Dopaminergic therapy disrupts decision-making in impulsive-compulsive Parkinsonian patients

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Conflict of Interest

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Abstract

Background

Impulsive-compulsive behaviors (ICB) are common non-motor symptoms of Parkinson's disease (PD). The relationship between these behaviors and dopaminergic drugs (DD) is still debated.

Objectives

Assess the acute effects on economic decision-making of DD in Parkinsonian patients with and without ICB.

Methods

PD patients with ICB (ICB+, n=14), without ICB (ICB-, n=16), and healthy controls (HC, n=12) performed twice a risk-based decision-making task with a learning component. The optimal strategy in the task was risk aversion. PD patients performed the task before DD intake (DD OFF) and repeated it after intake (DD ON).

Results

During the first session, all groups progressively increased the fraction of low-risk choices. In DD ON condition ICB- patients retained their risk aversion strategy while ICB+ patients progressively regressed toward risky behavior. Within the ICB+ group, this effect correlated with levodopa equivalent daily dosage.

Conclusions

In ICB+ patients intake of DD acutely affects decision-making.

Introduction

Parkinson's disease (PD) is primarily characterized by both motor dysfunctions such as bradykinesia, rigidity, and tremor, but presents also several non-motor symptoms. Impulsive-compulsive behaviors (ICB) such as pathological gambling, binge eating, hypersexuality, and compulsive buying occur in PD patients with a frequency close to 15% (1). ICB has been linked to intake of dopaminergic drugs (DD) aimed at improving PD motor symptoms (1,2). Several works have shown that dopamine neurons are involved in learning and decision processes (3–5), which are altered in PD patients following DD therapy (6). Overstimulation of the meso-cortico-limbic dopaminergic system, caused by DD, alters the function of the frontostriatal network (7–9), leading to abnormal patients' goal-directed behaviors. Recent results suggest that DD effect may be particularly evident in PD patients with ICB (10–12), but the dynamics underlying this selective effect remain unclear. While DD is an important factor in inducing ICB, there is evidence supporting the need for a sensitive neural substrate to develop these disorders: demographic, neural, and genetic risk factors have been associated with ICB (2,13–15).

Here we investigate the hypothesis of a differential effect of DD in ICB patients by studying the acute effects of DD tacking on reinforcement-learning in PD patients, both with (ICB+) and without ICB (ICB-), in an economic risk-decision task. We found that DD intake does not significantly alter the behavior of ICB- PD patients, while selectively affects ICB+ PD patients, acutely inducing risk-seeking behavior.

Materials and methods

Participants

This study was conducted after the approval of the ethical committee of Careggi Hospital (Florence, Italy) and in accordance with the Declaration of Helsinki. 14 Parkinsonian patients with ICB (ICB+) and 16 without ICB (ICB-) were recruited by the Parkinson Unit of the Careggi Hospital. Only patients with a Mini-Mental state examination (MMSE) >24 (16) were included. There were no differences between groups regarding age, sex, education, disease duration, MMSE, and L-dopa-equivalent daily dose (LEDD) (Table 1). Moreover, groups showed no difference in motor severity, assessed with part three of the Unified Parkinson's Disease Rating Scale (UPDRS) (17) (Table 1). Groups differed only in the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Diseases-Rating Scale (18) (QUIP-RS, Table 1). We also tested 12 healthy controls (HC) matched with Parkinsonian patients for age, sex, and education (Table 1).

Experimental procedure

All participants performed two sessions of economic risk-decision-making tasks within the same day. PD patients performed the first task session after overnight DD withdrawal and the second task session after ~1h from DD intake. HC patients repeated the same task after the same waiting time. Each task consisted of 40 decisions in which participants had to choose between two options: a low-risk (LR) option with a high probability (80%) of obtaining a low reward (6€) and a 20% probability of obtaining no reward (expected value = 4.8); and a high-risk (HR) option with a low probability (20%) of obtaining a high reward (18€) and an 80% probability of obtaining no reward (expected value = 3.6). In this task, the LR option is the optimal to maximize reward.

Subjects were aware of the reward amount for both options and unaware of the reward probabilities since they had to learn this last aspect empirically during the task. After each decision, the outcome of both options was displayed. (Details in supplementary materials).

	Values			**Test p-values**		
	HC	**ICB-**	**ICB+**	**HC vs ICB-**	**HC vs ICB+**	**ICB- vs ICB+**
Dunn Test						
Age	67.50±12.75	68.00±6.25	69.00±13.75	1.0	1.0	1.0
Education	13.00±5.00	13.00±1.75	13.00±4.25	0.82	1.0	1.0
Fisher Exact Test						
Sex M(F)	7(5)	10(6)	9(5)	1.0	1.0	1.0
Mann-Whitney U Test						
Disease years	-	12±9.75	9±7.75	-	-	0.41
MMSE		28.35±3.07	26.70±3.80			0.32
QUIP-RS	-	0.00±4.25	8.00±13.25	-	-	**0.011**
UPDRS III DD OFF	-	36.50±28.25	26.00±14.5	-	-	0.49
UPDRS III DD ON	-	14.50±20.25	18.50±14.00	-	-	0.56
LEDD	-	582.00±321.5	572.5±596.5	-	-	1.0

Table 1: Demographic and clinical data of HC, ICB- and ICB+ groups. Demographic data: Dunn test and Fisher exact test with Bonferroni correction were used respectively for continuous and categorical variables. Clinical data: The Mann-Whitney U Test was used. Values of variables are shown in terms of median and interquartile range, except for sex where the number of males (number of females) are reported.

Statistical analysis

We measured each subject's post-learning risk aversion (RA) as the fraction of LR choices in the last 20 trials (12)). We used a one-sample Wilcoxon signed-rank test to assess for each group, block, and session the difference from chance level (RA=0.5), applying an FDR correction (Benjamini-Hochberg). We used a Kruskal-Wallis test to compare differences in RA between groups, followed by post-hoc comparisons (Dunn test, Bonferroni correction). Statistics are reported as median ± interquartile range unless otherwise specified.

To characterize the learning phase, we computed the fraction of LR choices in each group for each trial, obtaining three curves per session. We used logarithmic regression analysis for each session to assess the effect of groups (HC, ICB-, ICB+) (see Supplementary Materials). We used the model intercept to measure the initial bias towards one of the two options, while the effect of trials was used to quantify the slope of the learning curves. T-test was used to assess the significance of bias and slope, applying a Bonferroni correction separately for each parameter (three tests for each parameter) and session. The same procedure was used for the pairwise comparison of bias and slope interaction (three comparisons for each parameter).

Next, we evaluated how DD affected the slope of different subjects. To estimate individual subjects' slopes, we employed a generalized linear mixed-effects model with the logit function as a link function and the binomial distribution for decision distribution. This model was fitted only on Parkinsonian patients, and, to avoid introducing a group effect on slope estimation, the group was not included as a regressor. Finally, we investigated the effect of LEDD and group on both estimated slopes and RA in drugs ON condition, employing a linear regression analysis.

Data availability statement

Data available on request due to privacy/ethical restrictions

Results

We evaluated behavioral differences between ICB- and ICB+ groups of PD patients in an economic risk-based decision-making task before and after the prescribed DD dose intake (see Methods). Results were compared with those of an age-matched HC group, repeating the same task twice.

All groups started without significant bias toward one of the two choices (see Supplementary Material). As the session progressed, we observed a significant increase in LR choices for all groups (slope, HC: CI: [0.01,0.10], p = 0.0055, Figure 1A; ICB-: CI: [0.049, 0.14], p=4e-6, Figure 1B; ICB+: CI: [0.004, 0.095], p=0.028, Figure 1C; t-test, Bonferroni correction; slope-group interaction p>0.05, t-test, Bonferroni correction). No significant difference was found between groups in terms of final strategy (RA, see Methods, Figure 1D, $\chi^2(2) = 3.83$, p = 0.14, Kruskal-Wallis test). However, while both HC and ICB- groups displayed a significant preference for LR options (RA>0.5) at the end of the session, the ICB+ group did not (Figure 1D, HC: RA=0.775 ± 0.15, p=0.002; ICB-: RA=0.775 ± 0.225, p=0.002; ICB+: RA=0.65 ± 0.3, p=0.07, Wilcoxon one-sample test with FDR correction).

In the second session, all groups started with a bias toward LR (RA>0.5) thanks to the experience of the first session (bias; HC: CI: [0.59,0.96], p=0.00087, Figure 1E; ICB-: CI: [0.58, 0.94], p=0.002, Figure 1F; ICB+: CI: [0.65, 1.0], Figure 1G; p=4.45e-5, t-test, Bonferroni correction; interaction test, p>0.1). As expected, HC retained their risk averting strategy (slope CI: [-0.056, 0.069], p=1.0, t-test Bonferroni correction, Figure 1E). Interestingly, the same occurred for ICB- in the DD ON condition (slope, CI: [-0.088,0.037], p=0.96, t-test Bonferroni correction, Figure 1F). ICB+ patients, instead, during the DD ON session gradually reduced the fraction of LR choices, showing a significant negative slope (Figure 1G, slope, p=0.0036, CI: [-0.149, -0.023], t-test Bonferroni correction), significantly lower than the one of HC (interaction, p=0.039, t-test, Bonferroni correction). The final strategy indeed was associated with a RA significantly above 0.5 for HC and ICB- but not for ICB+ (Figure 1H, HC: RA=0.8 ± 0.17, p=0.002; ICB-: RA=0.725 ± 0.15, p=0.0036; ICB+: 0.575 ± 0.2, p=0.27 Wilcoxon one-sample test, FDR correction) and a significant difference between HC and ICB+ (p=0.0016, Cohen's d = 1.570, Dunn test, Bonferroni correction).

Finally, we examined if the behavior of ICB groups during the DD ON session was related to the DD dose, measured with LEDD. A linear regression model showed a significant effect of LEDD on RA on ICB+ but not on ICB- (Figure 1I, interaction LEDD-group: p=0.016; LEDD effect: ICB+: p=0.017; ICB-: p=0.70, t-test, Bonferroni correction). Consistently, we found a significant effect of LEDD on LR choices slope for ICB+ but not for ICB- (Figure 1L, interaction LEDD-group p=0.033; LEDD effect: ICB+: p=0.014; ICB-: p=1.0, t-test, Bonferroni correction).

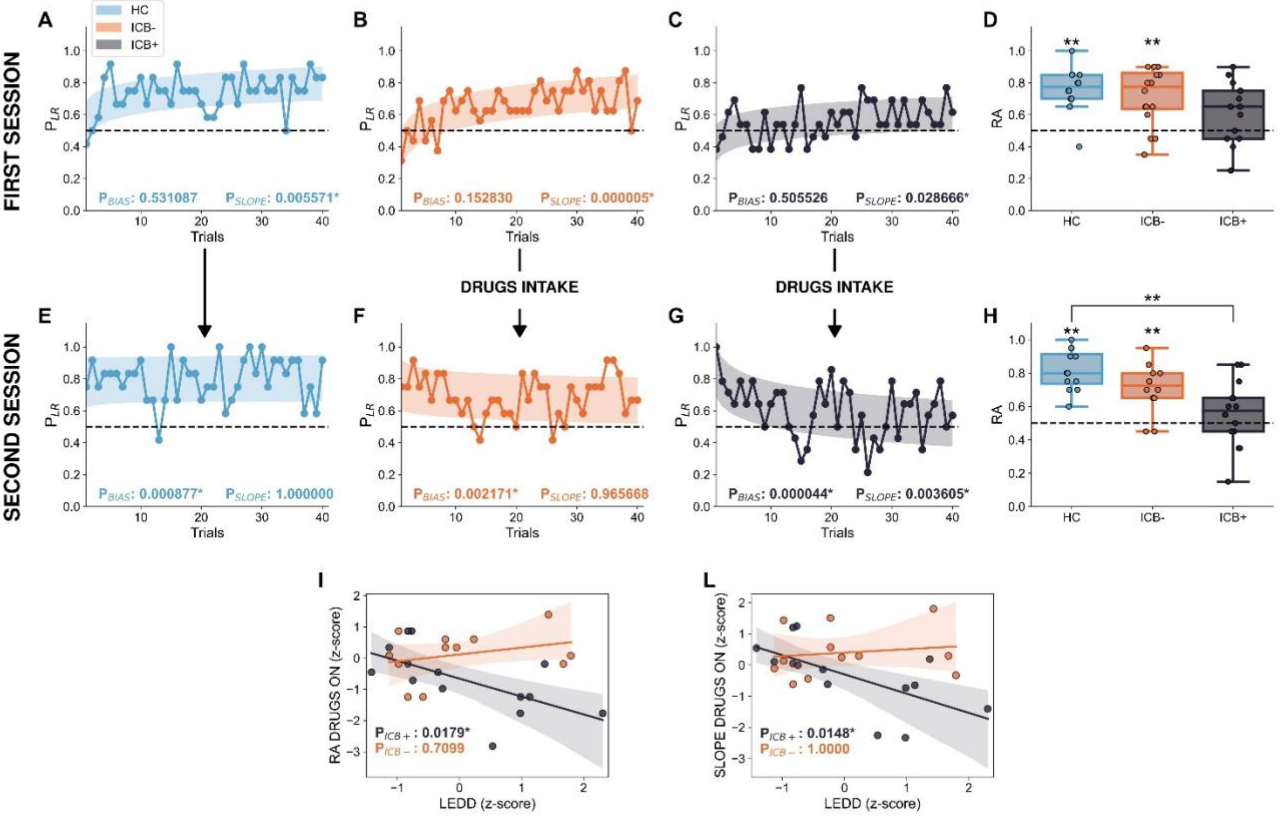

Figure: Behavioral analysis of HC (cyan), ICB- (orange), and ICB+ (black) subjects during two sessions of risk-based decision-making task. **(A)** Probability of choosing the LR option across trials for HC. The shaded area is the prediction's standard deviation of the logarithmic model (see methods). Texts indicate the p-values of bias (vs RA=0.5) and slope. **(B)** and **(C)** same as (A) but for ICB- and ICB+. **(D)** Comparison of RA in the first session among the three groups. Asterisks above the boxplots indicate significance against chance level (Wilcoxon test, FDR correction; *: $p<0.05$, **: $p<0.01$). **(E)**, **(F)**, and **(G)** same as (A), (B), and (C) respectively, but for the second session. **(H)** same as (D) but for the second session. The asterisks on the line above the boxplots show significant differences between the indicated groups (Dunn test, Bonferroni correction, **: $p<0.01$). **(I)** and **(L)** effect of LEDD on RA and slope, respectively, in the second session for ICB- and ICB+. The text shows the p-values of the LEDD effects on RA and slope for both groups.

Discussion

Our results show that after DD assumption, ICB+ patients (but not ICB-) progressively worsen their performance during a risk aversion task proportionally to their LEDD. The result suggests that DD intake has a strong acute effect on ICB+ decision-making processes, to the point of disrupting previously developed efficient economic strategies. During the first DD OFF session of the task, ICB+ patients progressively increased the fraction of LR choices, as ICB- and HC groups did, indicating correct learning of the options' expected values. However, after DD intake, ICB+ patients began the session with a correct bias towards the LR option, but gradually increased the probability of choosing the HR option, ending the task without a significant RA. In contrast, ICB-, similarly to HC, did not alter their strategy and continued choosing the LR option correctly. Notably, for ICB+ patients, the LEDD correlated with the increased tendency for risky HR choices at the individual level: patients with the highest intake displayed a faster decrease in LR choices. Again, this was not the case for ICB- patients, even if they assumed a comparable LEDD.

Dopamine-induced modifications have been observed in various nodes of the decision-making neural circuitry, including the ventral-medial prefrontal and orbitofrontal cortex (19,20)), ventral and dorsal striatum (21)), Internal globus pallidus (22)), and subthalamic nucleus (9,12,22,23)). These alterations are hypothesized to affect outcome evaluation, reducing the weight given to losses (6,10,11,20) and increasing that given to gains (21,24)). Our results are consistent with this mechanism, which might cause the ICB+ individuals to drift towards suboptimal choices with high potential gains but also high risks. However, the DD effect alone does not account for the behavioral data, as ICB- patients have taken comparable doses without noticeable behavioral alterations. Our results support the hypothesis that dopaminergic therapy per se does not cause learning and decision-making impairment but rather seems to act as a trigger when it finds a dopamine-hypersensitive neural substrate. Indeed, recent studies have highlighted how genetic (14,25)), neural (13,15,26), and demographic (1,2) factors may play a specific role in ICB onset.

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Authors’ Roles

	Design study	Execution	Analysis	Writing	Editing
Fabio Taddeini	X	X	X	X	X
Erica Ordali	X	X		X	X
Alessandra Govoni	X	X			X
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Eleonora Russo	X		X		X
Aldo Rustichini	X				X
Chiara Rapallini	X	X		X	X
Silvia Ramat	X	X		X	X
Alberto Mazzoni	X	X	X	X	X

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Supplementary materials

Experimental procedure

Patients were diagnosed with ICB in presence of medical history of one or more of the following behaviors: pathological gambling, compulsive buying, compulsive sexual behavior, and binge or compulsive eating. Data was collected during the morning with two experimental sessions: the first from 9 AM to 11 AM, and the second 11 AM to 13 AM. Comprehensively, we were able to schedule one PD patient, or up to two healthy controls, in each experimental session. A standard experimental session was structured as follows (see Supplementary Figure 1). After obtaining informed consent, experimental tasks were administered to the patient in the hospital outpatient room.

The patient was asked to suspend antiparkinsonian therapy 12 hours before the visit (OFF condition), and the following evaluations were performed: UPDRS (1), MMSE (2) test and experimental task. Subsequently the patient was taking the morning antiparkinsonian therapy, and the same assessments were repeated about 60 minutes after taking the drugs (ON condition). Subjects were then debriefed on the scope and aim of the experimental task. All participants received a small reimbursement for the expenses correlated to the hospital visit. Thie reimbursement was defined as the sum of two randomly extracted trials between two of the six played lotteries (one for the first and second session, respectively). On average, participants received a reimbursement of 8€.

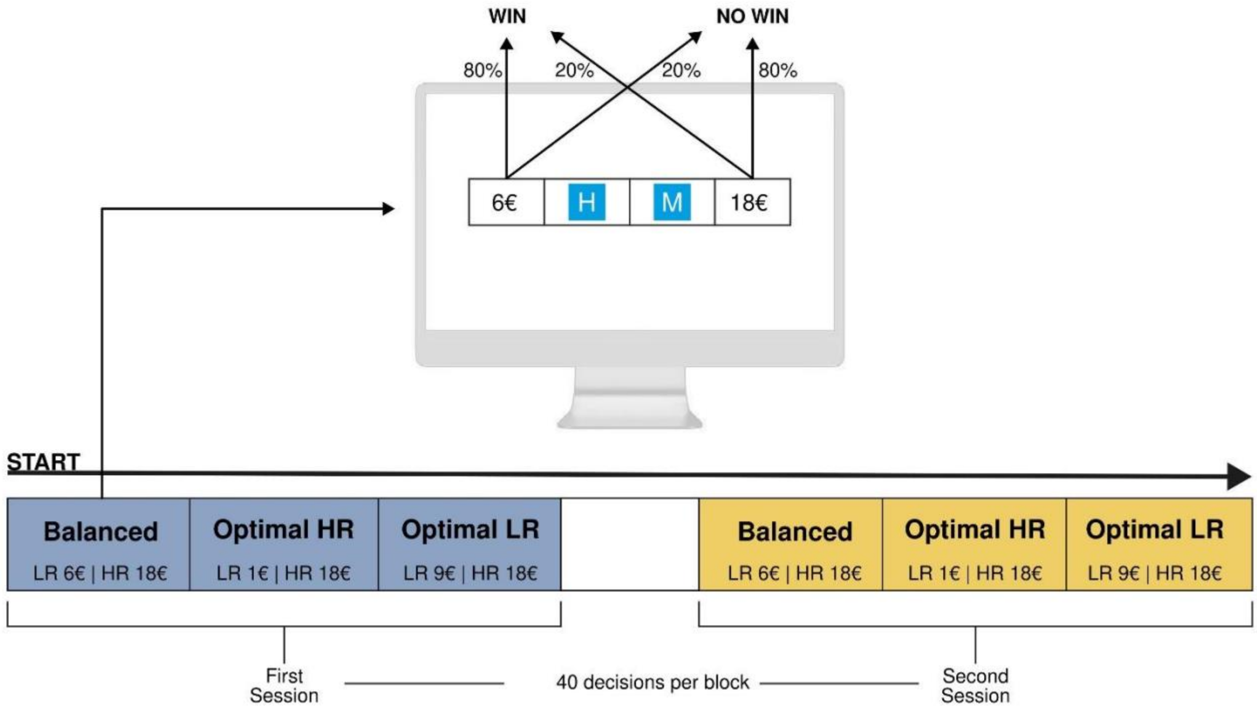
Each session consisted of 3 blocks of 40 decisions each (120 decisions in total) and was programmed using oTree, a framework based on Python language widely used to program economic experiments (3), and the task was performed using the computer in the hospital office.

In the first two screens, participants could read detailed instructions about the task. Specifically, it was explained that two letters, e.g., H and M, will appear on the screen, associated with two monetary rewards (i.e., 6€ and 18€). From the instructions, participants knew that the rewards were associated with different winning probabilities. These probabilities were unknown, and participants had to learn them by themselves, trial by trial. After each decision, participants received feedback. The feedback information was split into two different screens: the first screen informed participants whether they had won, and the amount won, the second screen displayed the amount they could have won if they had chosen the alternative option.

After the first 40-choices block, participants were informed of the amount won in the block. The letters and the amount associated were distinct in each block. Blocks were constructed so that there were different optimal strategies to maximize one's final payoff. In the first block participants could choose between a letter associated with a low reward, 6€, with 80% winning probability (and 20% of having 0€), and a letter associated with a high reward, 18€, with 20% winning probability (and 80% of having 0€). We named this block as 'Balanced' since, even if choosing the low reward option is the optimal strategy, the difference between the expected values of the two options is small (expected value, EV: 6*0.80=4.8 vs. 18*0.2=3.6. On the contrary, the other two blocks have options with very different EVs, leading to different optimal strategies. In the Optimal High Reward (Optimal HR, i.e., 1€ vs. 18€) block, the optimal strategy is to choose the high-reward/low-probability choice. In the Optimal Low Reward (LR, i.e., 9€ vs. 18€) block, the optimal strategy is to choose the low-reward/high-probability option.

Not all patients have completed all blocks (first or second session) due to excessive fatigue. An ICB+ patient in the first session did not complete the blocks in the usual order, so only the data from the second session were considered for him. For some patients, the second session of the experiment was discarded because they performed a different version (different reward) of the task.

Supplementary table 1 shows the exact number of subjects for each block.



Supplementary figure 1: Experimental setup

	HC	ICB-	ICB+
First Session			
Balanced	12	16	13
Optimal HR	12	15	13
Optimal LR	12	14	12
Second Session			
Balanced	12	12	14
Optimal HR	12	12	14
Optimal LR	12	12	12

Supplementary table 1: Number of subjects for each block and session

Statistical analysis

Logarithmic regression

To analyze the learning in the first block of both sessions we computed the ratio of LR choices for each trial within each group, obtaining three curves of 40 points for each session. We then employed a logarithmic regression analysis, using the natural logarithmic of trial number (trials were numbered in ascending order from 1 to 40) and the type of group (HC, ICB-, ICB+) as independent variables, while the ratio of LR choices was the dependent variable. We assessed the initial bias towards one of the choices with the intercepts of the models (a significant bias was present if the intercepts significantly deviated from 0.5) and the slopes of the learning curves with the effects of trials.

$$\mathrm{P_{LR}(trial)} = \mathrm{bias} + \mathrm{group} + \mathrm{slope} * \ln\,(\mathrm{trial}) + \ln(\mathrm{trial})\colon \mathrm{group}$$

Single-subject slope

To estimate the slope parameter for each subject, we employed a generalized mixed effect model, using the logit function as the link function, the binomial distribution as the distribution of decision (1-LR, 0-HR), and subjects as a random effect. For this analysis, the model was fitted only on PD patients (ICB+, ICB-), as we were interested in testing the effect of dopaminergic therapy on learning. Additionally, the group was not included as a regressor to avoid introducing group effect on slope estimation.

$$\begin{cases} \mathrm{P_{LR}(trial)} = \dfrac{e^{z}}{1+e^{z}} \\ z = \mathrm{bias} + \mathrm{slope} * \mathrm{trial} + (\mathrm{trial}|\mathrm{subjects}) \end{cases}$$

Supplemental Results

Decision bias

In the first decision-making session, no group displayed a significant bias toward the HR option (HC CI: [0.44,0.7], p=0.51; ICB-: CI: [0.27,0.55], p=0.15; ICB+ ICB+ bias CI: [0.29,0.55], p=0.48, t-test Bonferroni correction).

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