX (FMRIB, Oxford, UK) once the T1 lesion mask had been used to avoid pixel misclassification. No subject suffered a clinical reactivation of the disease during the period between the neurological and the MRI assessments.

Statistical analysis

We compared the different task scores between groups using a T-test and an analysis of variance (ANOVA) test for variables that were normally distributed. We used the Mann–Whitney test and Kruskal–Wallis test for variables that were not normally distributed. Differences in decision-making tasks were further assessed between MS subgroups using a multivariate ANOVA. Significant differences were followed up using post hoc Tukey's and Bonferroni correction for multiple testins to assess differences between pairs of groups. We performed bivariate correlations using Pearson's or Spearman's correlation tests depending on whether or not the variables were normally distributed, respectively, to assess associations between decision-making components and

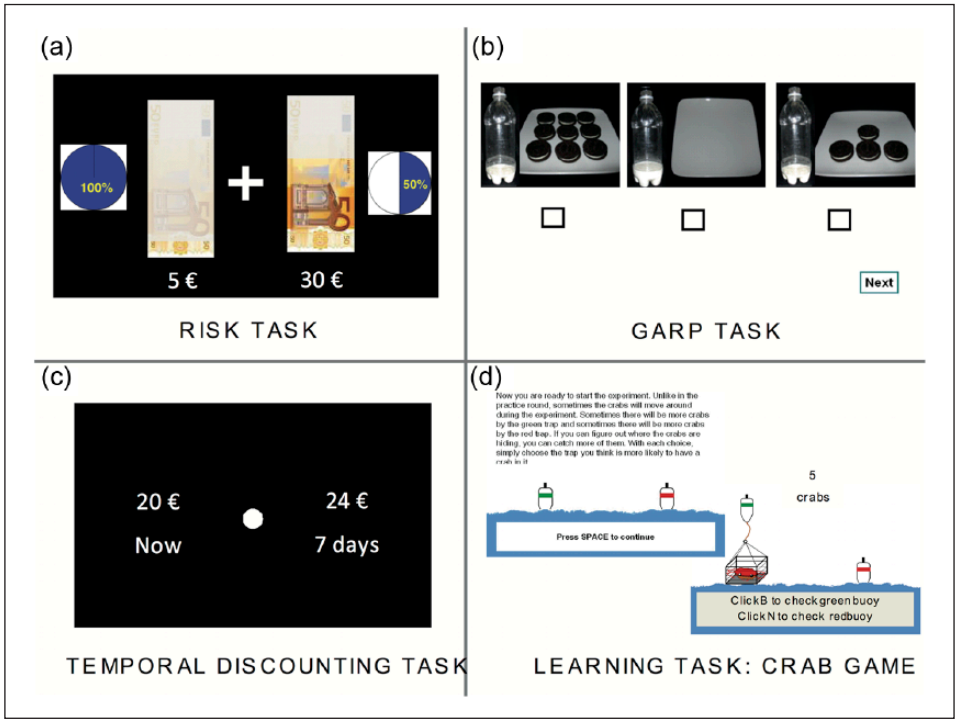

Figure 1. *Decision-making tasks.* The picture shows a representative image of each tasks: (a) *risk preferences* (*risk task*): subjects were requested to choose between a certain small reward (the *reference* option) and a stated probability of either winning a larger amount of the same reward (money or food) or getting nothing (the *lottery* option); (b) *Consistency in choices* (*GARP task*): consisted of 16 trials that involved explicit tradeoffs between milk and cookies. This task examines how consistent a subject is in their choices; (c) *Delay of gratification* (*temporal discounting task*): patients must choose between a fixed immediate small amount of monetary reward (the smaller sooner option) and a larger amount of monetary reward but delayed in time (the larger later option); and (d) *Learning rate* ("*crab game*" *task*): on each trial, subjects choose either a red or a green option (animated crab traps attached to red and green buoys). When a reward had been scheduled for their chosen option, the chosen trap was raised from the ocean to reveal a crab inside. Otherwise, the chosen trap was revealed to be empty.

verbal memory, visual memory, executive-attention function, or MRI variables (normalized lesion load and gray matter volumes) in MS patients (correction using Bonferroni's method for the five correlations, α-level of 0.010). We used a logistic regression to assess whether social variables were predicted by demographic, radiological, BRB-N, or decision-making variables. Finally, we used a linear regression to assess whether decision-making components were best predicted by EDSS, radiological, or cognitive variables. All *p*-values were two-tailed, and they were considered significant at $p<0.05$. Statistical analyses were performed using SPSS version 19.0 (SPSS Inc, Chicago, IL) software.

Results

Socio-demographic, clinical, and cognitive characteristics of the cohort

We recruited 84 patients with MS, with median EDSS score of 1.5 (range: 0–7.5) and mean disease duration of 10.1 years (Table 1). As expected, patients with progressive forms were older (mean age: 53.4 vs 41.1 years, $p<0.001$), had higher LV ($p=0.007$), and lower gray matter volume ($p=0.042$) than relapsing patients (Table 1). Regarding socio-demographic variables, MS patients were less likely to be currently employed or have childcare responsibilities than controls. There were no significant differences regarding educational level, gender, or age (Table 1).

In total, 16 patients (19%) were categorized as cognitive impaired. As expected, cognitively impaired patients had higher disability (median EDSS score: 1.8 vs 1.5, $p=0.020$), higher LV ($p=0.007$), and lower white ($p=0.023$) and gray matter ($p=0.002$) volumes (Supplementary Tables S1 and S2). In addition, the proportion of patients with progressive disease between the patients with cognitive impairment was higher (18.7% vs 10.3%) although did not reach statistical significant, and so was the unemployed proportion (50% vs 23%, $p=0.077$) (Supplementary Table S2).

Table 1. Demographic and clinical characteristics of controls and MS patients.

	Controls, $n=21$	MS patients, $n=84$	RRMS, $n=75$	PMS, $n=9$
Age at inclusion, years	41.1 (4.8)	42.4 (9.4)	41.1 (8.9)	53.4 (5.5)[b]
Ratio men:women, % women	8:13 (61.5)	30:54 (64.3)	28:47 (62.7)	2:7 (77.8)
Educational level, *n* (%)				
Elementary school	2 (9.5)	8 (9.5)	6 (8)	2 (22.2)
High school diploma	6 (28.6)	34 (40.5)	31 (41.3)	3 (33.3)
Further education or university	13 (61.9)	35 (41.7)	32 (42.7)	3 (33.3)
Higher degrees	0	7 (8.3)	6 (8)	1 (11.1)
Marital status, *n* (%)				
Single	12 (57.1)	15/69 (21.7)[a]	14/61 (23.0)	1/8 (12.5)
Married/partnered	7 (33.3)	45/69 (65.2)	38/61 (62.3)	7/8 (87.5)
Divorced	2 (9.5)	9/69 (10.7)	9/61 (14.8)	0
Employed, *n* (%)	19 (90.5)	53/73 (72.6)	49/65 (75.4)	4/8 (50)
Guardianship of children, *n* (%)	9 (42.9)	22/62 (35.5)	21/56 (37.5)	1/6 (16.7)
Income, €[c]	23,809.5 (8679.5)	25,293.8 (10,828.8)	24,113.1 (10,019.2)	23,520.7 (7820.3)
Disease duration, years	–	10.1 (6.9)	9.7 (6.7)	14.1 (7.3)
EDSS, median (range)	–	1.5 (0–7.5)	1.5 (0–4.5)	5.5 (4.0–7.5)
NLV, cm^3	–	11.3 (12.3)	10.0 (10.1)	22.8 (17.1)
NGMV, cm^3	–	785.6 (55.4)	790.5 (53.9)	743.5 (534.7)
NWMV cm^3	–	725.9 (55.5)	729.9 (53.1)	692.4 (67.8)
NBPV, cm^3	–	1511.5 (99.9)	1520.4 (95.1)	1436.0 (114.2)

RRMS: relapsing–remitting MS; PMS: progressive MS; NLV: normalized whole brain T1-MPRAGE lesion volume; NGMV: normalized gray matter volume; NWMV: normalized normal-appearing white matter volume; NBPV: normalized brain parenchymal volume.
Values are expressed as mean (standard deviation) except for EDSS.
[a]$p<0.05$.
[b]$p<0.01$ (comparisons are for the whole MS group against healthy controls or MS clinical subgroups against healthy controls).
[c]Data obtained from all controls and $n=50$ patients ($n=45$ relapsing and $n=5$ progressive MS patients).

Decision-making performance in MS patients

MS patients showed higher risk aversion (less tendency to choose the lottery options: 0.51 vs 0.64, $p=0.009$), both for money and for food rewards (Table 2). It is important to note that the differences between the groups were always stronger for food than for monetary rewards, which would reflect more basic preferences. In addition, MS patients had slower reaction times than the controls in all decision-making tasks (Table 2). In the temporal discounting task, MS patients showed a trend toward choosing the *smaller sooner* option more than controls, suggesting that they may have a tendency to prefer an immediate but a smaller gratification at the expense of waiting for a larger reward given in the future, although the difference did not reach statistical significance. We did not find differences between the groups in either the Afriat index (AI) and the Houtman–Maks index (HMI) indices in the GARP task. This suggests that patients with MS are consistent in their choices to the same extent, as healthy controls. Finally, MS patients were not different from healthy controls in their rate of learning as measured using the crab game. In total, 7 healthy controls (33%) and 41 MS patients (49%) had impaired behavior (task score>1.96 SDs below the mean score of the control group, $p=0.230$) in at least one decision-making task. A total of 10 patients (12%) had impaired behavior in two different decision-making tasks and 4 patients (5%) had impaired behavior in three out of the four tasks, but none of the controls had impairments in more than one test.

We found that reaction time was correlated with the age at inclusion ($r=0.23$, $p=0.020$) and higher scores of HADS and Beck Depression inventory correlated with longer reaction times ($r_s=0.20$, $p=0.022$, $r_s=0.21$, $p=0.019$, respectively). The analysis by disease subtype showed that patients with progressive forms of the disease were slower to choose than patients with relapsing forms (Table 2). Patients with cognitive impairment were also slower in their decisions than non-impaired patients, especially in the temporal discounting task (3667.2 vs 3019.0 ms, $p=0.040$) (Supplementary Table S3).

Table 2. Decision-making test results for controls and patients with MS.

	Controls, $n=21$	MS patients, $n=84$	RRMS, $n=75$	PMS, $n=9$
Hunger level	6.2 (2.4)	5.9 (2.0)	6.0 (1.0)	4.5 (2.0)
Risk preferences (risk task)				
General tendency	0.64 (0.2)	0.51 (0.2)[b]	0.51 (0.2)[a]	0.50 (0.3)
Propensity_money	0.62 (0.2)	0.58 (0.2)	0.58 (0.2)	0.54 (0.3)
Propensity_food	0.60 (0.3)	0.43 (0.3)[b]	0.43 (0.3)[a]	0.46 (0.3)
Reaction time (RT)	3857.5 (1713.2)	4931.5 (1978.8)[a]	4958.1 (2054.1)	4710.3 (1238.5)
RT_money	3820.9 (1910.0)	4863.2 (2005.4)[a]	4904.5 (2071.2)	4518.6 (1376.5)
RT_food	3894.1 (1846.4)	4999.9 (2179.8)[a]	5011.6 (2274.1)	4901.9 (1204.4)
Consistency in choices (GARP task)				
Rational choice (AI)	0.97 (0.06)	0.96 (0.1)	0.96 (0.1)	0.95 (0.1)
Rational choice (HMI)	10 (1)	10 (1)	10 (1)	10 (1)
Delay of gratification (temporal discounting task)				
General tendency	0.45 (0.3)	0.35 (0.2)	0.36 (0.2)	0.33 (0.2)
Reaction time	2407.4 (1011.4)	3142.5 (1196.8)[a]	3061.7 (1197.4)	3815.7 (1013.1)[a]
Learning rate ("crab game" task)				
Number of crabs	92 (5)	93 (4)	93 (4)	92 (5)
Reward	0.29 (0.02)	0.29 (0.01)	0.29 (0.01)	0.29 (0.01)
% Correct choices	0.49 (0.03)	0.49 (0.04)	0.48 (0.04)	0.49 (0.03)
% Same-side choices	0.66 (0.13)	0.63 (0.10)	0.63 (0.10)	0.64 (0.12)
Learning rate	0.89 (0.20)	0.90 (0.24)	0.90 (0.25)	0.93 (0.12)
Reaction time	1396.0 (225.0)	1569.0 (458.0)[b]	1562 (480)	1620 (209)[a]

RRMS: relapsing–remitting MS; PMS: progressive MS; AI: Afriat index; HMI: Houtman–Maks index.
All values are expressed in mean (standard deviation). Reaction times are expressed in milliseconds.
[a]$p<0.05$.
[b]$p<0.01$ (comparisons are for the whole MS group against healthy controls or MS clinical subgroups against healthy controls).

We found that delay of gratification task performance correlated with physical disability measured using the EDSS ($r_s=0.28$, $p=0.009$), which is in agreement with the partial correlation between EDSS and measurements of cognitive impairment. We found a significant correlation between the reaction time in the temporal discounting task and the NGMV ($r=-0.32$, $p=0.005$) and between the learning rate and the normalized LV ($r=-0.29$, $p=0.010$). These findings are in agreement with the notion that higher lesion burden (e.g. gray matter atrophy) implies higher disability in the different cognitive and physical domains (e.g. decision-making).

Association between decision-making performance and other cognitive domains

We next examined the association between behaviors in the decision-making tasks with other cognitive domains. We found a significant correlation between verbal memory measured using the SRT and the rationality index (AI, $r_s=0.29$, $p=0.009$). In addition, visual memory measured using the SPART correlated with the propensity to choose the risky option ($r_s=-0.37$, $p=0.001$). Similarly, the executive-attention tasks (PASAT) correlated with reaction times in the temporal discounting task ($r_s=-0.32$, $p=0.001$). When we repeated the correlations between decision-making and cognitive functions after adjusting for anxiety and depression levels (partial correlations), we did not found a significant effect in the associations with temporal discounting task or the propensity to choose the risky option. Moreover, the correlation between verbal memory and rationality was no longer significant.

Decision-making performance by gender

Female patients showed a trend to worse performance on information processing speed (measured by the PASAT3) when compared to male patients (Bonferroni correction $p=0.086$, Supplementary Tables S4 and S5). On the contrary, male patients performed worse than female patients on verbal fluency (measured by the WLG), although this comparison neither survived Bonferroni correction ($p=0.053$). Female patients

punctuated higher in anxiety ($p=0.022$) and depression ($p=0.032$) scores than male patients. High scores of anxiety (measured by HADS) correlated with worse performance of PASAT3 ($r_s=-0.56$, $p=0.046$) but only in the group of female controls. Finally, male patients showed significantly longer reaction times compared to their sex-matched controls, especially during the temporal discounting task (Bonferroni correction $p=0.030$, Supplementary Table S6) and exhibited higher risk aversion than female patients, although this comparison was no longer significant after Bonferroni correction ($p=0.105$). In addition, female patients presented also higher reaction time compared to male controls (Bonferroni correction $p=0.041$) but not compared to female controls.

We next wanted to examine the interaction between each of the decision-making tasks and the various MRI and clinical measures using a multiple linear regression model. We entered into the model the MRI measures (LV, brain parenchyma volume, normalized gray matter volume, and NWMV), and age at inclusion, disease duration, EDSS, and BRB cognitive scores as parameters. We found that the model explained 12%–42% of the variance of the decision-making scores. The visual memory global score was the main element associated with each *z*-score of the decision-making test. Among the radiological variables, only the brain parenchyma volume was able to explain the variance of the crab game test (Table 3).

Decision-making performance and social impact in patients with MS

We performed logistic regression models in order to assess the role of decision-making performance, controlling for other relevant variables (cognition, EDSS, and gray matter volume), in explaining the social impact of MS (living alone, employment and child-care responsibilities as categorical variables). We found that in MS patients, having a job (employment) was significantly related to the attentional domain of the BRB measured by PASAT ($\text{Exp}(\beta)=2.11$, $p=0.022$). However, we did not find a relation with any of the radiologic, mood cognitive or decision-making scores, and other social variables.

Discussion

In this study, we found that patients with MS suffer significant alterations in their decision-making processes, characterized by higher risk aversion, a tendency for higher preference for immediate options, and a general slowing of reaction times when making choices. These abnormalities were present even in patients with short disease duration and low disability, as well as in patients without global cognitive impairment, but were more severe in patients with cognitive impairment, higher brain atrophy, or progressive disease. Surprisingly, we did not find differences in choice consistency (also known as choice rationality) or learning rates—a finding which differs from several other neurological diseases such as Parkinson's disease[2,3] and frontotemporal dementia.[4] This may argue for a less selective damage of neural networks involved in the decision-making process in patients with MS. Our results also support the interaction between decision-making processes and other cognitive domains such as verbal and visual memory, attention, speed of information processing, and with the global burden that the brain lesions inflict on the patients.

Several previous studies exploring decision making in patients with MS using the Iowa Gambling Task (IGT),[8–13] the Game-of-Dice Task (GDT), and the Cambridge Gambling Task (CGT)[14–17] have showed a poorer performance on the GDT and on the final IGT trials, supporting an impairment of the ability to decide in patients with the disease. Nevertheless, there are some conceptual limitations with regard to the specific decision-making processes that are being measured or estimated when using the aforementioned tasks. Although the IGT is well known and has been used many times as a measurement of subjects' risk preferences, it confounds several aspects of the choice process. Because this task is a sequential choice task in which risk and rewards are learned from experience, impairments might arise due to differences in "actual" risk preferences, the ability to learn from feedback, the learning rate of the individual, or even just differences in sensitivities to magnitudes. In the GDT, the analysis combines together options with different expected values of the lotteries and this strategy might ignore subtler differences in risk preferences across individuals.

In addition, all these previous studies have been used hypothetical rewards, which in many cases result in a potential bias in which responses are overstated compared to decision-making tasks that are incentivized using real rewards[25–30] or plans.[31–33] These behavioral studies are accompanied with data that show differences in value representations between real and hypothetical choice situations.[34,35]

Recent studies,[15–17] using GDT or CGT, were able to designate risk and slow deliberation as the most affected components of decision-making in MS,

Table 3. Multiple linear regression analyses of decision-making tasks and clinical and imaging variables in patients with MS.

Decision-making task		NLV	NGMV	NWMV	NBPV	Disease duration	EDSS	BRBz_v	BRBz_vi	BRBz_a	WLGz	R^2
Risk task	General tendency	ns	ns	ns	ns	ns	ns	ns	Exp(β)=−0.408 p=0.004	ns	ns	0.12
	General propensity food	ns	ns	ns	Exp(β)=−0.569 p=0.050	ns	ns	ns	Exp(β)=−0.507 p=0.001	Exp(β)=0.289 p=0.041	ns	0.15
Consistency in choices	Afriat index	ns	ns	ns	ns	ns	Exp(β)=−0.335 p=0.027	ns	Exp(β)=−0.464 p=0.005	ns	ns	0.28
Delay of gratification	Reaction time	ns	ns	ns	ns	ns	Exp(β)=0.257 p=0.034	ns	ns	Exp(β)=−0.227 p=0.042	ns	0.14
Learning rate "crab game"	Number of crabs	ns	ns	ns	Exp(β)=0.929 p=0.002	ns	ns	Exp(β)=0.309 p=0.028	Exp(β)=0.334 p=0.048	Exp(β)=−0.760 p<0.001	ns	0.42

NLV: normalized whole brain T1-MPRAGE lesion volume; NGMV: normalized gray matter volume; NWMV: normalized white matter volume; NBPV: normalized brain parenchymal volume; EDSS: Expanded Disability Status Scale; BRBz_v: verbal memory domain z-score=(z-score SRT-S+z-score SRT-R+z-score SRT-D)/3);[5] BRBz_vi: visual memory domain z-score=(z-score SPART 10/36+z-score SPARTD 10/36)/2);[5] BRBz_a: attentional domain z-score=(z-score PASAT3+z-score SDMT)/2);[5] WLGz: Word List Generation z-score; R^2=variance; Exp(β)=standardized beta.

except one,[14] where patients' performance did not differ from that of controls at the GDT.

In this study, we examined various decision-making processes while implementing a comprehensive and rigorous approach using several well-known tasks from behavioral economics using real-world reward outcomes (food or money) in different real-life conditions. In addition to supporting risk and deliberation time as decision-making compounds altered in MS patients, we directly examined each subject's risk preferences and found that MS patients, in general, were more risk averse than healthy controls. We also examined other decision-making aspects that have never been examined before in MS patients. Specifically, we found that MS patients tend to prefer immediate over delayed rewards suggesting that their time preferences are altered, although patients with MS have not shown a more impulsive behavior.[16] We have also demonstrated that although risk, and perhaps time, preferences are altered in MS patients compared to healthy controls, these alterations are not associated with a problem in choice consistency or in the ability to learn the reward probabilities of the environment. This suggests that choice consistency and learning abilities are far more robust and immune to impairments due to brain lesions.

In contrast with previous studies, MS patients participating in our study were mostly low disabled (median EDSS: 1.5) and with a short disease duration (mean (SD): 10.1 (6.9) years). The proportion of progressive MS forms in this study was also very low (9/84, 10.7%). A decline in decision-making process early in the disease was also noted in Simioni et al.,[11] but in this study, authors could not relate the dysfunction in the decision-making process to executive or other cognitive impairments.

The correlation between white matter damage and the severity of the abnormal decision-making behavior found in MS patients is still unclear. Whereas some studies have failed to demonstrate correlation between white matter damage and the decision-making alteration,[9,10,15,25] Muhlert et al.[15] demonstrated a significant, although moderate, association between white matter LV and deliberation time. [AQ: 1] Radomski et al.[16] also showed that decision-making was linked to both third ventricle width and intercaudate ratio, a secondary marker of white matter damage. [AQ: 2]

In MS, there is damage to various neural networks.[36–38] The damage in neural networks, supporting the decision-making process, can be due to the combination of focal white matter damage by plaques combined with diffuse damage in the gray and white matter. Because the highest volume of neural tissue is in the frontal lobes, the highest lesion burden in MS is taking place in this region. Previous studies have shown the importance of brain areas in the frontal lobes, especially the ventromedial prefrontal cortex (vmPFC) and orbitofrontal cortex, for decision-making processes.[19,20,39] This suggests that the decision-making impairments in MS patients are at least partly due to their frontal lobe lesions and associated networks. An additional possible mechanism for the impaired decision-making behavior is to consider MS as a disconnection syndrome, producing impairments in processing and integration of information due to disconnections between participating neural networks.[40] Brain synchronization studies have shown impairments in signal integration in MS, which was associated with cognitive impairments[41] and probably contributes to the impaired decision-making processes that we found in this study.

Finally, we did not observe any association with social variables. This might be because the social variables that we examined are complex and multifactorial. Hence, a single cognitive domain—even if it is as relevant as a decision-making process— might not have the power to explain the complex social variables.

This study has several limitations. Intelligence quotient was not assessed and may have differed between patients and controls (impacting on cognitive and decision-making comparisons). Another limitation is the lower percentage of patients with MS who have progressive disease, and thus, our patient group may not be representative of MS in general, especially in relation to cognitive abnormalities. However, we were interested in studying performance in decision-making tasks in early to medium stage patients which are still active and with social and professional burdens. Therefore, the differences we have found are preliminary and would benefit from replication in other samples. Despite these limitations, our study has showed using tasks with real-world reward outcomes that patients with MS suffer significant alterations when making choices, especially higher risk aversion, a general slowing of reaction times and a tendency for higher preference for immediate options. Our results also highlight the interaction between decision-making processes and other cognitive domains and with the lesion burden.

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Author contribution

M.S. recruited patients, performed clinical and neuropsychological tests, performed the statistical analysis, and wrote the article; B.F.-D. recruited patients, performed clinical and neuropsychological tests, performed the analysis, and wrote the article; E.H.M.-L. performed the neuropsychological tests and revised the manuscript; S.S. performed patient evaluation and reviewed the manuscript; N.S.-V. performed patient evaluation and reviewed the manuscript; I.Z. performed patient evaluation and reviewed the manuscript; Y.B. performed patient evaluation, statistical analysis, and reviewed the manuscript. A.S. performed patient evaluation and reviewed the manuscript; D.L. designed the decision-making tasks, analyzed the results, and reviewed the manuscript; P.G. designed the decision-making tasks and analyzed the results; P.V. designed the study, analyzed the results, and wrote the article.

Declaration of Conflicting Interests

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