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Proton Magnetic Resonance Spectroscopy Changes in Parkinson's Disease With and Without Psychosis

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ABSTRACT

Background: Psychosis prevalence in Parkinson's disease is estimated at 8-30%. Proton magnetic resonance spectroscopy measures specific metabolites as markers of cell functioning. **Objective:** To study *N*-acetyl-aspartate and glutamate levels in the caudate and putamen nuclei in subjects with Parkinson's disease with and without psychosis. **Methods:** We included 20 non-demented Parkinson's disease patients with psychosis and 20 Parkinson's disease patients without psychosis matched for age, sex, disease duration, and levodopa equivalent daily dose, all attended at an academic medical center. Proton magnetic resonance spectroscopy scans were performed in a 3T GE whole-body scanner. **Results:** Decreased glutamate levels scaled to creatine were found in the dorsal caudate ($p = 0.005$) and putamen ($p = 0.007$) of the Parkinson's disease psychosis group compared with the without psychosis group. Glutamate plus glutamine levels scaled to creatine and *N*-acetyl-aspartate levels scaled to creatine were also significantly reduced in the dorsal caudate of the Parkinson's disease with psychosis group ($p = 0.018$ and $p = 0.011$, respectively). No group differences were found for any of the other metabolites in the two regions of interest. **Conclusions:** Our findings suggest that decreased metabolite levels in specific brain areas may be implicated in the development of psychosis in Parkinson's disease. (REV INVES CLIN. 2015;67:227-34)

Key words: Parkinson's disease. Psychosis. Magnetic resonance spectroscopy. Glutamate. *N*-acetyl-aspartate.

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INTRODUCTION

With the increasing understanding of neuropsychiatric symptoms in Parkinson's disease (PD), this entity is no longer conceptualized as a pure motor disorder. Among the non-motor symptoms, psychosis stands out due to the important detrimental consequences for patients and their families and caregivers[1]. Psychosis prevalence in PD has been reported to be between 8 and 30%. Risk factors for psychosis include older age, longer duration of disease, disease severity, and dopamine agonist use[2]. Visual hallucinations are considered the most frequent clinical manifestation of Parkinson's disease psychosis (PDP)[3].

Dopamine/acetylcholine disbalance and alterations in serotoninergic neurons have been proposed to have a role in the mechanism of visual hallucinations in PDP[4]. Ten anatomical regions have been implicated in the physiology of the sleep/wake cycle and visual processing. These same regions may be related with the pathophysiology of PDP[5]. The caudate and putamen nuclei are of particular interest since these are regions densely populated by dopaminergic neurons. These neurons are lost with the progression of PD.

Proton magnetic resonance spectroscopy (^{1}H-MRS) measures specific metabolites as markers of cell functioning. *N*-acetyl-aspartate is the most abundant cerebral metabolite, and is thought to be a marker of neuronal functional integrity. Glutamate is the second most abundant cerebral metabolite; decreased levels of glutamate suggest a decrease in excitatory tone in a specific region. Changes in glutamate are activity dependent and may indicate an alteration in the integrity of excitatory neurons[6]. Lower *N*-acetyl-aspartate/choline plus creatine concentration in the lenticular nucleus contralateral to the symptomatic side, and lower glutamate/creatine concentrations in the posterior cingulate cortex in PD subjects have been reported[7,8]. To the best of our knowledge, no ^{1}H-MRS studies specifically on PDP subjects have been reported.

The objective of the present study was to compare *N*-acetyl-aspartate and glutamate levels in the caudate and putamen in subjects with PD with psychosis with those in PD subjects without psychosis.

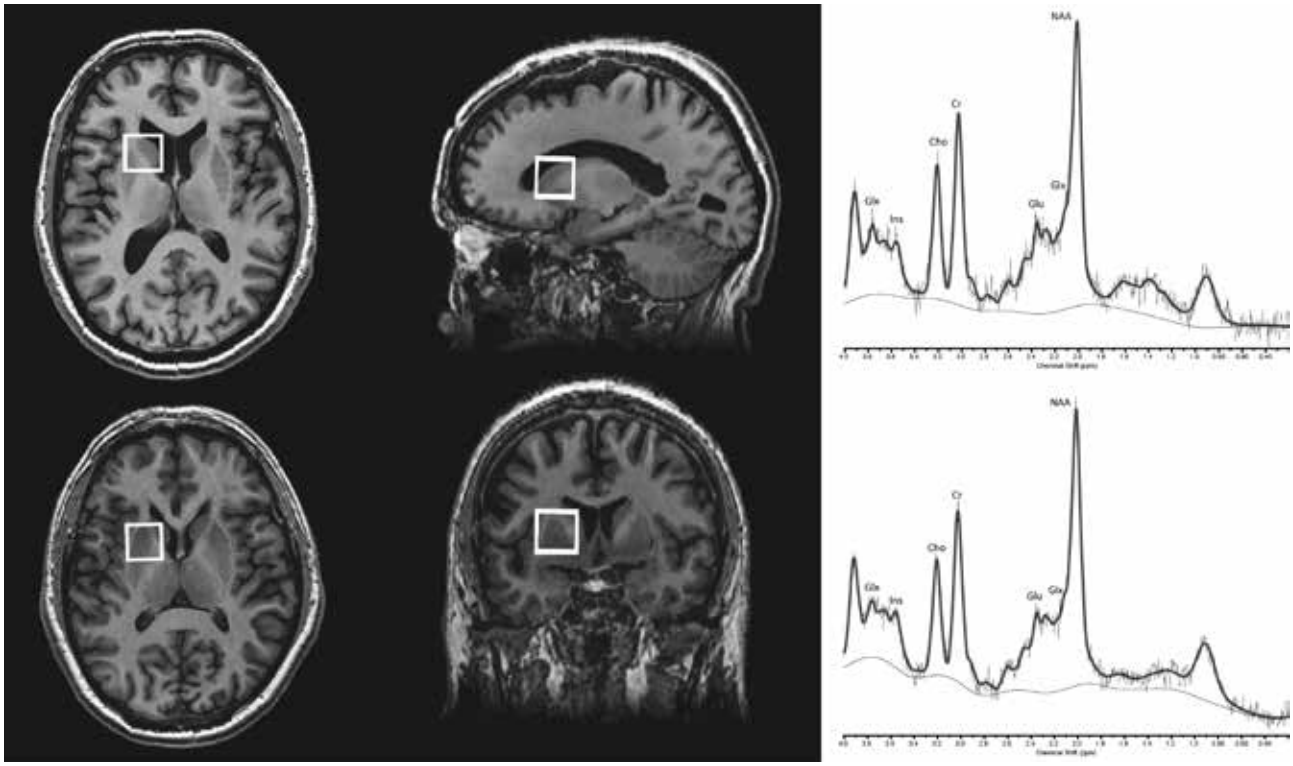
MATERIAL AND METHODS

Participants

Parkinson's disease participants who fulfilled the United Kingdom Brain Bank Criteria[9] were screened for psychosis at the Movement Disorders Outpatient Clinic of the National Institute of Neurology and Neurosurgery (INNN) of Mexico. The presence of psychotic symptoms was determined using a structured interview based on current accepted criteria[10]. Inclusion criteria were age > 40 years and current treatment with dopaminergic replacement therapy. A Mini-Mental State Examination cutoff score of < 26 and a Beck Depression Inventory cutoff score of > 16 were used as exclusion criteria. Subjects who were on antipsychotic treatment or who had undergone recent (< 8 weeks) modifications on their anti-parkinsonian drug scheme were also excluded. The diagnosis of PDP was confirmed using the criteria proposed by the U.S. National Institute of Neurological Disorders and Stroke (NINDS)[10]. These criteria are inclusive and take into account a full range of symptoms, chronology of onset, duration of symptoms, as well as differential diagnoses and associated features. These criteria include the presence of hallucinations (visual and non-visual) and delusions, and minor symptoms such as sense of presence, visual illusions, and passage hallucinations.

Demographic and clinical data were collected, including age, age of onset, severity of Parkinson's disease in terms of Hoehn and Yahr stage (1, being unilateral involvement with minimal functional disability, to 5, being confinement to bed), current anti-parkinsonian treatment and total daily dose. Levodopa-equivalent daily dose (LEDD) was calculated by multiplying the total daily dosage of each anti-parkinsonian drug by its potency relative to a standard levodopa preparation assigned the value of 1, as described elsewhere[11]. In addition, age-, sex-, disease duration-, and LEDD-matched PD subjects without psychosis were included for imaging study comparison. Control subjects did not have a family history of primary psychotic illnesses. All participants provided written informed consent according to the determination of the local Institutional Review Board and Ethics committee. All participants underwent a motor evaluation using the Unified Parkinson's Disease Rating Scale part III (UPDRS III)[12]. The Positive and Negative Syndrome Scale (PANSS) was applied only to PDP subjects[13].

Figure 1. Voxel placement in two regions of interest: the dorsal caudate and the putamen. Representative spectra with the raw and fitted data are shown for each region.
Glu: glutamate; Glx: glutamate + glutamine; NAA: *N*-acetyl-aspartate + *N*-acetylaspartylglutamate acid; Cho: glycerophosphocholine + phosphocholine; Ins: *myo*-Inositol; Cr: creatine + phosphocreatine.



Magnetic resonance studies

Proton magnetic resonance spectroscopy scans were performed in a 3T GE whole-body scanner (Signa Excite HDxt; GE Healthcare, Milwaukee, WI) with a high-resolution 8-channel head coil at the Neuroimaging Department of the INNN. The participant's head was positioned along the cantho-meatal line and immobilized by means of a forehead strap. The participants were initially scanned with a T_1-weighted spoiled gradient echo, 3D axial acquisition (SPGR, TE = 5.7 ms, TR = 13.4 ms, TI = 450 ms, flip angle = 20°, FOV = 25.6 cm, 256 × 256 matrix, slice thickness = 1 mm), oriented above and parallel to the anterior-posterior commissures line (AC-PC). These T_1-weighted SPGR images were reformatted to sagittal and coronal views and were used for optimal ^{1}H-MRS voxel placement. The ^{1}H-MRS spectra were obtained using point-resolved spectroscopy (PRESS, TE = 35 ms, TR = 1,500 ms, spectral width = 5,000 Hz, 4,096 data points used, 128 water-suppressed, and 16 water-unsuppressed averages) in volume elements (voxels) of 8 ml (2 × 2 × 2 cm), centered on the dorsal caudate nucleus and putamen. Voxels were placed contralateral to the affected side of each participant. The lower ends of the dorsal caudate and putamen voxels were located 3 mm dorsal to the AC to include the maximum amount of gray matter (Fig. 1).

Proton magnetic resonance spectroscopy data analysis

Water suppressed spectra were analyzed using LCModel, version 6.2-1T[14], a fully automated, commercially available curve-fitting software that uses a least squares analysis method for estimating metabolite concentrations. A standard basic set of metabolites was used for analysis: L-alanine, aspartate, creatine, phosphocreatine, γ-aminobutyric acid, glucose, glutamate, glutamine, glycerophosphocholine, phosphocholine, glutathione, L-lactate, myo-inositol, *N*-acetyl-aspartate, *N*-acetylaspartylglutamate acid, scyllo-Inositol, taurine, creatine

Table 1. Demographic and clinical characteristics of Parkinson's disease patients with and without psychosis

	PDP	PD without psychosis	p
(n)	20	20	
Male/Female	9/11	10/10	> 0.99
Age (years)	69.9 ± 7.5	66.7 ± 7.4	0.18
Non-smokers	17 (85%)	16 (80%)	> 0.99
Age at motor onset (years)	62.1 ± 10.3	59.3 ± 9.5	0.36
Disease duration (years)	8.0 ± 4.6	7.6 ± 5.5	0.80
Tremor dominant (%)	14 (70%)	16 (80%)	0.72
Right asymmetry (%)	13 (65%)	15 (75%)	0.73
Hoehn & Yahr stage	2.7 ± 0.6	2.5 ± 0.6	0.14
On dopaminergic agonist (%)	11 (55%)	14 (70%)	0.51
Pramipexole daily dose (mg)	1.5 ± 0.9	3.1 ± 1	0.001
On L-Dopa (%)	19 (95%)	18 (90%)	> 0.99
L-Dopa dose (mg/day)	686.1 ± 341.7	580.3 ± 218.4	0.27
LEDD	694.3 ± 420.8	734.4 ± 259.4	0.66
UPDRS III score	28.6 ± 10.5	33 ± 24.8	0.47
PANSS positive symptoms	16.8 ± 5.4	NA	
PANSS negative symptoms	18.6 ± 7.4	NA	
PANSS general symptoms	37.3 ± 10.5	NA	

PDP: Parkinson's disease with psychosis; PD: Parkinson's disease; LEDD: levodopa equivalent daily dose; UPDRS: Unified Parkinson's Disease Rating Scale; PANSS: Positive and Negative Syndromes Scale.

methylene group, guanidinoacetate, lipids (Lip) (Lip13a, Lip13b, Lip09), and macromolecules (MM) (MM09, Lip20, MM20, MM12, MM14 and MM17). This basic set, which was included in the LCModel, was acquired with the same sequence parameters used in our study.

Water-scaled metabolites were normalized with respect to creatine-containing compounds (creatine and phosphocreatine). All metabolites with a Cramér-Rao lower-bound (CRLB) of > 20%, as reported by LCModel, were considered of poor quality and were excluded from further analyses. The reported metabolites included glutamate (Glu), glutamate plus glutamine (Glx), creatine plus phosphocreatine (Cr), glycerophosphocholine plus phosphocholine (Cho), myo-inositol (Ins) and *N*-acetyl-aspartate plus *N*-acetylaspartylglutamate acid (NAA). Spectroscopic values are expressed in "institutional units".

Statistical analysis

The results are presented in terms of mean, standard deviation, and percentages. Statistical analyses were performed using SPSS v16.0 software (SPSS, Chicago, IL). Group differences were assessed using dependent *t*-test for paired samples for quantitative variables. Qualitative variables were compared using a McNemar test. Metabolite concentrations were tested for normal distribution using a Schapiro-Wilk test. Metabolite measures between groups were compared using a paired *t*-test due to the matched-pair design. Spearman's correlations (non-parametric) rather than Pearson coefficients were used due to the relatively small sample size. Significance level was set at $p < 0.05$.

RESULTS

Demographic and clinical characteristics

A total of 236 subjects with PD were screened for the presence of psychosis; 33 of them fulfilled the criteria for PDP, of whom 13 were excluded since they were receiving antipsychotic treatment. The final sample consisted of 20 PD subjects with psychosis. According to the PANSS scores, all of the subjects with PDP had hallucinations (80% were visual hallucinations) and 50% had delusions. We recruited 20 controls without psychosis from the initial sample using the same exclusion criteria, matched for age, sex, disease duration, and LEDD. Clinical and demographic characteristics from both groups are shown in table 1. No statistically significant difference in the mean Hoehn and Yahr stage was found between groups. Nine subjects

Table 2. Means (± standard deviation) for each metabolite in the two regions of interest in Parkinson's disease with psychosis and Parkinson's disease participants

Region	Group	Metabolites						Spectra quality	
		Glu/Cr	Glx/Cr	NAA/Cr	Ins/Cr	Cho/Cr	Cr	FWHM, ppm	SNR
Dorsal caudate	PD-Psychosis	1.36 ± 0.12* †n = 1	1.49 ± 0.16* †n = 1	1.19 ± 0.12* †n = 1	0.73 ± 0.09 †n = 1	0.28 ± 0.02 †n = 1	15.53 ± 3.16 †n = 1	0.088 ± 0.013	11.80 ± 3.38
	PD	1.52 ± 0.20 †n = 1	1.68 ± 0.29 †n = 1	1.28 ± 0.09 †n = 1	0.73 ± 0.14 †n = 1	0.29 ± 0.05 †n = 1	13.79 ± 3.19 †n = 1	0.091 ± 0.016	12.94 ± 3.15
Putamen	PD-Psychosis	1.37 ± 0.20*	1.61 ± 0.19	1.36 ± 0.15	0.60 ± 0.07	0.28 ± 0.2	16.79 ± 3.75	0.078 ± 0.017	14.75 ± 3.49
	PD	1.52 ± 0.12	1.59 ± 0.15	1.37 ± 0.16	0.64 ± 0.10	0.27 ± 0.03	16.81 ± 4.92	0.111 ± 0.111	13.92 ± 4.58

Glu: glutamate; Glx: glutamate + glutamine; NAA: *N*-acetyl aspartate + *N*-acetyl aspartyl glutamic acid; Ins: myo-Inositol; Cho: glycerophosphocholine + phosphocholine; Cr: creatine + phosphocreatine; FWHM: full width at half maximum; SNR: signal to noise ratio; PD: Parkinson's disease.
*$p < 0.05$.
†Number of spectra rejected due to a Cramer-Rao lower-bound > 20%.

in the PDP group and five subjects in the PD group were taking anticholinergics. Two subjects in the PDP group and two subjects in the PD group were treated with monoamine oxidase B inhibitors. Subjects in the PD without psychosis group received a larger dose of pramipexole compared with PDP subjects.

Cerebral metabolites

The ^{1}H-MRS data from one PDP subject and one PD subject, both from the dorsal caudate, were excluded due to poor quality. There was a significant difference in Glu/Cr levels in the dorsal caudate ($p = 0.005$) and putamen ($p = 0.007$), with a markedly decreased concentration in the PDP group. The Glx/Cr was also significantly reduced in the dorsal caudate in the PDP group ($p = 0.018$). The NAA/Cr levels were significantly different only in the dorsal caudate, with lower levels in the PDP group ($p = 0.011$). No group differences in the levels of the other metabolites (Cho/Cr, Ins/Cr, Cr) were found in any voxel (Table 2). No correlation was found between PANSS total score and measured metabolites.

DISCUSSION

Psychosis in Parkinson's disease comprises a wide array of symptoms including hallucinations, delusions, and minor symptoms such as illusions and false sense of presence[10]. Of these symptoms, visual hallucinations are the most frequent in the context of PD[3].

Simple visual hallucinations include flashes, lines, abstracts, shapes, swirls, and repeating patterns, while complex hallucinations are coherent objects, people, animals, and landscapes. Synucleinopathies like PD are hallmarked by the presence of complex visual hallucinations rather than simple hallucinations[15].

Regarding the physiopathology of psychosis in PD, most of the current knowledge is based on visual hallucinations as a complex symptom. Voxel-based morphometry has demonstrated lower gray matter volume in primary visual cortex, visual association cortex, limbic regions, cholinergic structures such as pedunculopontine nucleus and sustantia innominate in non-demented patients with PD[16]. In addition, two main visual processing pathways appear to be affected in PD: the ventral stream, which processes orientations to objects, and the dorsal stream, involved in spatial location. The latter has been involved in the development of minor hallucinations in PD[17].

The functional connections between basal ganglia and frontal areas may also play a role in the development of hallucinations in PD. A recent SPECT study reported a significant reduction in the caudate uptake in patients with PD and visual hallucinations[18]. The striatum has been proposed to be involved in the pathophysiology

of hallucinations; increased caudate activation has been shown during visual stimulation in PD patients with hallucinations compared to PD patients without hallucinations[19]. The striatum is subdivided into three anatomo-functional areas: the sensorimotor area, the associative area, and the limbic area[20]. The projection of these areas to the cerebral cortex enables the regulation of normal adaptive behavior. In this manner, the basal ganglia are involved in switching behavior according to internal or external sensory stimuli[21].

To our knowledge, this is the first study using ^{1}H-MRS to describe metabolite changes in subjects with psychosis. ^{1}H-MRS evaluates neurochemical changes in specific areas of interest. Most of the acute and chronic neurologic disorders are associated with an imbalance between excitatory and inhibitory neurotransmission. As such, the detection of Glu and NAA changes by ^{1}H-MRS may improve our understanding of these diseases.

In addition to its role as the main excitatory neurotransmitter, Glu mediates synapse formation, dendrite pruning, cell migration, differentiation, and death. Furthermore, Glu acts as a precursor for g-aminobutyric acid in neurons and glutamine in astrocytes[22].

Here, we describe a ^{1}H-MRS study in PD subjects with psychosis and this is, to the best of our knowledge, the first report of metabolite concentrations in putamen and dorsal caudate in PDP subjects. In the present study, 13.9% of the total PD population presented with psychosis, which is similar to what has been reported in other countries[23]. Risk factors for psychosis in PD include older age and disease stage[2]. For our study, groups were paired by age group and disease duration, and no statistical difference was found in disease severity as assessed by the Hoehn and Yahr scale between groups. Despite similar disease duration in both groups, PDP subjects were in a more advanced disease stage than PD subjects without psychosis.

Reports regarding treatment with dopaminergic agonists as a risk factor for the development of psychosis in PD patients are varied[24,25]. Also, there are studies reporting hallucinations in drug-naive PD subjects[26]. In addition, the dosage of dopaminergic agonists does not appear to be correlated with the risk of hallucinations[27]. Interestingly, in our study, PD subjects without psychosis received a higher dose of pramipexole than PDP subjects, which opposes the hypothesis of dopamine agonist as a risk factor for psychosis.

The findings of the present study indicate that the Glu/Cr in the dorsal caudate and putamen and Glx/Cr in the dorsal caudate are significantly reduced in PDP subjects compared with PD patients without psychosis. Previous studies have failed to show abnormalities in Glx/Cr in the striatum, cortex, and lentiform nucleus in PD patients[28-30]. However, these studies were performed in 1.5T scanners and measured Glu as a component of the Glx peak. On the other hand, Griffith, et al., using 3T ^{1}H-MRS, reported decreased Glu/Cr in the posterior cingulate gyrus of subjects with idiopathic PD[8].

Given that Glu detected by magnetic resonance is thought to represent the intracellular compartment[31], our findings of reduced Glu in PDP patients suggests that Glu-containing neurons are reduced in number in the dorsal caudate. The degeneration of the dopaminergic nigrostriatal pathway results in profound changes within this loop. Specifically, decreased glutamatergic function has been postulated to be a significant factor in the physiopathology of psychosis. An important contribution to this hypothesis is the observation that compounds such as ketamine or phencyclidine, *N*-methyl-D-aspartate receptor antagonists, can produce psychotic symptoms. The interaction between glutamate and dopamine is widely documented[32-34], so an increase of dopaminergic activity and/or a reduction of Glu activity may contribute to the development of hallucinations.

The glutamatergic corticostriatal innervation of medium-sized spiny neurons is considered the main synapse of the striatum[35]. Findings from human studies indicate that changes in the Glu neurotransmitter system are complex. Autoradiography of *N*-methyl-D-aspartate Glu receptors performed on neuropathologic specimens from subjects with PD have shown reduced binding of Glu receptors in basal ganglia[36].

The NAA can be found exclusively in neurons, and reductions in NAA have been proven to occur after exposure to neurotoxic lesions. Therefore, NAA has been proposed as a marker of neuronal integrity[37,38]. Previous studies comparing ^{1}H-MRS findings in basal ganglia, motor cortex, temporoparietal cortex, and cingulate cortex between subjects with PD and healthy

subjects have shown inconclusive results regarding differences in the NAA/Cr ratio[7,39,40]. A decrease in striatal NAA/Cho has been reported in elderly patients with PD when compared to healthy subjects[41]. A recent study found significant differences in NAA/Cr, NAA/Cho, NAA/(Cho+Cr) in the substantia nigra between PD patients and healthy controls, but also between PD subjects with mild and severe disease[42]. In our study, no differences were found between PDP and PD without psychosis in terms of Hoehn and Yahr stage, thus our results cannot be attributed to disease severity. The NAA/Cr in the putamen nucleus was also significantly reduced in PDP subjects. Several studies have indicated cortical reductions in NAA/Cr in subjects with PD. Lucetti, et al. propose that the reduction in NAA/Cr in the motor cortex may be due to a loss of thalamocortical excitatory inputs[43]. Camicioli, et al. reported similar results in the pre-supplementary motor area[44].

The limitations of this study need to be considered. First, we did not include cognitive evaluations; therefore, we could not address the possible effect of cognition on Glu or NAA levels[45]. Second, direct measurement of Glu neurotransmission is not possible with ^{1}H-MRS since the technique can only measure total tissue levels, including metabolic, synaptic, and vesicular pools. Third, macromolecules were not measured and they have a potential influence on glutamate and glutamine quantification. However, the contribution of macromolecules was modeled using the default LCModel function. In addition, dopamine concentration was not measured, so a possible interaction between glutamate and dopamine levels could not be analyzed. It should also be mentioned that due to the high frequency of visual hallucinations, there might be a concern regarding the possibility of misdiagnosing as PD, patients with dementia with Lewy Bodies. In this regard, patients were selected using the Brain Bank Criteria, which exclude by definition these cases; moreover, the NINDS criteria for psychosis in PD also exclude these patients. Finally, patients with cognitive decline were excluded using a mini-mental cut-off value of < 26, and the sample had a large mean disease duration.

In conclusion, ^{1}H-MRS revealed decreased glutamate levels in the dorsal caudate and putamen, and decreased NAA in putamen of PD subjects with psychosis. Furthermore, we did not find an association between the use of dopamine agonist and psychosis. These findings suggest that decreased metabolite levels in specific brain areas may be implicated in the development of psychosis in Parkinson's disease.

DECLARATION OF INTEREST

Mayela Rodríguez-Violante has served as consultant and/or speaker for UCB, Boehringer Ingelheim, Teva, Vanquish, Ever Pharma, Novartis, Medtronic and the International Parkinson and Movement Disorders Society. Amin Cervantes-Arriaga has received travel grant support from Boehringer Ingelheim and UCB. Camilo de la Fuente-Sandoval has received grant support from Janssen (Johnson & Johnson), and has served as consultant and/or speaker for AstraZeneca, Eli Lilly, and Janssen.

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