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Reflection impulsivity perceptual decision-making in patients with restless legs syndrome

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Abstract

Objectives: The objective of this study was to investigate perceptual decision-making and reflection impulsivity in drug naïve patients with restless legs syndrome (RLS) and patients with dopaminergic therapy. **Methods**: A total of 35 RLS patients (20 who were drug naïve regarding dopaminergic medication and 15 patients treated with dopaminergic therapy without augmentation or impulse control disorders) were included in this study. We used the Beads task and the Pixel task which assess reflection impulsivity and perceptual decision-making, respectively. Results were compared to 20 healthy controls. **Results**: Both RLS patient groups gathered less evidence than healthy controls in the Beads task before making a decision ($P < 0.001$), but patients with dopaminergic treatment gathered less information than drug naïve patients ($P = 0.026$). Moreover, both patient groups made more choices against the evidence than healthy controls (both $P < 0.01$), but there was no difference between the two patient groups. In the Pixel task, we found an effect of task difficulty on reaction times with patients and controls responding faster with reduced task difficulty. There was neither an effect of group on reaction times nor an effect of group on error rates. **Conclusions**: Reflection impulsivity is common in RLS patients, regardless whether they are drug naïve or treated with dopaminergic therapy. Thus, RLS patients tend to gather less information compared to healthy controls which could have a negative effect on decision-making in daily life and should be investigated further.

Introduction

Dopamine agonists are still frequently used to treat restless legs syndrome (RLS),[1] but these drugs can sometimes cause impulse control disorders (ICDs), such as binge eating, compulsive shopping, gambling disorder, compulsive sexual behavior, or punding.[2] It is unclear why some RLS patients develop these complications while others do not. It has been speculated that a dysfunction of the mesolimbic reward system, which includes the ventral striatum, and a reduction in prefrontal cortex inhibition are triggering behavioral addictions.[3] Furthermore, striatal sensitization with increased ventral striatal dopamine release following intake of levodopa,[4] during gambling,[5] or following reward-related cues[6] has been observed in patients with Parkinson's disease who had ICDs. It is also likely that tonic dopaminergic stimulation, which attenuates prefrontal cortex activation, contributes to the development of ICDs.[3]

It seems, however, that the dopaminergic dose does not correlate with the incidence of ICDs in RLS patients.[2,7] The prevalence rates of these behavioral addictions range between 7% and 20%.[2,7,8] Moreover, it is unknown whether dopamine agonist therapy alone is responsible for impaired decision-making in RLS patients, or whether RLS patients in general are more susceptible to make disadvantageous decisions compared to healthy subjects.

Investigations on cognitive functions in treated and drug naïve RLS patients have provided conflicting results. One small study showed that drug naïve RLS patients

outperformed healthy controls on tests measuring verbal recognition and semantic verbal fluency despite having higher depression scores,[9] while another study revealed no difference between drug naïve RLS patients and controls in a wide area of cognitive functions.[10] Furthermore, results regarding cognitive performance in RLS patients treated with dopaminergic therapy (DT) are also conflicting. While some studies showed cognitive deficits in interference inhibition and verbal fluency,[11,12] others found either no difference between RLS patients and healthy controls on multiple cognitive domains[13] or even a better performance in phonemic and semantic verbal fluency[14] in RLS patients. Moreover, one study reported improved working memory function as well as faster reaction times in drug naïve patients following 12 weeks of dopamine agonist therapy.[15]

Detailed neuropsychological assessments using tasks specifically designed to assess impulsivity have not been performed in drug naïve RLS patients so far. Thus, the aim of this study was to assess cognitive impulsivity, specifically reflection impulsivity and perceptual decision-making, in drug naïve RLS patients and those treated with DT. The Pixel task (assessing perceptual decision-making)[16,17] and the Beads task (assessing reflection impulsivity)[18–21] have been used in a large cohort of patients with and without behavioral addictions. In both tasks, information has to be sampled. In the Beads task, participants need to actively gather information by drawing a further beads, whereas in the Pixel task, reaction times inversely correlate with the amount of information participants sample before making a choice.[22] Thus, longer reaction times in the Pixel task can increase the probability to provide a correct answer.[23]

In this study, we sought to investigate whether these neuropsychological changes are caused by dopaminergic medication or are disease specific. Thus, we recruited drug naïve RLS patients and patients treated with DT and compared results to healthy controls.

Given the available literature, we hypothesized that drug naïve RLS patients would perform similar to healthy controls, while RLS patients treated with DT would perform worse than healthy controls and drug naïve patients.

Methods

The study was approved by the local Ethics Committee of the Medical University of Innsbruck, Austria, and all participants provided written informed consent according to the Declaration of Helsinki.

Twenty RLS patients, who were drug naïve for dopaminergic medication, and 15 RLS patients treated with DT were consecutively recruited from the sleep disorders outpatient clinic and sleep laboratory of the Medical University of Innsbruck, Department of Neurology. Of 15 patients, 13 RLS patients were treated with dopamine agonist monotherapy and two patients had levodopa only. Results were compared to 20 healthy controls (Table 1), who were tested in the same way as the patients. Detailed medical and psychiatric assessments as well as relevant demographic characteristics were obtained from all participants. All patients were seen by RLS specialists at the sleep disorders outpatient clinic and sleep laboratory of the Medical University Innsbruck, Department of Neurology, before they were included in the study. RLS severity was assessed using the International RLS Study Group Rating Scale (IRLS).[24] Moreover, all RLS patients were

Table 1. Demographic and clinical data of RLS patients (drug naïve and with DT) and healthy controls.

	Drug naïve *n* = 20	RLS + DT *n* = 15	HC *n* = 20	*P*-Value
Age (years)[1]	57.2 ± 12.3	58.5 ± 14.8	59.5 ± 9.6	0.87
Female:male[2]	9:11	8:7	12:8	0.65
Education (years)[1]	10.7 ± 2.7	10.9 ± 2.8	12.4 ± 3.0	0.12
Disease Duration (years)[3]	9.2 ± 10.7	13.1 ± 10.5	NA	0.12
IRLS (at time of assessment)[3]	17.3 ± 6.0	18.4 ± 6.6	NA	0.63
LEU Dose (mg)	NA	36.5 ± 28.1	NA	NA
Pramipexole (*n*)	NA	10	NA	NA
Rotigotine (*n*)		2		
Ropinirole (*n*)		1		
L-DOPA (*n*)		2		
MoCA[3]	28.4 ± 0.4	27.5 ± 0.4	NA	0.12

DT, dopaminergic treatment; IRLS, International Restless Legs Syndrome Study Group Rating Scale; LEU, levodopa equivalent unit; mg, Milligramme; MoCA, Montreal cognitive assessment; *n*, number; NA, not applicable.
[1]Kruskal–Wallis test.
[2]Fisher's Exact test.
[3]Mann–Whitney U test.

screened for cognitive deficits. RLS patients who scored less than 26/30 points on the Montreal Cognitive Assessment (MOCA)[25] or patients with RLS symptoms associated with major diseases[26] were excluded from the study. None of the study participants had a major or unstable psychiatric history. Furthermore, none of the participants had augmentation or symptoms of ICDs assessed in a semistructural interview based on the Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease-Rating Scale.[27]

Beads task

The Beads task, a commonly used information sampling task[28], has also been described elsewhere.[18,29] The examiners (B.H., A.D.) tested all participants on a laptop computer in a quiet environment to minimize distractions. Participants were asked to decide from which of two cups (blue or green) colored beads were drawn. One cup contains more green than blue beads and vice versa for the other cup. Initially, participants are presented with only one bead (either green or blue). They then can either draw up to 10 further beads before making a decision or they can immediately (or after each bead) guess from which of the two cups the bead was drawn. For each draw, 0.2 points are withdrawn from a virtual account. For correct guesses, participants are rewarded with 10 points.

Two different color ratios are used. In the easier trials, the ratio is 80:20 (80% blue and 20% green beads in the blue cup, 80% green and 20% blue in the green cup). In the more difficult trials, the ratio is 60:40 (60% blue and 40% green beads in the blue cup, 60% green and 40% blue beads in the green cup). Each ratio (80:20 or 60:40) consists of three trials each and is repeated twice, so that in sum, participants complete six trials per ratio. The best strategy is to gather enough evidence before making a decision, rather than "jumping to conclusions" and immediately choosing a cup. Therefore, we were interested in the number of draws participants made prior to making a choice ("drawing behaviour") and the number of decisions they made against the evidence they had at the time of their choice ("opposite color choice"/irrational decision-making, e.g., more blue beads than green beads drawn, but participants still chose the green cup). To ensure that participants knew how many beads were drawn, the researcher provided a memory aid by placing previously drawn beads next to the participant.

Pixel task

In the Pixel task, which is a perceptual decision-making task, participants need to filter task-relevant information from a noisy background.[23] Again, this task is performed in the same quiet environment on a laptop computer. Participants are shown a circle, which contains either more blue or more red pixels. Subjects then have to guess whether they think that the circle contains more blue or more red dots. Sixty trials are performed: 20 trials containing a high conflict 60:40 distribution of red and blue pixels, 20 trials containing a 70:30 distribution, and a further 20 trials starting with a 60:40 ratio gradually morphing into an easier 80:20 distribution after 2.5 sec (=morphing). The color of each pixel was updated every 100 ms with the proportions (60:40, 70:30, morphing) remaining fixed. Participants are told to press either the red- or blue-labeled key on a laptop computer whenever they think that they know the correct answer. Written feedback (correct/incorrect) in combination with an auditory tone is given immediately. For correct guesses, participants receive 0.25 units; for incorrect choices, no reward is given. For statistical analysis, we used reaction times (RTs) in seconds of both correct and incorrect answers as well as the number of errors.

Statistics

Statistical analyses were performed using SPSS 22.0. Parametric and nonparametric tests were used for statistical analysis depending on the distribution and the scale type of the variables.

Beads task

Drawing behavior and opposite color choice (e.g., more blue beads than green beads drawn -> green cup chosen) were calculated as described previously.[18]

A generalized linear model (Poisson) with a log-linear link function was used. As a dependent variable, we used the number of draws before making a decision and the number of times participants made an irrational decision. Beads ratio (80:20 or 60:40) was modeled as a fixed factor. Group (treated RLS, drug naïve RLS, healthy controls) was modeled as a between factor and subject was a random factor nested under group. All pairwise comparisons were Bonferroni corrected. A $P \leq 0.05$ was considered statistically significant.

Pixel task

A mixed model ANOVA was used. RTs were log transformed and residuals were found to be normally distributed. Condition (60:40, 70:30, morphing) and group (treated RLS, drug naïve RLS, controls) were modeled as fixed factors in a between-subject design. Subject was included as a random factor nested under group. For

group comparisons of error rates, a nonparametric test (Kruskal–Wallis) was used.

Results

Results of demographic and clinical variables of RLS patients with and without DT and healthy controls are shown in Table 1.

Demographic characteristics

There were no differences on any demographic variables between the three groups. For further details, see Table 1.

Drawing behavior in the beads task

Table 2 summarizes the results of the drawing behavior in the beads task.

First, we examined the number of draws each participant made in the different conditions (Fig. 1A). There were significant effects of group (Wald $\chi^2 = 47.4$, $P < 0.001$), beads ratio (Wald $\chi^2 = 31.5$, $P < 0.001$), and a significant beads ratio by group interaction (Wald $\chi^2 = 7.2$, $P = 0.027$).

Pairwise comparisons showed that both groups of RLS patients drew fewer beads than controls (both $P < 0.001$). Furthermore, treated patients gathered less evidence than drug naïve RLS patients ($P = 0.023$).

Next, we analyzed the groups separately depending on the ratio (60:40 vs. 80:20). In the 60:40 ratio, we found a significant group effect (Wald $\chi^2 = 32.01$, $P < 0.001$). Pairwise comparisons showed that both RLS groups drew significantly less beads than controls (both $P < 0.001$), and that drug naïve patients drew more beads than patients with DT, which did not reach significance ($P = 0.08$). In the 80:20 ratio, we also found a significant group difference (Wald $\chi^2 = 9.09$, $P = 0.011$). Pairwise comparisons showed that both RLS groups drew less beads than controls ($P < 0.001$), but there was no significant difference between the two patient groups ($P = 1.0$). Thus, all participants gathered more information in the more difficult 60:40 than 80:20 ratio.

Opposite color choice in the beads task

Furthermore, we assessed the number of irrational choices (Fig. 1B), which are decisions against the evidence participants had at the time they chose a cup. There was a main effect of group (Wald $\chi^2 = 11.3$, $P = 0.003$). Pairwise comparisons revealed that controls chose the opposite cup less frequently than drug naïve ($P = 0.005$) and

Table 2. Reflection impulsivity and perceptual decision-making in patients with RLS (drug naïve and with DT) and healthy controls without RLS symptoms.

	Drug naïve $n = 20$	RLS + DT $n = 15$	HC $n = 20$	P value
Beads task				
Total draws[5]	3.3 ± 6.4	2.7 ± 3.8	5.7 ± 5.2	<0.001[1]
Draws in the 60:40 ratio[5]	4.1 ± 7.0	2.9 ± 3.7	7.5 ± 6.4	<0.001[2]
Draws in the 80:20 ratio[5]	2.6 ± 5.6	2.5 ± 3.9	4.0 ± 2.7	0.011[3]
Opposite color choice[5]	1.9 ± 2.0	1.7 ± 1.6	0.4 ± 0.8	0.003[4]
Pixel task				
RT (sec)[6]	1.8 ± 1.8	1.7 ± 2.1	4.8 ± 1.8	0.7
RT 60:40 condition (sec)[6]	2.3 ± 2.3	1.8 ± 0.3	2.2 ± 0.3	0.52
RT 70:30 condition (sec)[6]	1.4 ± 0.6	1.5 ± 0.9	1.7 ± 1.6	0.82
RT morphing condition (sec)[6]	1.8 ± 1.3	1.7 ± 0.9	1.8 ± 1.3	0.98
Errors[7]	0.07 ± 0.1 (0.02)	0.03 ± 0.03 (0.0)	0.05 ± 0.06 (0.02)	0.25

Reflection impulsivity and perceptual decision-making in patients with RLS (drug naïve and with DT) and healthy controls without RLS symptoms. All values are mean ± SD, except for "errors."

RT, reaction time; STD, standard deviation. All values are mean ± SD, except for "errors."

Post hoc group comparisons were done when a significant main effect for group ($P < 0.05$) was revealed; all P values are corrected for multiple comparisons (Bonferroni):

[1]Drug naïve versus RLS + DT (with dopaminergic treatment), $P = 0.023$; Drug naïve versus HC (healthy controls without RLS symptoms), $P < 0.001$; HC versus RLS + DT, $P < 0.001$.

[2]Drug naïve versus RLS+DT, $P = 0.08$; Drug naïve versus HC, $P < 0.001$; HC versus RLD + DT, $P < 0.001$.

[3]Drug naïve versus RLS+DT $P = 1.0$; Drug naïve versus HC, $P < 0.001$; HC versus RLD + DT, $P < 0.001$.

[4]Drug naïve versus RLS + DT, $P = 1.0$; Drug naïve versus HC; $P = 0.005$; HC versus RLS+DT, $P = 0.033$.

[5]Results of generalized linear model (Poisson) are reported as means ± SD.

[6]Results of mixed model ANOVA are reported as means ± SD.

[7]Kruskal–Wallis test (means ± SD [median]).

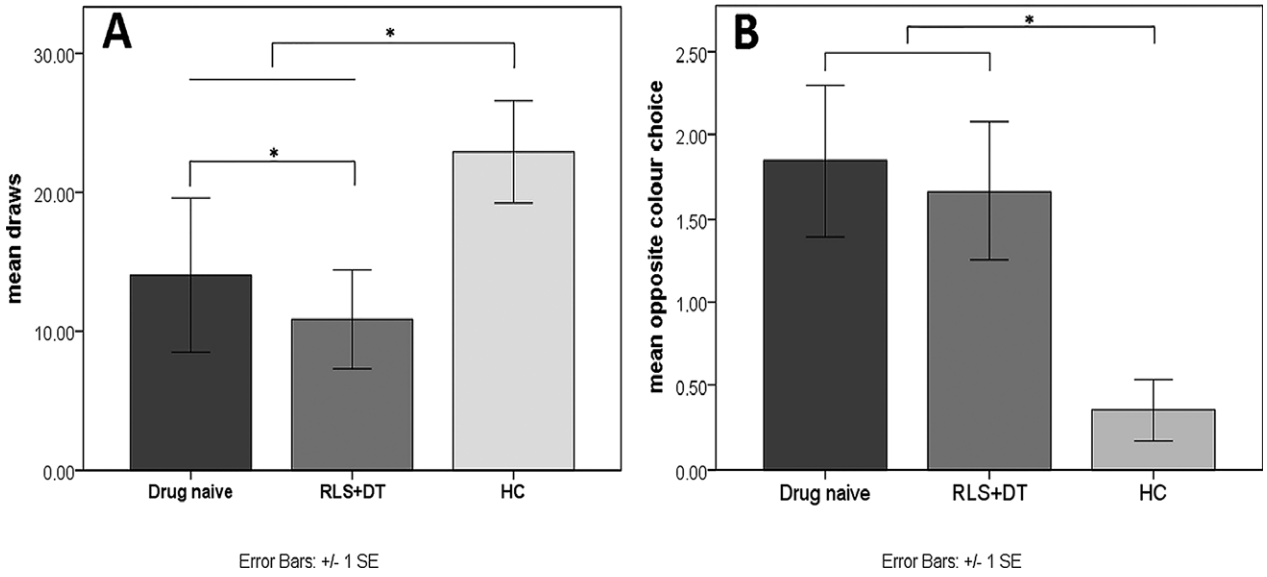

Figure 1. (A) Mean number of draws in drug naïve RLS patients, RLS patients with dopaminergic treatment (RLS + DT) and HC; $*P < 0.05$. (B) Mean number of opposite color choice in drug naïve RLS patients, RLS patients with dopaminergic treatment (RLS+DT), and healthy control (HC); $*P < 0.05$. HC, healthy controls; RLS, restless legs syndrome; DT, dopaminergic therapy.

treated RLS patients ($P = 0.033$). There was no difference between the two patient groups ($P = 1.0$).

Pixel task

We performed a 3×3 mixed ANOVA with group (RLS+DT, drug naïve RLS, healthy controls) as between-subjects factor and condition (condition 1 [60:40], condition 2 [70:30], condition 3 [morphing]) as within-subjects factor. A significant effect of condition ($F_{(2,90)} = 45.2$, $P < 0.001$) was revealed. Participants responded fastest in the easiest 70:30 condition. The effect of group ($F_{(2,45)} = 0.2$, $P = 0.7$) and the interaction between group and condition ($F_{(4,90)} = 1.1$, $P = 0.3$) were not significant.

Finally, we assessed total errors summed across all three conditions but found no significant group difference ($\chi^2 = 2.81$, $P = 0.25$).

Discussion

In this study, we assessed decision-making in RLS patients with and without DT using two distinct information sampling tasks. While in the Beads task, only little information is initially provided and participants have to actively gather more information; in the Pixel task motor, inhibition is necessary to obtain more evidence. In the Beads task, we found that all patients gathered significantly less information than healthy controls and that RLS patients treated with DT drew even fewer beads than drug naïve RLS patients. Furthermore, both RLS groups made more irrational decisions than healthy controls. This suggests that reflection impulsivity and irrational decision-making are enhanced in RLS patients regardless of dopaminergic treatment, but that RLS patients with DT tend to jump to conclusions even more than drug naïve patients. Our findings are in line with studies in RLS patients with augmentation,[29] drug naïve patients with Parkinson's disease (PD) and PD patients treated with DT who also tended to jump to conclusions on the Beads task.[20,21] While in PD, it is possible that, according to the inverted "*U*" shape hypothesis, too little or too much dopamine D2/D3 stimulation causes jumping to conclusion behavior and poor task performance,[30] the reasons for the poor performance in RLS are unclear. Imaging studies regarding definitive dopaminergic deficits in RLS patients have provided mixed results,[31,32] and no consistent anatomical pathology has been found so far. However, given the excellent clinical response to even very low doses of dopaminergic therapy, it is likely that at least some form of dopaminergic dysfunction plays a role in RLS[33] possibly due to dopamine receptor downregulation.[34]. Furthermore, a potential dopaminergic dysfunction in RLS is also supported by imaging studies showing that both tasks used here activate the basal ganglia.[23,35]

We also found that both patient groups made significantly more often decisions against the evidence than controls, but there was no difference between drug naïve and treated RLS patients. Decisions against the evidence on the Beads task have also been reported in patients with substance abuse,[19] drug naïve PD patients,[21] patients with

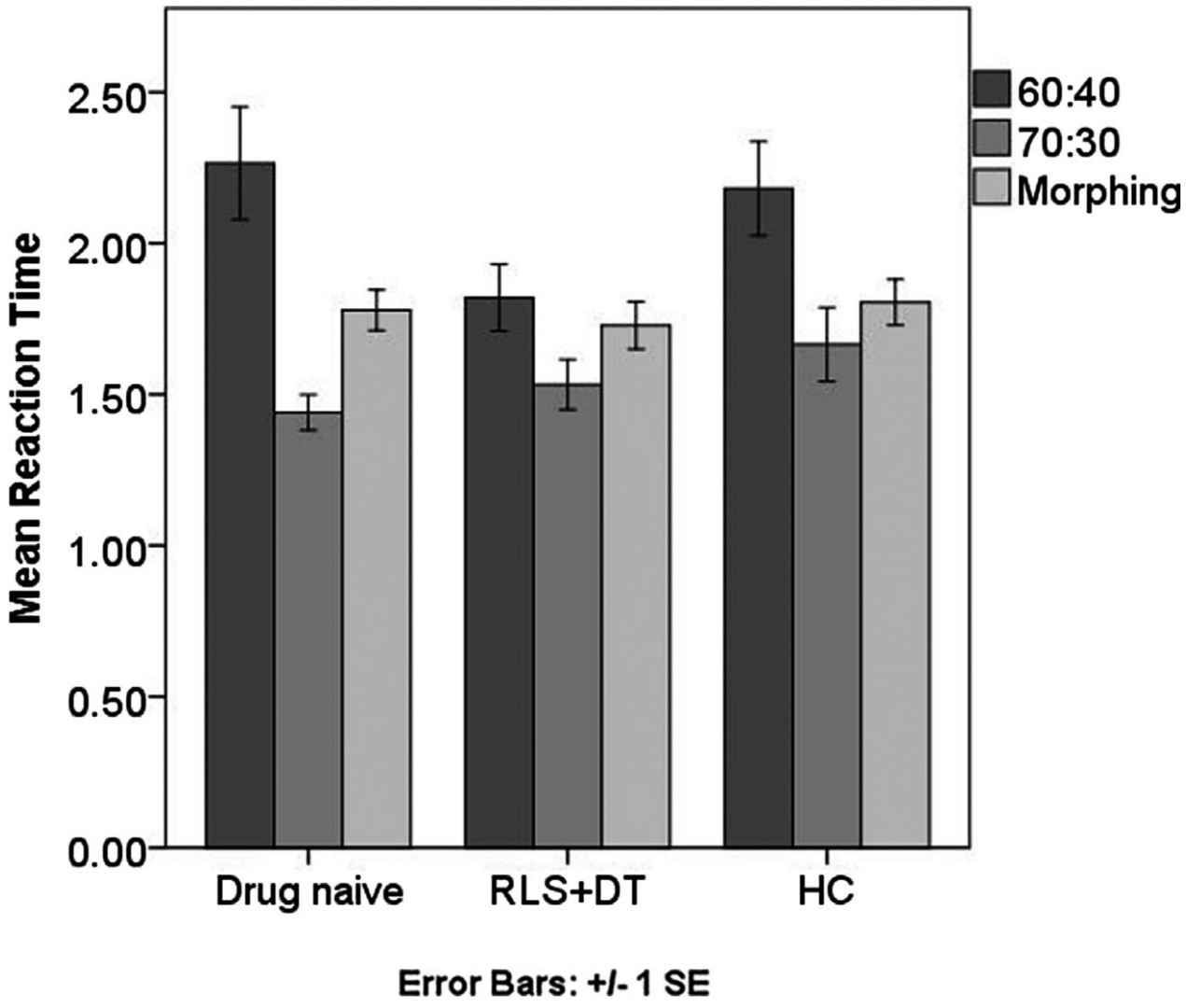

Figure 2. Mean reaction time in seconds regarding the different conditions (60:40, 70:30, morphing) in drug naïve RLS patients, RLS patients with dopaminergic treatment (RLS+DT), and healthy controls. RLS, restless legs syndrome; DT, dopaminergic therapy.

behavioral addictions,[36] and PD patients with and without impulse control disorders.[18]

Results of the Pixel task showed that all participants responded faster with reduced task difficulty, but there was no group difference in RTs or error rates.

Although functional magnetic imaging studies have shown that both tasks used here activate the striatum,[23,35] there are also differences in other brain areas that are activated during task performance. Perceptual decision-making tasks activate frontal areas, the anterior insula,[37] while in the beads task, parietal cortex activation has been found.[35] Neuropsychologically, it is important to highlight significant differences between the Beads task and the Pixel task. The Beads task is visually less explicit (e.g., participants only see one bead at the time) and subjects need to actively gather information, while in the Pixel task, waiting is necessary to gain more evidence. Furthermore, in the Pixel task, information is delivered and updated instantaneously, while in the beads task, more information will only appear on participants' request. Thus, our results suggest that RLS patients have no deficit in filtering task relevant information from a pool of distractors and have no deficit in suppressing fast motor responses, at least on perceptual decision-making tasks.

The small sample size poses some limitations to the generalizability of the present results. We have used stringent criteria in the treated RLS group to exclude patients with augmentation as well as those who have signs of increased impulsivity. This was necessary, as we have previously demonstrated increased reflection impulsivity in RLS patients with augmentation.[29] Nevertheless, our results suggest that reflection impulsivity is common in

RLS patients. This appears to be independent of medication, although patients treated with DT gathered even less information than drug naïve patients and tended to make decisions under higher uncertainty. Furthermore, our results suggest that even untreated RLS patients make disadvantageous choices compared to healthy controls and that dopamine agonist therapy may likely further impair their decision-making as seen in our cohort.

Conflict of Interest

The authors of this work (B.H., M.P., A.S., A.H., L.Z., E.B., B.A., M.D., K.S., B.H., W.P., A.D.) certify that there are neither competing interests nor do the authors have affiliations with any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

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