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Dissociation between decision making under ambiguity and risk in patients with juvenile myoclonic epilepsy

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ABSTRACT

Introduction: Decision making (DM) is one aspect of impulsivity that can be defined by the ability to decide between two or more options in a given situation. To date, there are at least two types of DM that differ in the level of uncertainty, and how much information about consequences is provided. In this study, we aimed to evaluate the two domains of DM — under risk and ambiguous — with a comprehensive evaluation in a group of patients with juvenile myoclonic epilepsy (JME), and correlate with patients' characteristics, clinical variables, and neuropsychological evaluation for executive functions.
Methods: We evaluated 35 patients with JME and 39 healthy controls using the Iowa Gambling Task for DM under ambiguity and the Game Dice Task for DM under risk. We assessed the performance in Iowa Gambling Task and Game Dice Task through net scores, safe and risky choices, besides the type of decisions across time.
Results: Patients with JME had a higher number of risky choices compared to controls in the Game Dice Task. There was no significant difference between patients and controls in the Iowa Gambling Task. However, patients with higher seizure frequency had worse scores on decks C and D (safe choices) from the Iowa Gambling Task.
Conclusion: Patients with JME have worse performance on DM under risk. The same was not observed for DM under ambiguity. Epilepsy-related factors and the presence of psychiatric disorders, but not executive dysfunction, were associated with a lower tendency for safe choices. These findings showed a dissociation between DM processes in patients with JME and a tendency to make disadvantageous decisions with measurable risks.

1. Introduction

Juvenile Myoclonic Epilepsy (JME) is a generalized genetically determined epilepsy with a well-delineated electroclinical phenotype [1]. It is the most common genetic generalized epilepsy syndrome, accounting for 5–10% of all epilepsy cases and 26% of generalized genetic epilepsies [2]. The syndrome is characterized by the presence of myoclonic seizures (100% of the cases), myoclonic–tonic–clonic seizures (MTC) (80–90% of the cases) and typical absence seizures (30% of the cases). The treatment consists of a balance between the avoidance of precipitating factors and the use of antiseizure medication (ASM) [3]. Most cases of JME are drug-responsive with easy-to-control seizures that demand long-life treatment [3].

Previous studies have found that patients with JME have impulsive personality traits [4,5], and others have shown personality disorders related to impulse control [6,7]. Impulsivity is a multifaceted construct characterized by "a predisposition toward rapid, unplanned reactions to internal or external stimuli [with diminished] regard to the negative consequences of these reactions to the impulsive individuals or others" [8,9]. Patients with JME may manifest impulsivity through unnecessary exposure to risk factors (sleep deprivation), nonadherence to ASM, and use of alcohol and other drugs [10].

Decision making (DM) is one aspect of impulsivity defined as the ability to decide between two or more options in a given situation [11]. To date, there are at least two types of DM that differ in the level of uncertainty or ambiguity. Therefore, they are defined by the amount of useful information on consequences and their probabilities that is provided to the decision maker [12,13].

In DM under ambiguity, the outcomes and probabilities are implicit, and it involves a decision in which its consequences are unknown. According to the definition, "the decision maker has to initially infer the quality of the options by processing feedback of previous choices" [14]. The Iowa Gambling Task (IGT) is the most frequently used cognitive task to evaluate implicit DM [14]. As defined by Bechara et al. [15], dysfunctions in the IGT are interpreted as impairments in using feedback from previous trials for current decisions.

Abbreviations: DM, Decision Making; GDT, Game Dice Task; IGT, Iowa Gambling Task.
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On the other hand, in DM under risk, explicit information about possible outcomes and probabilities are either clearly provided or estimated, at least to a certain range. In this context, decision makers may evaluate preferable options concerning expected values [16,17]. To assess DM under risk, Brand et al. [18] developed a test called the Game Dice Task (GDT) that requires decision between distinct alternatives that are explicitly associated with a specific magnitude of gain or loss.

There is scarce data on DM in patients with epilepsy, namely JME. Two previous studies evaluated DM under ambiguity in patients with JME, using IGT, with controversial results [19,20]. According to Wandschneider et al. [20], only patients with ongoing seizures learned significantly less from previous experience. On the other hand, Zamarian et al. [19] found that patients with JME showed worse performance in IGT that was enhanced by the presence of drug-resistant seizures. Furthermore, Unterberger et al. [21] evaluated DM under risk, using GDT, and showed that patients with JME and controls had similar performances. However, patients with JME made more risky decisions than controls.

In certain diseases (e.g., Obsessive–Compulsive Disorder; pathological buying), patients can have a poor performance in one type of DM (DM under ambiguity), but not in other (DM under risk) showing that there may be a dissociation between the two types of DM that may represent a potential neurocognitive endophenotype [22,23]. Therefore, the current study aimed to evaluate DM with a comprehensive evaluation of patients with JME. Consequently, we assessed DM under risk with GDT and ambiguity with IGT and correlated with patient's demographics, clinical variables, and neuropsychological evaluation for executive and attentional deficits.

To the best of our knowledge, this is the first study evaluating DM under ambiguity and under risk in a group of patients with JME.

2. Methods

2.1. Participants

All participants signed an informed consent form approved by the Local Ethics Committee of the Hospital das Clínicas (HCFMUSP). We assessed patients and controls with a clinical protocol that included neurological and psychiatric evaluation.

2.1.1. Patients with JME

We prospectively evaluated 35 consecutive adolescents and adults with JME from the outpatient epilepsy clinic of the medical university from the University of São Paulo (Hospital das Clínicas da Faculdade de Medicina da Universidade de Sao Paulo [HCFMUSP]), between 2016 and 2018. All patients had a clinical and electroencephalographic diagnosis of JME according to Avignon's Consensus [3].

For this study, we excluded patients with a prior history of neurosurgery, current history of alcohol/substance abuse, nonadherence to the clinical protocol, and an estimated intelligence quotient (IQ) lower than 80.

The group with JME comprised 22 women (62.8%) with a mean age of 27.9 years (Min/Max: 16/49 years; SD ± 8.97) and 14.2 years of education (Min/Max: 7/19 years; SD ± 2.9). The mean estimated IQ was of 106.4 (Min/Max: 85/132; SD ± 11.5).

2.1.2. Healthy controls

We included healthy controls with no current or prior history of psychiatric and neurological disorders matched for age, gender, and IQ. We excluded controls with IQ lower than 80, neurological disease and psychiatric disorders that could impair the understanding and performance of the tests.

The control group comprised 39 healthy adults who were not related to patients. Nineteen participants were female (48.7%) with a mean age of 28.9 years (Min/Max = 19/58 years; SD ± 10.2). The average length of education was 16.5 years (Min/Max 10/31 years; SD ± 2.8). Mean estimated IQ was 114 (Min/Max: 83/135; SD ± 10.7).

Patients and controls were matched for gender ($p = 0.225$), age ($p = 0.782$), and years of education ($p = 0.071$). Patients with JME had lower IQ (mean = 106.4; SD ± 11.5) compared to controls (mean = 114.7; SD ± 10.7; $p = 0.010$) (Table 1).

2.2. Methods

2.2.1. Epilepsy-related factors

Clinical information about epilepsy was obtained with the patient and, if necessary, with family members, at the time of the evaluation with a standard questionnaire. The average age at onset was 15.7 years (Min/Max: 7/34 years; SD ± 2.94), and the mean disease duration of 12.7 years (Min/Max: 2/35 years; SD ± 9.07). Twenty-eight patients were under monotherapy (80%), and seven were under polytherapy (20%).

Despite the difficulties to assess the frequency of myoclonic seizures that may occur in cluster, especially at awakening, we used seizure diaries and direct questioning of patients and family members to delineate seizure frequency. In agreement with Prasad's et al. [24] criteria, we categorized seizure control as follows: MTC seizures — good (<1 seizure per year), moderate (1–4 seizures per year), or poor (>4 seizures per year); myoclonic seizures — good (<5 single seizures or clusters per month, rare seizures, or occasional seizures), moderate (5–14 single seizures or clusters per month, several seizures, or frequent seizures), or poor (>15 single seizures or clusters per month or daily seizures); and absence seizures — good (<5 seizures per month, rare seizures, or occasional seizures), moderate (5–14 seizures per month, several seizures, or frequent seizures), or poor (>15 seizures per month, frequent seizures, or daily seizures). According to these criteria, 29 patients (82.8%) had good MTC seizure frequency; 22 (62.8%) had good myoclonic seizure frequency, and 24 (68.5%) had good absence seizure control. Seven patients (20%) declared that they never had absence seizure, and at the time of this evaluation, 25 patients (83%) had well-controlled epilepsy (Table 2).

We also categorized patients with JME into two subgroups: hard and easy to control JME. This categorization was based on seizure control associated with the dose (e.g., valproate above 1.0 g/day) or need of polytherapy. In our sample, 25 (71.4%) patients were considered easy to control.

In addition, the time between the last MTC seizure (measured in months) was documented and analyzed. Twenty-six (74.3%) patients were controlled for 1 year or more (six controlled for more than 6 years), and none had MTC seizures in the three months preceding the neuropsychological evaluation. The mean time between the last MTC seizure and the neuropsychological evaluation was 44 months (SD ± 49.6). Table 2 summarizes the clinical characteristics of the patients with JME.

Table 1
Sample description.

	JME	Controls	p-Value
	mean (SD)	mean (SD)	
Age	29.03 (±9.14)	28.97 (±10.26)	0.750[a]
Education (Years of schooling)	15.00 (±2.92)	16.54 (±3.91)	0.221[a]
IQ	108.03 (±13.58)	114.87 (±14.01)	**0.036**[b]
Sex (Female)	20 (62.5%)	19 (48.72%)	0.248[c]

Bold indicates statistical significance.
IQ: intelligence quotient; JME: Juvenile Myoclonic Epilepsy; SD: standard deviation.
[a] Mann–Whitney test.
[b] *t*-Test.
[c] Pearson's Chi-squared test.

Table 2
Clinical variables description.

Variable	Level	Count	Percent/Mean (SD)
Age at onset (years)	–	32	15.66 (5.22)
Epilepsy duration (years)	–	32	13.69 (9.43)
ASM	Monotherapy	26	81.25%
	Polytherapy	6	18.75%
	None	1	3.13%
MTC frequency	Good	23	71.88%
	Moderate	8	25%
	Poor	0	–
Myoclonic frequency	Good	21	65.62%
	Moderate	10	31.25%
	Poor	3	3.13%
	None	5	15.63%
Absence frequency	Good	23	71.88%
	Moderate	3	9.38%
	Poor	1	3.13%
JME control	Easy	24	75%
	Difficult	8	25%
Interval between last MTC and evaluation (in months)	≤3	0	–
	>3–6	4	12%
	>6–12	2	6.2%
	≥12	26	81.2%

[a]Values in percentage (%) [b]values described with mean and SD.
ASM: Antiseizure medication; MTCG: Myoclonic–tonic–clonic generalized seizure.

2.2.2. Psychiatric evaluation

The same psychiatrist interviewed patients and controls using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) Axis I and II Disorders [25]. Twenty-one (60%) patients had psychiatric disorders, being categorized as 13 (37.1%) with anxiety disorder; five (14.3%) with personality disorder; and four (11.4%) with depressive disorder. One patient presented personality disorder related to impulse control and depressive disorder.

2.2.3. Neuropsychological evaluation

The IQ score was derived from Matrix Reasoning and Vocabulary subtests from the Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) [26]. Neuropsychological evaluations were performed at least 48 h after the last seizure, with a battery of executive and attentional neuropsychological tests, all of which were administered, in a standard sequence, by a trained neuropsychologist (MLP). This battery comprised the following tests:

- Digit Span Forward (DSF) and Digit Span Backward (DSB) [27], which evaluate attention span, working memory, and mental control with auditory;
- Stroop Color–Word Test (SCT) [28], which evaluates the ability to inhibit responses to visual–verbal stimuli;
- Trail Making test (TMT) [29], which evaluates self-monitoring, visuospatial orientation for simple and alternating sequences, sustained attention, and divided attention;
- Wisconsin Card Sorting Test (WCST) [30], which evaluates concept building, mental flexibility, and goal maintenance; and
- Controlled Oral Word Association (COWA) test [29], which evaluates verbal fluency and control inhibition.

2.3. Measures for decision making

2.3.1. Game Dice Task (GDT)

The GDT was developed by Brand et al. [18], translated and adapted to Portuguese by Rzezak et al. [31]. According to these authors' description [18,31], in the computerized Game of Dice Task, a single virtual dice and a shaker are used. The subjects are asked to increase their fictive starting capital (R$ 1000.00) within 18 throws of the dice. Before each throw, subjects have to choose a single number or a combination of numbers (two, three, or four numbers). Each choice is related to specific fictive gains and losses that depend on the probability of occurrence of choice (a single number: R$ 1000.00 gain/loss; combination of two numbers: R$ 500.00 gain/loss; combination of three numbers: R$ 200.00 gain/loss; combination of four numbers: R$ 100.00 gain/loss). The rules and extent of gains and losses are explicitly described and visualized. The winning probability of the different choices can be reasoned easily using the ratio of occurrence (1:6, 2:6, 3:6, and 4:6). Therefore, the amount of risk associated with each choice is obvious (e.g., in the choice of a single number, there is a 1:6 chance to win R$ 1000.00 but a 5:6 chance to lose R$ 1000.00, whereas in the choice of four numbers, there is a 4:6 chance to win R$ 100.00 but only a 2:6 chance to lose R$ 100.00). Participants are also informed that they must make a total of 18 decisions. After each throw, the gain and loss are presented visually and pointed out by two different acoustic signals (gain = jingle of a cash desk; loss = dull noise). Furthermore, the number of remaining throws is also shown on the screen. The results of the throws are pseudorandomized, meaning that each of the six possible numbers occurs three times during task performance, but in a balanced order. The maximum capital at the end of the game is R$ 19,000.00 if the participant chooses a single number and is successful in each throw. The maximum deficit can be R$ 17,000.00 if the participant chooses a single number and is unsuccessful in each throw.

2.3.2. GDT analysis

To analyze risky decisions, we considered the total sum of each choice (one, two, three, or four numbers). Then, we classified one or two numbers (probability of winning less than 50% and high gains but also high penalties) as risky or disadvantageous, respectively, whereas the choices of three and four numbers (probability of winning 50% and higher, low gains but also low penalties) as nonrisky or advantageous. The frequency of each chosen alternative (one number, two numbers, three numbers, or four numbers) was also analyzed separately. We computed the net score by subtracting the amount of the number of low-risk from high-risk choices. A positive net score indicates a low-risk performance (advantageous behavior), whereas a negative net score shows a high-risk performance (disadvantageous behavior). Consecutively repeated choices (a bet in the same number of dice alternatives) made regardless negative feedback were also analyzed and named as perseverative choices, based on and modified from Brand et al. [18] conception. Besides, we divided the latter into safe (repeating a safe choice despite the loss) and risky (repeating a risky decision despite failure) perseverative decisions. At last, to measure DM flexibility and change of strategies, we included the analysis of choices shifting, which means, changing your bet after negative feedback (loss of money) to a safer (safe shifting) or riskier (risky shifting) alternative.

2.3.3. Iowa Gambling Test (IGT)

The IGT was developed by Bechara [14], translated and adapted to Portuguese by Malloy-Diniz [32]. According to the authors [14,15,32], in the computerized version of the gambling task, the subject sees four decks of cards on a computer screen. The decks are labeled A', B', C', and D'. Every time the subject clicks on a deck 'to pick a card', the computer generates a distinct sound (similar to a Casino slot machine). The face of the card (red or black) appears on top of the deck, and a message is displayed on the screen indicating the amount of money the subject has won or lost. On the top of the computer screen is a green bar that changes according to the amount of money won or lost after each selection. A gain is indicated by a proportionate increase in the length of the green bar, and a loss is shown by a commensurate decrease in the length of the same bar.

As stated by Bechara [14], the total number of trials was set at 100 card selections. The experiment shuts off automatically when the 100th selection trials are complete. In summary, after clicking to turn each card, the subject receives some money (displayed on the screen). On some cards, the subject wins money and pays the penalty (shown on the screen). Clicking to turn any card from deck A' or deck B' yields more money than turning any card from deck C' or deck D'. However, the ultimate future yield of each deck varies. The penalty amounts are higher in the high paying decks (A' and B'), leading to a negative balance, and lower in the low paying decks (C' and D'), leading to a final gain. Thus, decks A' and B' are 'disadvantageous', while decks C' and D' are 'advantageous'. However, each deck has its particularities: in deck A', the frequency of punishment increases, but the average magnitude remains constant. In deck B', the frequency of punishment remains constant, but the magnitude increases. In Deck C', there is a net gain of R$ 250 in the first ten card selections. This net gain increases in increments of R$ 50 per each block of ten cards until it reaches R$ 375 in the sixth block. Finally, in Deck D', the net gain obtained is equal to deck C'. The only difference between deck C' and deck D' is that in deck C', the frequency of punishment increases, but the average magnitude remains constant. In deck D', the frequency of punishment remains constant, but the magnitude increases.

From a methodological perspective, studies on DM in patient groups must attend to the different parts of the IGT when interpreting results, since they likely tax different types of decisions (A and B represent ambiguous decisions while C and D represent more risk decisions, similar to GDT) (Brand et al., 2007) [46].

2.3.4. IGT analysis

The total number of card selections from the disadvantageous decks (A and B) and the total number of selections from the advantageous decks (C and D) were counted. Subsequently, an overall net score was derived by subtracting the total number of disadvantageous from advantageous choices ($C + D - [A + B]$). Net scores above zero indicate that subjects select advantageously; net scores below zero indicate disadvantageous choices. Besides, we also analyzed IGT scores by dividing the 100 trials into five blocks of 20 cards selections and then calculating the difference, or net score, between the number of selections from advantageous decks and the number of selections from disadvantageous decks. A higher net score in block five than in block 1 suggests improvement in DM performance across time and learning from feedback.

2.3. Statistical analysis

Statistical standard procedures were carried out with IBM SPSS Statistics (version 23.0, 2012, SPSS inc. IBM, Chicago). Descriptive evaluations were performed to obtain the mean and standard deviation values from each numerical variable observed. The absolute (n) and relative (%) frequencies were calculated from the nominal variables. A significance level of 5% was adopted for all tests.

2.3.1. Sociodemographic variables

Initially, we verified the normality of data using Kolmogorov–Smirnov normality tests for the sociodemographic variables and IQ. For such analysis, the two-sample *t*-test (parametric data) or the Wilcoxon–Mann–Whitney test (nonparametric data) was used for age, years of education, and IQ. We also analyzed the homogeneity of the groups regarding gender, through the chi-square test.

2.3.2. Comparison of performance between groups

After checking the normality of data in each of the tests, the *t*-test (for parametric variables) and the Mann–Whitney test (for nonparametric variables) were used.

2.3.3. Analysis of the influence of clinical variables

To verify the influence of clinical variables in DM tests, we used Kendall's tau correlation coefficient for categorical variables and Pearson's correlation for numerical variables. Besides, *t*-test and Mann–Whitney or analysis of variance (ANOVA) and Kruskal–Wallis tests were used (depending on the number of groups compared and the normality of the data). The clinical variables evaluated were as follows: epilepsy duration, age at onset, seizure frequencies (absence, myoclonic, and MTC), seizure control, pharmacotherapy (mono- vs. polytherapy) and drug-responsiveness. For these analysis, we applied Bonferroni's adjustment for multiple comparisons, which resulted in an alpha level of $\alpha = 0.004$.

Patients with JME were categorized into two groups according to the presence of psychiatric disorders. Their performance on tests of DM was compared using the Student *t*-test.

To analyze the performance of our sample in executive function tests, first raw scores were transformed into z scores using the normative data of each test as the reference. Then we used one-sample *t*-test to compare patients' performance to a reference mean of 0. A linear regression analysis was used to evaluate the impact of neuropsychological evaluation on DM tests. (See Table 3.)

To evaluate the correlation between time of the last seizure and the neuropsychological evaluation, we used Pearson's product-moment correlation.

3. Results

3.1. Decision making under risk (GDT) in patients with JME

3.1.1. NET score and type of choice

Patients with JME had a higher number of risky choices/lower number of safe choices ($p = 0.020$), and lower GDT NET score ($p = 0.012$) compared to controls (Table 4).

3.1.2. Number of choices of each combination of dices

Patients with JME decided more frequently to choose a single number (the riskiest) ($p = 0.004$) compared with controls. No other individual alternative had a significant difference between JME and controls.

3.1.3. Safe and risky shifts

Patients with JME had less consistent responses than controls considering the number of shifts for safe ($p = 0.004$) and risky ($p = 0.014$) choices.

3.2. Decision making under ambiguity (IGT) in patients with JME

3.2.1. Net score

There was no significant difference between patients and controls in IGT NET score ($p = 0.266$). (Table 4)

There was no significant correlation between epilepsy-related factors, demographics and IGT NET score. (Table 5).

3.2.2. IGT deck choices

There was no significant difference between patients and controls in IGT disadvantageous decisions (deck A [$p = 0.489$] and IGT deck B [$p = 0.468$]), and advantageous decisions (IGT deck C [$p = 0.349$] and IGT deck D [$p = 0.167$])

Table 3
JME performance in executive function tests.

	JME	t	p
Digit	0.16 (0.89)	0.9	0.33
Stroop 1	−0.51 (1.12)	−2.6	**0.01**
Stroop 2	−0.83 (1.76)	−2.7	**0.01**
Stroop 3	−0.32 (1.38)	−1.3	0.20
TMT A	−1.47 (1.8)	−4.6	**0.00**
TMT B	−1.24 (1.54)	−4.6	**0.00**
COWA	−0.93 (1.0)	−5.2	**0.00**
WCST cat	0.6 (1.7)	1.9	0.06
WCST errors	0.14 (1.4)	0.6	0.56
WCST pers. err	0.6 (1.51)	2.2	**0.03**
WCST pers. tot	0.3 (1.5)	1.3	0.26

COWA: Controlled Oral Word Association Test; JME: Juvenile Myoclonic Epilepsy; TMT: Trail Making Test; WCST: Wisconsin Card Sorting Task.
Bold indicates statistical significance.

Table 4
Decision making in patients with JME and controls.

	JME		Controls			
	Mean	SD	Mean	SD	F value	p-Value
GDT NET	5.31	10.16	10.62	7.62	840	**0.012**[a]
GDT safe choices	11.69	5.08	14.18	3.87	825	**0.020**[a]
GDT one	2.90	4.07	1.18	2.62	3.002	**0.004**[b]
GDT safe shift	3	1.41	1.95	1.47	329.5	**0.004**[a]
GDT risky shift	1.83	1.20	1.13	1.21	363.5	**0.014**[a]
IGT NET	1.87	17.38	7.33	20.91	698.5	0.266[a]
IGT deck A	20.90	6.39	19.92	5.40	−0.695	0.489[c]
IGT deck B	27.77	7.15	26.41	8.21	−0,730	0.468[c]
IGT deck C	23.26	6.22	25.26	7.15	683.5	0.349[a]
IGT deck D	25.65	6.91	28.41	8.53	721	0.167[a]
IGT block 1	−2.58	3.80	−1.44	5.37	0.914	0.364[c]
IGT block 2	0.92	5.11	1.49	4.35	0.473	0.638[c]
IGT block 3	0.67	5.58	2.77	6.23	1.351	0.182[c]
IGT block 4	1.33	7.02	3.28	7.38	1.0369	0.304[c]
IGT block 5	0.92	6.24	2.21	8.93	514.5	0.508[a]

GDT: Gambling Dice Task; IGT: Iwoa Gambling Task; JME: Juvenile Myoclonic Epilepsy; SD: standard deviation.
Bold indicates statistical significance.
[a] Wilcoxon–Mann–Whitney test.
[b] Brunner–Munzel test.
[c] Two Sample *t*-test.

3.2.3. Performance across time

Both patients and controls learned throughout the task. Group comparison considering differences in net score and number of shifts from block one to block five showed a gain in DM performance, with a lower stabilization of choice strategy across time (Graph 1).

3.3. Correlation with clinical variables

There was no significant correlation between epilepsy-related factors and all GDT measures (Table 5). Patients with a higher frequency of absence seizures chose deck C less frequently (p = 0.006). There was no significant correlation between other epilepsy-related factors and IGT deck choices (Table 5). The time of the last MTC seizure was not correlated with GDT (GDT risky [p = 0.086]; GDT NET [p = 0.090]) and IGT (IGT A [p = 0.807]; IGT B [p = 0.732]; IGT C [p = 0.897]; IGT D [p = 0.176]; IGT NET [p = 0.893]).

Table 5
Clinical variables and decision making tests.

		MTC Freq.[b]	MCL Freq.[b]	ABS Freq.[b]	ASM[b]	JME Control[b]	Age at onset[a]	Epilepsy duration[a]
GDT NET	p	0.122	0.062	0.934	0.942	0.315	0.792	0.507
GDT risky	p	0.127	0.068	0. 983	0.942	0.347	0.769	0.487
IGT NET	p	0.928	0.472	0.979	0.880	0.442	0.617	0.556
IGT A	p	0.928	0.920	0.427	0.698	0.539	0.102	0.139
IGT B	p	0.736	0.811	0.622	0.783	0.309	0.839	0.509
IGT C	p	0.310	0.128	**0.006**	0.393	0.167	0.405	0.167
IGT D	p	0.557	0.936	0.880	0.336	0.874	0.507	0.105
Block 1	p	0.557	0.664	0.318	0.051	0.484	0.590	0.490
Block 2	p	0.748	0.820	0.659	0.211	0.085	0.319	0.256
Block 3	p	0.148	0.139	0.613	0.800	0.039*	0.103	0.773
Block 4	p	0.012*	0.181	0.899	0.370	0.065	0.728	0.684
Block 5	p	0.461	0.105	0.681	0.630	0.503	0.463	0.056

ABS: Absences seizures; ASM: Antiseizure medication; GDT: Gambling Dice Task; IGT: Iowa Gambling Test; JME: Juvenile Myoclonic Epilepsy; MCL: Myoclonic seizures; MTC: Myoclonic–tonic–clonic seizure;
Bold indicates statistical significance.
[a] Pearson's correlation.
[b] Kendall's rank correlation.
* These findings loose significance after Bonferroni's adjustment.

The presence of psychiatric disorders was associated with IGT — lower number of choices on deck A (p = 0.02). (See Table 6)

3.4. Correlation with neuropsychological evaluation

Patients with JME performed more poorly than did the control subjects on the following: time to completion of Stroop Color–Word Test 1 (p = 0.015), and Stroop Color–Word Test 2 (p = 0.012); time to completion on the Trail Making Test, part A (p < 0.001) and part B (p < 0.001); the COWA the total score (p < 0.001); and the WCST, in terms of the total number of incorrect perseverative responses (p = 0.031). The time of last seizure was correlated with worse performance on Stroop Color–Word Test 3 (p = 0.032) and Trail Making Test, part A (p = 0.043).

The presence of executive dysfunction was not associated with worse scores on IGT and GDT (Supplementary Table 1).

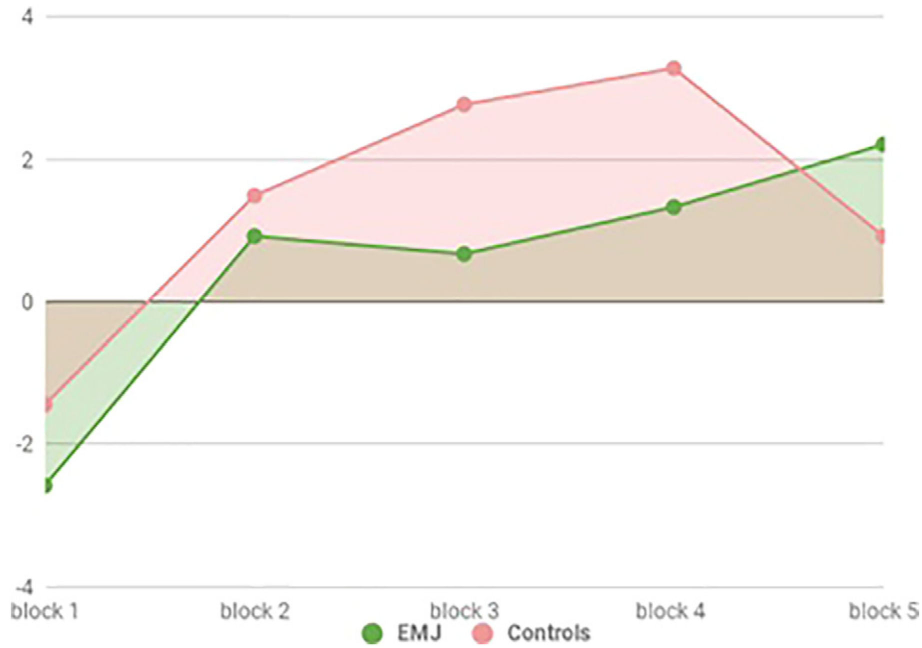
4. Discussion

This study provided three main findings. First, the clear dissociation between decision under risk versus ambiguity. While patients with JME had impairment on GDT, there was a similar performance in IGT compared to healthy controls. Second, patients with worse seizure control had a lower number of safe choices. Third, patients with psychiatric disorders made risky choices more frequently in IGT.

Our findings showed that patients with JME made significantly more risky decisions (explicit situations) than healthy controls, corroborating previous findings [21]. As stated by Brand, Labudda, and Markowitsch [12], DM under risk (explicit DM) is more representative of everyday life decisions than DM under ambiguous risks (implicit DM). In daily life activities, decisions have to be frequently made with explicit information about the potential consequences and the probabilities of reinforcement or punishment, such as driving over the speed limit. Therefore, DM under risk is associated with cognitive-rational functions [12]. In patients with epilepsy, they may be represented by the decision of getting exposed to precipitating factors (e.g., sleep deprivation, alcohol abuse) for seizures or non-adherence to proper drug treatment, despite the knowledge of increased seizure risk and its consequences. Interestingly, these behaviors were described by Janz [33], in the pioneer description about JME, and have been emphasized over the years with clinical observations [33–38] and psychiatric evaluations [39–41]. Therefore, our results on the impaired ability to make profitable decisions with clear and explicit rules corroborate previous clinical observations on these patients.

Furthermore, our patients also performed significantly worse in all measures of GDT throughout the whole task. The consistent selection of highly rewarding options despite the presence of adverse consequences may reflect poor impulse control [42–44]. In our sample, patients not only chose more frequently risky decisions, but also they had a higher number of single die choices. Patients choose the riskiest alternative from all possibilities, while controls, even when making a risky decision, select the two-dice combination alternative (less risky) more often. As previously demonstrated by our group [11], the poor impulse or inhibitory control in these patients is supported by the self-reported high impulsivity on Barratt Impulsive Scale [11], failure to stop the intrusive, irrelevant information with increased perseverative errors and difficulty in set-shifting, and an inability to learn from the feedback [35,41]. However, compared to controls, our patients had a more inconsistent performance during the task. A further look to GDT performance showed that patients had a higher number of shifts toward risky choices than controls. These findings suggest that patients may be less prone to adjust their type of decisions according to negative environmental feedback, possibly related difficulties in sustain an advantageous strategy to gain more money in long-term.

Considering decision under ambiguity, patients with JME and controls showed a similar learning process on IGT. Previous findings on



Graph 1. Iowa Gambling Task (IGT) performance across time between patients with JME and controls.

IGT in patients with JME are controversial. Zamarian et al. [19] found that patients with JME, in general, have difficulty in making profitable decisions. On the other hand, Wandschneider et al. [20] reported that the learning process of IGT was similar for patients and controls. In both studies, the persistence of seizures enhanced DM deficits. Our findings corroborate that seizure frequency is significantly associated with worse performance on IGT. Moreover, patients with higher frequency of absence seizures tended to choose deck C that represent safer choices less often than patients who were seizure-free. Besides, Unterberger et al. [21] found a positive correlation between the time of the last MTC seizure and the performance on GDT. In our series, we could not corroborate this finding. It must be taken into account that in this study the mean interval between the last MTC seizure and the neuropsychological assessment was longer (3.7 years) than documented in the previous study [21].

The analysis of every deck choice showed that both groups – JME and controls – had a preference for deck B. As previously stated [12], it indicates that patients with JME were more sensitive to the frequency of loss (deck B) than to the magnitude of loss (deck A). Although decks A and B are risky, the rate of loss in deck A is higher than in deck B. Deck B is not considered a good decision, but the avoidance of deck A should be expected in "most neurologically intact" individuals [12,14]. The assessment of the frequency of choices in decks A and B allows the identification of participants who have a more "pathological" DM (i.e., preference for deck A) versus those who are predisposed to risky decisions, but less impaired in DM overall (i.e., preference for deck B) [45]. As expected, patients with JME and psychiatric disorders followed the same pattern and chose deck B more often than deck A.

Table 6
Decision making results in patients with and without psychiatric diagnosis.

	JME with psychiatric	JME without psychiatric	t	p
GDT risky/safe	6.60 (4.72)	5.83 (5.81)	0.41	0.686
GDT NET	4.70 (9.43)	6.33 (11.62)	−0.43	0.667
IGT A	19.05 (6.57)	24.27 (4.58)	−2.33	**0.027**
IGT B	27.85 (7.88)	27.64 (5.95)	0.08	0.938
IGT C	23.5 (7.41)	22.82 (3.37)	0.28	0.776
IGT D	25.9 (7.25)	25.18 (6.53)	0.27	0.787
IGT NET	2.6 (15.27)	0.55 (21.45)	0.31	0.760

GDT: Gambling Dice Task; IGT: Iowa Gambling Test; JME: Juvenile Myoclonic Epilepsy.
Bold indicates statistical significance.

As a limitation of this analysis, the importance of the type of psychiatric disorder (e.g., personality disorder related to impulse control) could not be established.

As previously done by others [19,20], we also analyzed the pattern of the learning slope during IGT blocks. Patients with JME do not sustain their responses and tend to try more risky choices despite the positive/negative feedback and the understanding of its meaning. As described by Brand et al. [46], participants might already have deduced the rules of the task in the last blocks, and impairment on executive functions might thus become more important than feedback processing and implicit learning to make profitable decisions in this task [46]. The authors suggest that this tendency to risky behavior demonstrated by the way that patients respond seems to be as important as the final net-score.

Brand et al. [46] suggest that the processes underlying decisions under ambiguity and decisions under risk put different weights on the neural systems subserving executive functions: decisions under ambiguity seem to be minimally dependent on mechanisms of executive functions, whereas decisions under risk draw more heavily upon neural networks concerned with the processing of executive cognitive information [19,47]. In our series, although patients with JME had executive dysfunction (attention, inhibitory control, concept building, mental flexibility, and verbal fluency), as expected and demonstrated by others [33–37], it was not correlated with DM processes — under risk and under ambiguity. Toplak et al. [48] reviewed 43 studies that investigated the association between IGT performance and cognitive abilities, and showed that the majority of them did not find a significant correlation between executive function tests and IGT. Thus, our results are in line with what is predicted for DM under ambiguity, and reinforces the important separability between the constructs of DM and cognitive abilities. On the other hand, according to Brand's model [12,18,47,49], DM under risk, evaluated by the GDT, is intimately associated with executive dysfunction. However, this concept has been revisited by Schiebener and Brand [51], which states that the EF only seem to support DM process to some extent. Furthermore, DM processes are strongly modulated by individual attributes, external influences, and others cognitive abilities. This new model may represent a possible explanation for our results. Further studies in patients with JME with a more comprehensive analysis of potential influences plus neuropsychological evaluation for executive functions in a larger series will provide a more accurate delineation of DM based on revised model by Schiebener and Brand [50].

In agreement with the hypothesis of distinct mechanisms underlying the two types of DM, a discordance between DM under risk and decision under ambiguity has been reported in individuals with obsessive–compulsive disorder [22] and pathological buying [23]. These patients showed more disadvantageous choices under ambiguous (IGT) rather than under risk situation (GDT). Patients with JME had a distinct behavior with a tendency to make decisions that imply in a potential higher risk, as previously observed only in one group of patients — suicide attempters [51]. In suicidal attempters, these findings may be associated with a not-life focused way of thinking. In patients with JME, the risky behavior is probably correlated with the impulsive traits and lack or impaired of long-term consequences envisage. The authors believe that patients with JME have great difficulties to conceive desirable or undesirable future events and for this reason make more risky decisions, despite the clear understanding of their nature.

There is a consensus on the few studies on JME, despite the number of patients or the paradigm used to assess DM: patients with more severe epilepsy or that are hard-to-control (e.g., ongoing seizures, not seizure-free, or need of polytherapy) perform worse than patients with easy-to-control epilepsy. As previously stressed by our group and others, the impulsive traits in JME have a spectrum of severity [5,41]. In general, patients with personality disorder related to impulse control present frequent seizures and need of higher doses of ASM or polytherapy [52]. Therefore, it is reasonable to distinguish the “forest for the trees” when analyzing patients with JME. The presence of higher levels of novelty seeking, indicating a more impulsive behavior, impacts social functioning in more domains than the lack of seizure control [41].

Worse DM in patients with JME may lead more compromised patients to severe problems in everyday life and lack of treatment adherence. It may also represent an epiphenomenon, in which patients with hard-to-control epilepsy also have worse cognitive and psychiatric disorders implying in the well-known concept of a “more widespread disease.”

A possible limitation to be considered is the number of patients. However, it was similar or superior to other studies addressing the same issue [19,20] There is an overrepresentation of patients with drug-resistant epilepsy in our research and others. This fact is a consequence of the local healthcare system where patients with easy-to-control epilepsy are followed in secondary – and not in tertiary – care centers for epilepsy treatment. On the other hand, it provides the opportunity to evaluate this subgroup of patients, frequently neglected, that may present not only hard-to-control JME but also more psychiatric disorders and worse cognitive deficits [52].

In conclusion, this is the first study evaluating both aspects of DM in patients with JME and showed that these patients make more risk decisions with difficulties to envisage long-term outcomes. It also showed that this impairment is higher in a subgroup of patients with frequent seizures.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.106548.

Declaration of competing interest

There are no conflicts of interest.

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