

## RESEARCH ARTICLE

# Biased numerical cognition impairs economic decision-making in Parkinson's disease

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## Introduction

Parkinson's disease (PD) is characterized by motor impairment, although recently increased attention has been placed on nonmotor signs such as cognitive impairment.<sup>1–4</sup> One example of cognitive impairment known to functionally affect Parkinsonian patients in daily life is impaired decision-making.<sup>4</sup> In healthy individuals, we have recently illustrated the critical role of mechanisms associated with numerical magnitude allocation upon economic choice selection during decision-making (Arshad et al., In-press). Given that neurological dysfunction can impair magnitude perception,<sup>5,6</sup> herewith we ask whether (1) Parkinsonian patients exhibit biases in numerical

## Abstract

**Objective:** Previous findings suggest a context-dependent bihemispheric allocation of numerical magnitude. Accordingly, we predicted that lateralized motor symptoms in Parkinson's disease (PD), which reflect hemispheric asymmetries, would induce systematic lateralized biases in numerical cognition and have a subsequent influence on decision-making. **Methods:** In 20 PD patients and matched healthy controls we assessed numerical cognition using a number-pair bisection and random number generation task. Decision-making was assessed using both the dictator game and a validated questionnaire. **Results:** PD patients with predominant right-sided motor symptoms exhibited pathological biases toward smaller numerical magnitudes and formulated less favorable prosocial choices during a neuroeconomics task (i.e., dictator game). Conversely, patients with left-sided motor symptoms exhibited pathological biases toward larger numerical magnitudes and formulated more generous prosocial choices. Our account of context-dependent hemispheric allocation of numerical magnitude in PD was corroborated by applying our data to a pre-existing computational model and observing significant concordance. Notably, both numerical biasing and impaired decision-making were correlated with motor asymmetry. **Interpretation:** Accordingly, motor asymmetry and functional impairment of cognitive processes in PD can be functionally intertwined. To conclude, our findings demonstrate context-dependent hemispheric allocation and encoding of numerical magnitude in PD and how biases in numerical magnitude allocation in Parkinsonian patients can correspondingly impair economic decision-making.

magnitude allocation and (2) whether these biases can functionally impair decision-making.

Currently, however, the precise neural mechanisms that underpin numerical magnitude allocation remain unclear.<sup>5–10</sup> Previous neuropsychological studies have demonstrated that right hemisphere fronto-parietal lesions that invoke a rightward spatial attentional bias can induce an isomorphic pathological bias toward larger magnitudes.<sup>5</sup> Critically, subsequent research has illustrated that such pathological biases in numerical magnitude allocation are dissociated from any spatial attention bias.<sup>6,8</sup>

In agreement with the latter patient studies, our findings in healthy individuals demonstrate numerical magnitude allocation is subject to dynamic interhemispheric

competition between fronto-parietal networks independently of any spatial attention influences.<sup>10</sup> That is, the right hemisphere preferentially encodes smaller magnitudes, whereas the left hemisphere is responsible for encoding relatively larger magnitudes, and this is continually updated in a contextual manner.<sup>10</sup> Despite our finding, whether neurological dysfunction of the left hemisphere can systematically induce pathological biases in magnitude allocation toward smaller magnitudes remains unknown. This information is partly lacking because studies on numerical allocation have typically been probed in stroke patients, in whom lesions of the left hemisphere can result in dysphasia as well as dyscalculia, interfering with the ability to comprehend and carry out the numerical tasks, respectively.<sup>11</sup> Accordingly, we postulate that if numerical magnitude allocation is encoded in each hemisphere in a context-dependent manner, then PD patients will exhibit abnormal numerical biases relative to the degree of lateralized motor impairment, which reflect underlying hemispheric asymmetries.<sup>12</sup>

Furthermore, in this study we proceed to probe the functional significance of any such biases in numerical magnitude allocation upon decision making by implementing a widely used neuroeconomics task (i.e., the dictator game<sup>13,14</sup>). We predicted that PD patients will exhibit impaired decision-making attributable to biases in numerical magnitude allocation. The theoretical rationale underpinning our assumption was based on the fact that (1) modern economies rely upon a numerical-magnitude-dependent exchange of currency in return for goods and services,<sup>15</sup> and (2) our recent findings in healthy individuals in whom we have demonstrated that subliminally inducing systematic biases in numerical magnitude allocation leads to corresponding changes in economic decision-making (Arshad et al., In-press).

Thus, the aims of this study were twofold. Firstly, to clarify the neural mechanisms that underpin magnitude allocation by recruiting patients with asymmetric idiopathic PD (nondemented) which allowed us to selectively assess the effects of either right or left hemisphere neurological dysfunction while outwitting the confounding variables associated with dysphasia, dyscalculia, and a lateralized spatial attention bias. The secondary aim of our present study was to assess the functional significance, if any, of biases in magnitude allocation upon economic decision-making.

## Materials and Methods

This study was approved by the local ethics research committee. All participants provided written informed consent.

## Patient demographics

A total of 20 right-handed (assessed using the Edinburgh handedness inventory<sup>16</sup>) PD patients were recruited (Table 1) and 20 matched controls (67.1 years; 8F). Ten patients had predominantly right-sided motor symptoms (RPD) (mean age 66.7 years; 4F; mean disease duration onset 8.2 years) and ten predominantly left-sided motor symptoms (LPD) (mean age 67.3 years; 4F; mean onset 7.6 years). Patients were diagnosed based on clinical assessment using the Queen-Square Brain Bank criteria by movement disorder specialists (Consultant Neurologists (P.B) and (N.P)). Levels of cognition, apathy, depression, anxiety, hallucinations and psychosis were obtained from Part 1 of the unified Parkinson's disease rating scale (UPDRS) (Table 1). Patients were blindly classified as either RPD or LPD using section III (motor examination) of the UPDRS. Inclusion criteria required a Hoehn-Yahr scale of either 1 or 2. Scores from section III (motor examination) of the UPDRS were calculated and scored as % asymmetry by subtracting left-sided from right-sided scores divided by the right score X 100 (Positive scores RPD; Negative scores LPD). Critically, we screened 60 patients in total and subsequently selected 20 patients prior to any testing to ensure: (1) a broad range of variance in % asymmetry (N.B. we selected patients who had an asymmetry that fell within a range between 10 and 90%) in the UPDRS and (2) that the two groups were well matched (Table 1) ( $P > 0.05$  *t*-test).

## Medication status

All patients were on levodopa medication and calculation of L-dopa equivalent daily doses (LEDD, mg/day) based on theoretical equivalences.<sup>17</sup> This revealed no differences between the two groups ( $P > 0.05$ ; *t*-test).

## Experimental tasks

### Number pair bisection

Participants performed a number pair bisection task during which two numbers were presented via a radio-speaker situated directly behind them. Participants were required to estimate the midpoint (within 6 sec to avoid calculation) of the two numerical magnitudes across the following 20 trials presented in the following temporal sequence (randomized order) (33-87), (32-89), (37-91), (93-39), (66-41), (68-44), (47-90), (48-92), (52-91), (92-56), (89-57), (87-59), (61-99), (63-97), (67-95), (99-67), (58-124), (131-59), (131-55), and (58-132).<sup>5,10,18</sup> Note, as evident from the trials above, the number presented on the left of the pair varied from being either the larger or

**Table 1.** Patient characteristics summary.

Patient case	Age	Gender	UPDRS asymmetry score %	Hoehn-Yahr scale	Apathy	Depression	Anxiety
1	74	M	10	2	Mild	Nil	Mild
2	74	F	12	2	Nil	Mild	Mild
3	61	M	70	1	Nil	Nil	Nil
4	54	M	58	1	Nil	Moderate	Moderate
5	74	F	46	1	Mild	Nil	Nil
6	75	F	20	1	Nil	Nil	Moderate
7	60	F	14	2	Mild	Nil	Nil
8	71	M	52	1	Nil	Nil	Mild
9	66	M	50	1	Nil	Nil	Mild
10	58	M	48	2	Nil	Nil	Nil
11	59	M	-60	1	Nil	Mild	Nil
12	68	F	-30	2	Mild	Mild	Mild
13	69	F	-75	1	Moderate	Mild	Mild
14	65	F	-64	1	Nil	Mild	Nil
15	66	F	-60	2	Nil	Nil	Moderate
16	59	M	-72	2	Nil	Nil	Moderate
17	71	M	-50	1	Nil	Nil	Mild
18	74	M	-26	1	Nil	Nil	Nil
19	72	F	-90	1	Nil	Mild	Nil
20	70	F	-27	1	Nil	Nil	Nil

Age, sex, UPDRS asymmetry in motor function, Hoehn-Yahr scale, presence of apathy, depression, anxiety. Apathy, depression, and anxiety were all obtained from Part 1 of UPDRS. All patients were ON medication, had no cognitive impairment (assessed by the Mini Mental state examination), and no reported symptoms of either hallucinations or psychosis as assessed by part 1 of UPDRS.

For apathy, depression, and anxiety the scale is scored as follows; 0 = Nil, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

the smaller value, to avoid any effects associated with either spatial or temporal biasing. Bisection errors were calculated by subtracting the arithmetical midpoint from the participant-reported midpoint which we converted into percentage bisection errors by dividing the errors with the number interval size. Positive mean % bisection errors denote an overestimation, whereas negative mean % bisection errors denote underestimation from the actual midpoint.<sup>5,10,18</sup>

### Random number generation

As previous work has demonstrated the critical role of other cognitive processes (i.e., working memory) during the performance of numerical tasks, we employed a separate task to control for this, namely, random number generation. The rationale for selecting this task is that it recruits distinct neural mechanisms to those associated with number-pair bisection but critically is dependent upon numerical cognition and similarly invokes general cognitive functions akin to those during number-pair bisection.<sup>18-20</sup>

Participants were required to generate 20 random numbers between 1 and 9 in a random sequence.<sup>19</sup> The number generations were paced by a series of tones at 2 Hz, which lasted approximately 10 sec. Participants heard a different tone to initiate the number generation.<sup>19</sup> The

data were analyzed with a previously adopted approach to assess the spatial component in random number generation task by calculating the ratio of large digits (6, 7, 8, 9) indicating preferences for larger numerical magnitudes versus small magnitudes.<sup>19</sup>

### Decision-making tasks

1 Dictator game: In this paradigm participants must decide how much, if any, of a monetary endowment to donate to an anonymous individual in a theoretical social situation.<sup>13</sup> We implemented a modified version of the dictator game, based on the design by Morishima and colleagues,<sup>21</sup> so that we relied upon the distribution of the monetary splits verbally rather than visually. Participants were required to state how they would like to readjust the presented monetary split (e.g., you have £7 and the stranger has £3). Possible options included to (1) keep the split the same, (2) donate, or (3) take £X amount; from or to the stranger, respectively. No time limit was imposed. Notably, 20 trials were performed in total, 10 trials were positive and 10 trials were negative. In the positive trials, the participants' split was on the left and the stranger on the right, that is, £9-1. In the negative trials, the strangers' split was represented on the left and the participants on the right, that is, £2-8. Therefore, donating

and taking money meant the spatial movement of money varied dependent on the trial, that is, left-to-right and right-to-left, respectively. This ensured the task was counterbalanced minimizing any effect of any potential spatial biasing. Task performance was assessed by calculating the mean value donated by the participant across all trials. Note, in order to maintain consistency in the tactics employed, the participants were informed that their final pay-off would be based on how much they decided to donate to the stranger (who was a fellow participant in the study) in two trials selected at random. There was no deception.

- 2 Altruism Questionnaire: Altruistic tendencies were also assessed on an ordinal scale using a validated questionnaire which critically did not require a numerical-magnitude-dependent judgement.<sup>22</sup> Ten questions were asked (i.e., Q1. Would you help push a stranger's car in the snow? Q2. Would you give clothes to a charity?). In response to each question, participants were instructed to respond with one of three possible answers: yes (2 points), no (0 points), or possibly (1 point). The mean score out of 20 revealed individual altruism scores.

### Visuo-spatial assessment

We employed the BIT star cancellation and line bisection (18-cm lines) tasks as to assess for any potential biases in spatial attention. In the star cancellation task, 27 stars were presented on either side of the centre of the page among distractors. Performance was assessed by counting the number of missed stars either side of the midline (i.e., laterality ratio). Line bisection error was calculated as the deviation (in mm) from the midpoint. In half of the patient group (randomly selected) these tasks were performed either immediately before the main experiments or after in the other half of the patients. For the star cancellation task, 27 stars were presented on either side of the centre of the page and the performance was assessed by counting the number of missed stars either side of the midline. For the line bisection task, line bisection error was calculated as the deviation (in mm) from the midpoint of an 18-cm horizontal line.

### Results

RPD patients biased their judgments toward smaller magnitudes (mean bisection error  $-ve\ 7.81\% \pm 1.27$ , i.e., less than the actual midpoint), whereas LPD patients biased judgments toward larger magnitudes (mean bisection error  $+ve\ 4.49\% \pm 0.53$ , i.e., greater than the actual midpoint). Controls exhibited a small nonsignificant bias toward smaller magnitudes (mean bisection error  $-ve$

$1.9\% \pm 0.53$ , known as 'pseudoneglect').<sup>23</sup> One-way repeated measures ANOVA revealed a significant difference in numerical magnitude allocation when comparing the three groups ( $f = 12.79$ ;  $P < 0.001$ ; Fig. 1A). Pathological numerical biases were not related to any spatial attention bias as assessed by either the star cancellation ( $R^2 = 0.013$ ) or line bisection task ( $R^2 = 0.027$ ), but were strongly correlated with the degree of asymmetry in the UPDRS ( $R^2 = 0.753$ ; Fig. 1B). Importantly, in the random number generation task, a one-way repeated measures ANOVA revealed no significant difference in number generation when comparing the three groups ( $f = 1.05$ ;  $P > 0.05$ ).

We observed a significant correlation between biases in numerical-magnitude allocation and mean monetary amount donated during the dictator game (Fig. 2; [ $R^2 = 0.769$ ; controls]; PD patients;  $R^2 = 0.825$ ). Critically, a one-way repeated measures ANOVA revealed significant differences in money donated between patients with RPD, LPD, and controls ( $f = 10.89$ ;  $P < 0.001$ ; Fig. 3). Patients with RPD formulated less favorable prosocial choices as they took on average  $\pounds\ 1.85 \pm 0.45$  away from the stranger compared to LPD patients who donated on average  $\pounds\ 2.56 \pm 0.58$  to the stranger. Money donated during the dictator game task was correlated with the degree of lateralized motor symptoms ( $R^2 = 0.679$ ; Fig. 3B).

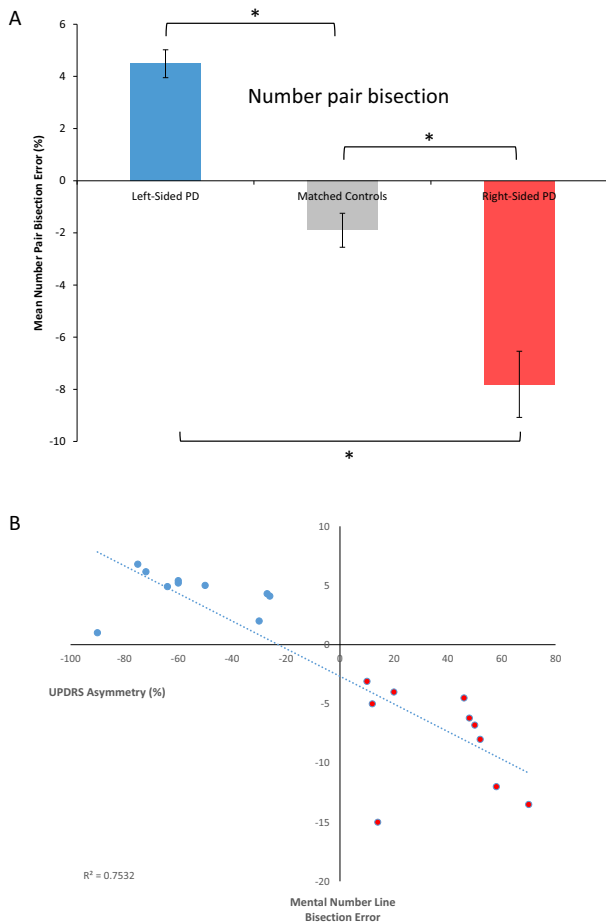
Assessment via the altruism questionnaire revealed: (1) no differences in prosocial tendencies between healthy controls and patients ( $f = 1.28$ ;  $P > 0.05$ ; one-way repeated measures ANOVA) and (2) no relationship between numerical biases and altruistic tendencies ( $R^2 = 0.034$ ; patients;  $R^2 = 0.019$  healthy controls).

Finally, we observed no relationship between the degree of UPDRS asymmetry and (1) line bisection errors in neither RPD ( $R^2 = 0.05$ ) nor LPD ( $R^2 = 0.07$ ) nor (2) the star cancellation laterality ratio in either RPD ( $R^2 = 0.08$ ) or LPD ( $R^2 = 0.04$ ).

Thus, given that there was no relationship between UPDRS asymmetry and spatial attentional biases, it implies that the relationship observed between UPDRS asymmetry and biases in numerical magnitude allocation was most likely attributable to underlying hemispheric asymmetries. Therefore, we proceeded to corroborate this account by applying our patient data to a previously validated computational model of hemispheric allocation of numerical magnitude.<sup>10</sup>

### Experiment (2) Computational model of numerical magnitude allocation

Following on from the findings that left hemisphere neurological damage (i.e., RPD) was associated with



**Figure 1.** (A) Results from the number pair bisection task; On the X axis we represent the different participant groups, either RPD patients (red bar), LPD patients (blue bar), and healthy matched controls (grey bar). On the Y axis we represent the mean% bisection error observed in the number pair bisection task. 0 on the Y axis represents the true midpoint, whereas a positive bisection error denotes an overestimation from the midpoint and a negative bisection error denotes an underestimation from the true midpoint. Healthy controls exhibited a small bias toward smaller numbers (i.e., pseudoneglect). LPD patients overestimated the midpoint toward larger numbers, whereas RPD patients underestimated the midpoint towards smaller magnitudes. \*Represents a  $P < 0.001$ ; the error bars represent the standard error. (B) Relationship between the mean % bisection error and the degree of calculated lateralized asymmetries in motor symptoms as assessed by the UPDRS. On the X axis we represent UPDRS % asymmetry, with positive asymmetries reflecting predominantly RPD and negative asymmetries reflecting LPD. The Y axis represents the mean % bisection error. We observed a significant negative correlation between bisection error and the degree of lateralized motor symptoms. Red dots depict RPD patients, whereas LPD patients are denoted by the blue dots. Patients with greater UPDRS asymmetries to either side manifested larger biases in magnitude allocation.

numerical biasing toward smaller numbers and right hemisphere neurological damage (i.e., LPD) was associated with biasing judgments toward larger numbers, we

sought to fit and corroborate our experimental data in patients to a pre-existing mathematical model of hemispheric allocation of numerical magnitude. This mathematical model has been previously validated in healthy controls and by applying it to the spatial numerical association response code effect (SNARC).<sup>10,24</sup>

As previously described in<sup>10</sup>, we implement  $x$  to denote the magnitude of the error in midpoint bisection and  $p(x)$  to denote the probability of this error. The distribution  $p(x)$  is affected only by hemispheric asymmetry (i.e., neurological dysfunction). Total stimulation of the right hemisphere is denoted by ( $r$ ) and total stimulation of the left hemisphere by ( $l$ ). The probability of making an error  $p(x)$  in the bisection task depends on both  $r$  and  $l$  (i.e.,  $p(x) = p(x;l,r)$ ). We implemented a statistical mechanical model, such that for  $p(x;l,r)$  we can represent it as a Boltzmann weight, whereby  $\beta$  is the parameter specifying the width of the probability distribution and  $E(x;l,r)$  is a function (i.e., energy). The denominator applied in Equation (1) is a normalization factor.

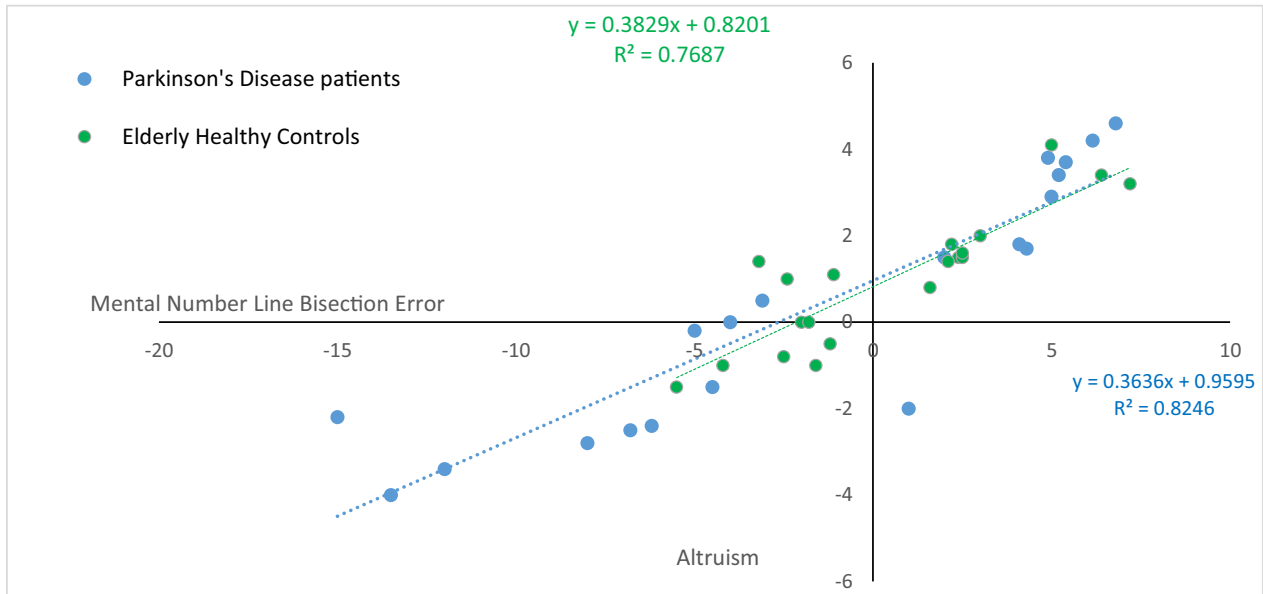
$$p(x;l,r) = \frac{\exp(-E(x;l,r)\beta)}{\int_{-\infty}^{\infty} \exp(-E(x;l,r)\beta) dx}, \quad (1)$$

The choice of the function  $E(x;l,r)$  completes the construction of the model as follows:

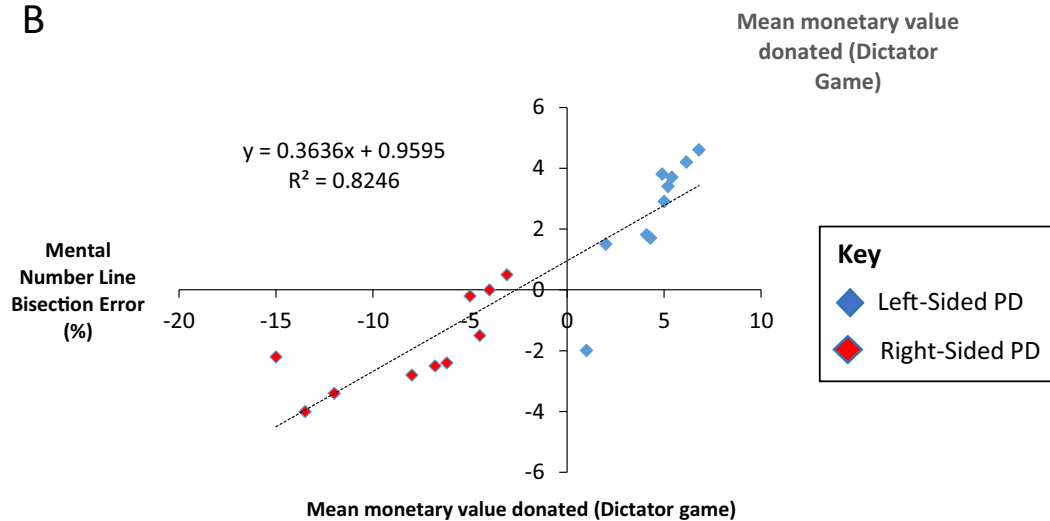
$$E(x;l,r) = (1-lr)x^2 + (-l^2r+lr^2)x + (1+lr)x^4 \quad (2)$$

Both Equations (1) and (2) can completely define the model and allow the calculation of various bisection errors based upon the relative bias (i.e., strength) of either the right or left hemisphere, respectively. Each term in Equation (2) has a physical meaning so that the first term is quadratic in  $x$  and when either ( $l$ ) or ( $r$ ) or both are equal to zero, it simply penalizes any deviations from the optimal value  $x = 0$  as found during hemispheric symmetry (i.e., no neurological dysfunction). In cases of hemispheric asymmetries following unilateral neurological dysfunction, both ( $l$ ) and ( $r$ ) are concurrently nonzero, leading to the bisection error shifts. During hemispheric asymmetry, having  $x = 0$  is no longer the optimum value and the most likely bisection errors are shifted toward either smaller or larger numbers. Due to the second term in equation [2] the shift observed is asymmetric. Hence, in patients with a predominant right hemisphere response (i.e., RPD) results in a bisection error shift toward smaller numbers (negative direction), whereas patients with a predominant left hemisphere (i.e., LPD) shifts the error in the positive direction (i.e., larger numbers). The last term in equation [2] is implemented in order to ensure that very large deviations of  $x$  from zero are unfavorable,

A



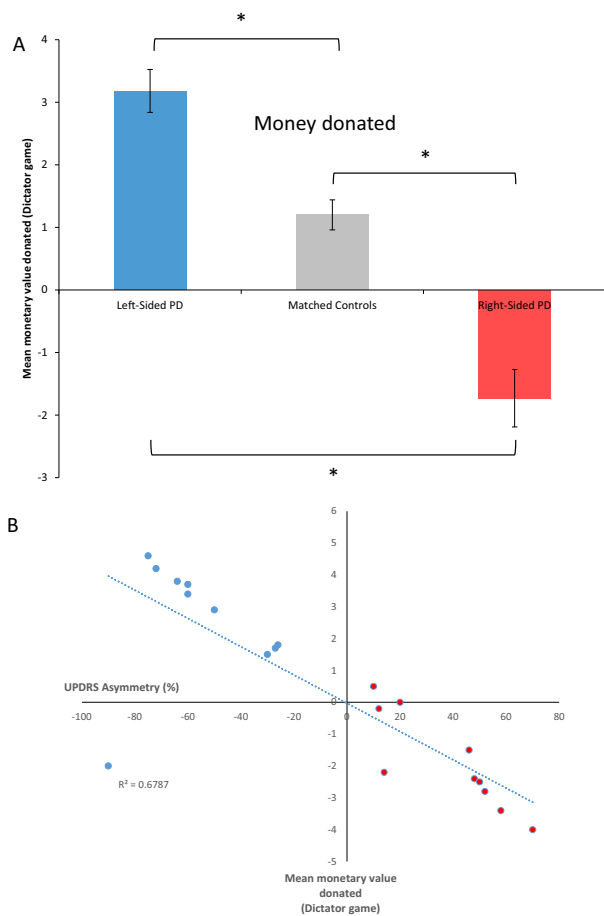
B



**Figure 2.** (A) Relationship between number pair bisection error (X axis; positive error denotes an overestimation; whereas negative error denotes underestimation from the true midpoint) and the mean monetary value donated during the dictator game (Y axis; positive value represents donating money, whereas a negative value implies taking money away from the stranger). The plot shows a significant positive correlation between mean number pair bisection error and the amount of money donated during the dictator game in the two groups tested; matched controls (green dots) and PD patients (blue dots). (B) That is, those participants who were biased toward larger magnitudes donated more money during the dictator game task. RPD patients who are biased toward smaller magnitudes (red dots) made less favorable donations toward the stranger in comparison to LPD patients whom manifest biases towards larger magnitudes (blue dots).

even in the presence of large hemispheric asymmetry (i.e., ceiling effect). Figure 4A and 4B illustrates several calculated probability distributions  $p(x; l, r)$  that can theoretically occur for several different values of  $(l)$  where the following fixed parameters were implemented in the model  $r = 5.0$  and  $\beta = 1$ . As the value of  $(l)$  changes (i.e., closer to 1) the probability of a negative bisection error

increases, as found in RPD patients. In Figure 4B we illustrate the probability distributions  $p(x; l, r)$  that occurs for several different values of  $r$  where the following fixed parameters were implemented in the model  $l = 5.0$  and  $\beta = 1$ . As the value of  $(r)$  changes (i.e., closer to 1) the probability of a positive bisection error increases, as found in LPD. In Figure 4C we illustrate the relationship between



**Figure 3.** (A) Results from the dictator game task; X axis represents the different participant groups, either RPD (red bar), LPD (blue bar), and controls (grey bar). Y axis represents the mean monetary amount donated to the stranger during the dictator game task. Zero on the Y axis represents no donation; positive value reflects a donation; negative value reflects money taken away from the stranger. Healthy controls exhibited a small donation to the stranger. LPD patients gave money away to stranger, whereas RPD patients took money away from the stranger. \*Represents a  $P < 0.001$ ; the error bars represent standard error. (B) Relationship between the mean monetary amounts donated during the dictator game task (Y axis) and the degree of calculated lateralized asymmetries in motor symptoms as assessed by the UPDRS (X axis). The plot illustrates a significant negative correlation between the mean monetary amount donated and the degree of lateralized motor symptoms (N.B. RPD patients red dots, LPD patients blue dots).

an individual's calculated value of hemispheric asymmetry ( $l$ ) derived from the individual's number-pair bisection error and the degree of asymmetry in motor symptoms as assessed by the UPDRS, in RPD patients. As shown, we observed a significant positive correlation ( $R^2 = 0.52$ ). Finally, in Figure 4D we illustrate the relationship between an individual's calculated value of hemispheric asymmetry ( $r$ ) as derived from individual's number-pair bisection

error and the degree of asymmetry in motor symptoms as assessed by the UPDRS, in LPD patients. As shown we observed a significant negative correlation ( $R^2 = 0.54$ ).

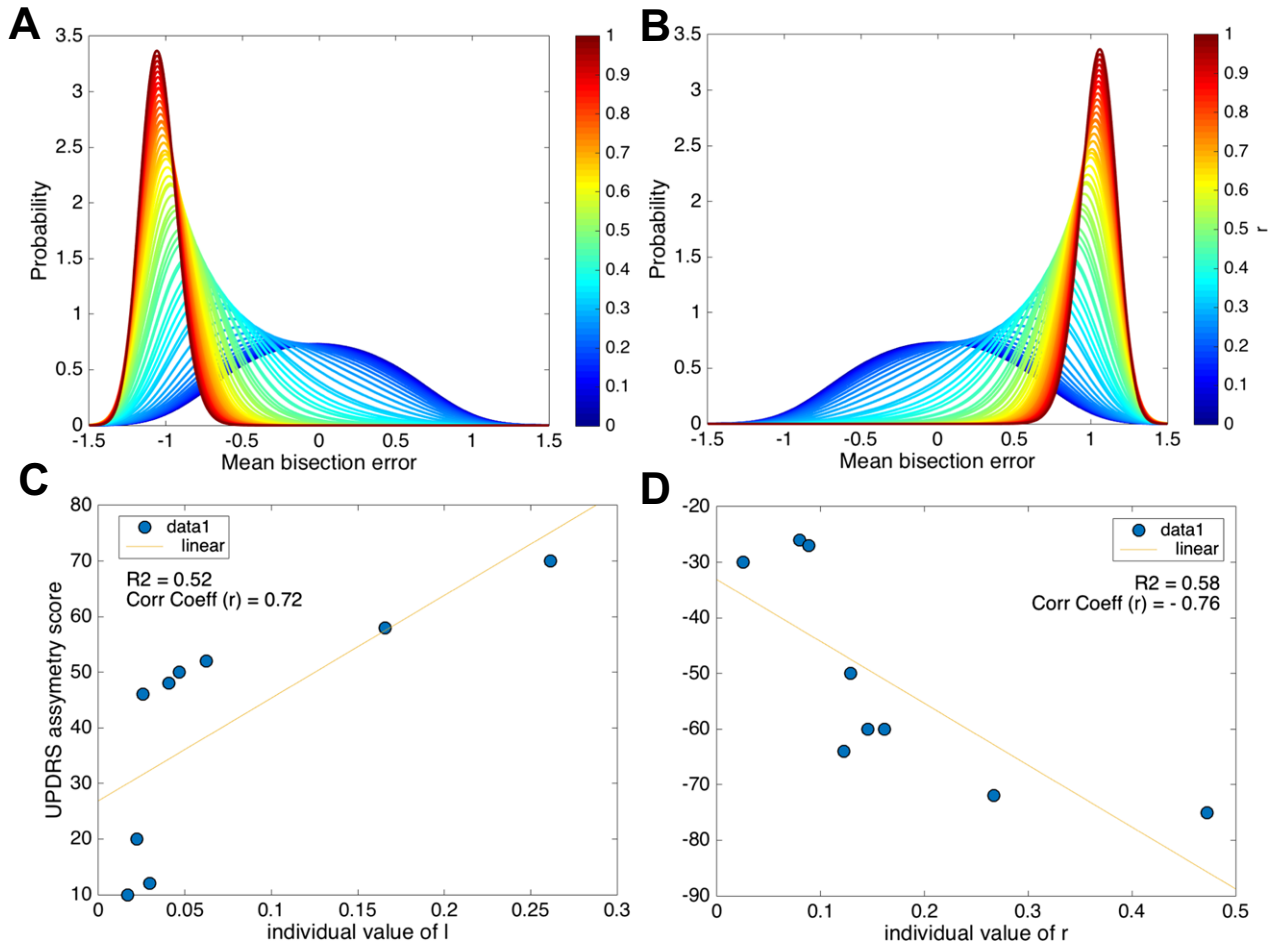
## Discussion

We examined whether hemispheric asymmetries as reflected by lateralized motor symptoms induced biases in numerical magnitude allocation and whether such numerical biasing functionally impacts upon decision-making in PD. We observed that RPD patients biased numerical judgments toward smaller magnitudes, whereas LPD patients were biased toward larger magnitudes. Moreover, these biases led to corresponding changes in choice formulation during neuroeconomic tasks.

Given that it has previously been demonstrated that a spatial motor task (i.e., tapping in a specific hemi-space) can affect numerical processing,<sup>25</sup> then accordingly one possible account for the observed numerical biasing is that in patients the motor symptoms are directing spatial attention toward the side of predominant symptoms and thus shifting patients along the mental number line.<sup>25</sup> That is, in RPD attention would be shifted toward the right-hand side of space<sup>26</sup> (i.e., side of predominant symptoms), which would map onto larger numbers on the metaphorical "mental number line".<sup>5,24</sup> Conversely, in patients with LPD, attention would be shifted leftward<sup>26</sup> and thus theoretically biasing numerical judgments toward smaller numbers.<sup>5,24</sup> However, we observed numerical biasing in a opposite manner to that predicted by the above spatial account.

Our results demonstrate that RPD patients, with predominantly left hemisphere dysfunction, biased judgments toward smaller magnitudes mediated by the right hemisphere.<sup>10</sup> Conversely, LPD patients exhibited a bias toward larger magnitudes, attributable to a left hemisphere predominant response.<sup>5,6,8,10</sup> Furthermore, our findings are in line with previous studies that illustrate dissociation between numerical and spatial mechanisms<sup>6–10</sup> as no relationship was observed between numerical magnitude biases and any lateralized spatial attention bias. Thus, our findings support the generalized notion of hemispheric allocation of numerical magnitude.<sup>8,10</sup>

We speculate that this effect is attributable to either one of two mechanisms, namely, asymmetric (1) cortical atrophy of fronto-striatal, orbitofrontal, dorsolateral frontal areas and middle temporal cortices or (2) cortical disruption to global neurotransmitter systems.<sup>27</sup> Notably, these aforementioned implicated cortical areas are linked to those in the fronto-parietal attentional control network,<sup>26,28,29</sup> findings in line with neuropsychological observations demonstrating that focal lesions to this network can induce pathological biases in magnitude allocation.<sup>5,6</sup>



**Figure 4.** Computational Model: (A and B) Figure illustrates the probability distribution  $p(x; l, r)$  that occurs for several different values of  $l$  (A) or  $r$  (4B) where the following fixed parameters were implemented in the model  $r$  or  $l = 5.0$  and  $\beta = 1$ . A (C and D) relationship between calculated values of  $l$  -RPD (4C) and  $r$  -LPD (4D) and UPDRS asymmetry. Note two patients (one RPD and one LPD) were excluded as they were outliers.

We proceeded to investigate whether such numerical biasing functionally impaired decision-making that required an appreciation of numerical magnitude. Our results demonstrate a pivotal role for numerical-magnitude allocation on the formulation of economic prosocial choices during the dictator game as biases in numerical-magnitude perception were strongly correlated with decisions during the dictator game. Critically, these biases were not predictive of prosocial choices during performance of the non-numerical altruism questionnaire. These findings are in line with our recent results in healthy individuals where we demonstrated that subliminally inducing biases in numerical magnitude toward either higher or lower magnitudes, respectively, led to corresponding changes during the dictator game but not during performance of the questionnaire (Arshad et al., In-press).

One could argue that our presented findings of lateralized motor symptoms (reflecting underlying hemispheric asymmetries) inducing numerical biasing which then subsequently impacts upon decision-making is an oversimplification as we do not consider other generalized cognitive processes. However, we have controlled for any nonspecific cognitive processes affecting numerical task performance by (1) employing the random number generation task<sup>18–20</sup> and not observing any effect and (2) by applying our data to a pre-existing computational model that supports a hemispheric account of numerical processing<sup>10</sup> and observing significant concordance.

Notably, in the patient group, both magnitude biases and economic prosocial choices correlated with the degree of asymmetry in motor symptoms (UPDRS). That is, patients with larger asymmetry in motor symptoms manifested larger pathological biases in magnitude allocation



(toward either smaller or larger magnitudes depending upon the side of the predominant motor symptoms) which was found to have a proportional impact on numerically based decision making in the corresponding direction. Taken together, our results support the notion of context-dependent hemispheric allocation of numerical magnitude in PD and provide a novel demonstration of how this can impact upon economic decision-making in Parkinsonian patients.

To conclude, our findings add to the understanding of cognitive impairment in PD by demonstrating that biases in numerical cognition and their subsequent influence on decision-making are linked to the degree of lateralized motor impairment. Critically, had we grouped our PD patients we would not have observed any biasing, demonstrating the importance of considering individual hemispheric influences upon certain cognitive processes. Moreover, these results raise the important clinical consideration of whether patients with magnitude biases are influenced more heavily by the development of impulse control disorders<sup>30</sup> due to the fact that they erroneously perceive the magnitude/frequency of events in which they partake.

## Author Contributions

Q.A. conceptualized study and designed the experiments; Q.A., A.B., R.L., and A.S.F. performed the experiments; R.L. and A.S.F. performed analysis and statistics and prepared the figure for the manuscript; R.S. Performed the computational model; P.B. and N.P. clinically assessed the patients; Q.A. and A.M.B. wrote the manuscript; P.B. and N.P. edited the manuscript; Q.A., A.M.B., and N.P. supervised the project.

## Conflict of Interest

Authors declare no competing financial interests.

## References

- Mimura M, Oeda R, Kawamura M. Impaired decision-making in parkinson's disease. *Parkinsonism Relat Disord* 2006;12:169–175.
- Pedersen KF, Larsen JP, Tysnes OB, Alves G. Natural course of mild cognitive impairment in parkinson disease: a 5-year population-based study. *Neurology* 2017;88:767–774.
- Brand M, Labudda K, Kalbe E, et al. Decision-making impairments in patients with parkinson's disease. *Behav Neurol* 2004;15(3–4):77–85.
- Pagonabarraga J, García-Sánchez C, Llebaria G, et al. Controlled study of decision-making and cognitive impairment in parkinson's disease. *Mov Disord* 2007;22:1430–1435.
- Zorzi M, Priftis K, Umiltà C. Brain damage: neglect disrupts the mental number line. *Nature* 2002;417:138–139.
- Doricchi F, Guariglia P, Gasparini M, Tomaiuolo F. Dissociation between physical and mental number line bisection in right hemisphere brain damage. *Nat Neurosci* 2005;8:1663–1665.
- Rotondaro F, Merola S, Aiello M, et al. Dissociation between line bisection and mental-number-line bisection in healthy adults. *Neuropsychologia* 2015;75:565–576.
- Aiello M, Jacquin-Courtois S, Merola S, et al. No inherent left and right side in human 'mental number line': evidence from right brain damage. *Brain* 2012;135(Pt 8):2492–2505.
- Fattorini E, Pinto M, Rotondaro F, Doricchi F. Perceiving numbers does not cause automatic shifts of spatial attention. *Cortex* 2015;73:298–316.
- Arshad Q, Nigmatullina Y, Nigmatullin R, et al. Bidirectional modulation of numerical magnitude. *Cereb Cortex* 2016;26:2311–2324.
- Pia L, Corazzini LL, Folegatti A, et al. Mental number line disruption in a right-neglect patient after a left-hemisphere stroke. *Brain Cogn* 2009;69:81–88.
- Stewart KC, Fernandez HH, Okun MS, et al. Side onset influences motor impairments in parkinson disease. *Parkinsonism Relat Disord* 2009;15:781–783.
- Kahneman D, Knetsch JL, Thaler R. Fairness as a constraint on profit seeking: entitlements in the market. *Am Econ Rev* 1986;728–741.
- Ruff CC, Ugazio G, Fehr E. Changing social norm compliance with noninvasive brain stimulation. *Science* 2013;342:482–484.
- McKinnon RI. Money in international exchange: the convertible currency system. Oxford University Press: England, United Kingdom, 1979.
- Oldfield RC. The assessment and analysis of handedness: the edinburgh inventory. *Neuropsychologia* 1971;9:97–113.
- Tomlinson CL, Stowe R, Patel S, et al. Systematic review of levodopa dose equivalency reporting in parkinson's disease. *Mov Disord* 2010;25:2649–2653.
- Arshad Q, Nigmatullina Y, Roberts R, et al. Perceived state of self during motion can differentially modulate numerical magnitude allocation. *Eur J Neurosci* 2016;44:2369–2374.
- Ferrè ER, Vagnoni E, Haggard P. Galvanic vestibular stimulation influences randomness of number generation. *Exp Brain Res* 2013;224:233–241.
- Priftis K, Zorzi M, Meneghello F, et al. Explicit versus implicit processing of representational space in neglect: dissociations in accessing the mental number line. *J Cogn Neurosci* 2006;18:680–688.
- Morishima Y, Schunk D, Bruhin A, et al. Linking brain structure and activation in temporoparietal junction to explain the neurobiology of human altruism. *Neuron* 2012;75:73–79.

22. Rushton JP, Chrisjohn RD, Fekken GC. The altruistic personality and the self-report altruism scale. *Personality Individ Differ* 1981;2:293–302.
23. Loetscher T, Brugger P. Exploring number space by random digit generation. *Exp Brain Res* 2007;180:655–665.
24. Dehaene S, Bossini S, Giraux P. The mental representation of parity and number magnitude. *J Exp Psychol : Gen* 1993;122:371.
25. Cattaneo Z, Fantino M, Silvanto J, et al. Tapping effects on numerical bisection. *Exp Brain Res* 2011;208:21–28.
26. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* 2002;3:201–215.
27. Silbert LC, Kaye J. Neuroimaging and cognition in parkinson's disease dementia. *Brain Pathol* 2010;20:646–653.
28. Corbetta M, Shulman GL. Spatial neglect and attention networks. *Annu Rev Neurosci* 2011;34:569–599.
29. Claassen DO, McDonell KE, Donahue M, et al. Cortical asymmetry in parkinson's disease: early susceptibility of the left hemisphere. *Brain and Behavior* 2016;6:1–10. e00573, doi: 10.1002/brb3.573
30. Sescousse G, Barbalat G, Domenech P, Dreher JC. Imbalance in the sensitivity to different types of rewards in pathological gambling. *Brain* 2013;136(Pt 8): 2527–2538.
31. Arshad Q, Nigmatullina Y, Siddiqui et al. Influence of Biases in Numerical Magnitude allocation on Human Pro-Social Decision-Making; *Journal of Neurophysiology* In-press.