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ORIGINAL RESEARCH

Amantadine and cognitive flexibility: decision making in Parkinson's patients with severe pathological gambling and other impulse control disorders

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Introduction: Dopamine replacement therapy for Parkinson's disease (PD) was recently linked to the development of impulse control disorders such as pathological gambling (PG), hypersexuality, compulsive shopping, and binge or compulsive eating. Antiglutamatergic agents including amantadine (Ama) reduce these behaviors in PD and non-PD patients. The aim of our study is to evaluate the changes in executive functions, emotions, and reward/loss processing during Ama treatment in PD patients.

Methods: Thirty-three patients affected by idiopathic PD were selected from a cohort of 1,096 PD patients and categorized in three different groups: ten affected by PG (PD-PG); nine PD patients with other impulse control disorder (PD-ICD); and 14 PD patient without any psychiatric disorder (PD-CTR-controls). For the neuropsychological evaluation, the following behavioral tasks where administered: the Stroop, the emotional Stroop, and the monetary reward/loss risk-taking tasks.

Results: During Ama treatment, PD-PGs showed a decrease in risky choices and an increase in non-risky choices ($t(9)=-2.40$, $P<0.05$ and $t(9)=2,67$, $P<0.05$ uncorrected, respectively). Between-group comparison showed a significant decrease in risky choices for PD-PG with respect to PD-CTR ($t(22)=-4.16$, $P<0.01$), and a decreased accuracy for positive words in comparison between PD-PG and PD-ICD ($t(17)=-7,49$, $P<0.01$) and PD-PG and PD-CTR ($t(22)=-4.29$, $P<0.01$). No within- and between-group differences were observed for Stroop task.

Discussion: Our data showed that Ama add-on therapy reduces hypersensitivity to reward and sustains activation toward uncertainty in PD-PG patients. These finding might explain the behavioral mechanism underlying the effect of antiglutamatergic drugs.

Keywords: Parkinson's disease, executive functions, emotion

Introduction

Nonmotor symptoms occur across all Parkinson's disease (PD) stages. The symptoms are unrecognized, underestimated, and under-treated or not treatable.[1]

Dopamine replacement therapy for PD was recently related to aberrant or excessive dopamine receptor stimulation resulting in the development of a number of nonmotor behavioral control problems,[2] which consist of a set of complex disinhibitory pathologies such as impulse control disorders (ICDs). ICDs, and in particular pathological gambling (PG), represent a significant clinical concern in PD patients, as described by Housden et al.[3]

These behavioral addictions are clinical entities in which repetitive impulsive behaviors occur, with negative effects on the patients' and their relatives' lives; the

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prominent features of such conditions are: cognitive salience, as the activity dominates the subject's thoughts and behaviors; conflict with other persons or activities; euphoria or relief, a feeling of short term pleasure from engaging in the behavior; tolerance or loss of control over the behavior; withdrawal, as experiencing unpleasant feelings when unable to engage in the behavior; and relapse and reinstatement, indicated when people unsuccessfully attempt to cut down on the behavior and subsequently engage in similar or higher levels of the activity than they had previously. Behavioral addictions are rather common in the general population, with a wide diffusion from adolescents[4] to geriatric age.[5] The impairment of functioning, with the presence of impulsiveness and other psychiatric symptoms, can be relevant and distressing in PD.[6]

In PD, typical ICDs include hypersexuality, PG, compulsive shopping, and/or compulsive eating; 6%–7% of PD patients meet criteria for one of these disorders.[3] Lifetime prevalence of ICDs is 6.1% in all PD patients, and 13.7%–17.1% in PD patients on dopamine agonists (DA).[2,7] The burden of these symptoms results in a negative impact on quality of life for patients and relatives.[1]

Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) recently inserted PG among the group defined as "Addiction and related problems"; it refers to persistent and recurrent gambling behavior characterized by preoccupation with gambling, increasing amounts of money spent, unsuccessful attempts to control gambling, restlessness or irritability when cutting down on gambling, lying to others about gambling, work or education, and relying on others for money. PG is the most extensively studied ICD in both PD and non-PD populations.[8,9]

Pathophysiology and evaluation

Neuroimaging studies observed alterations in the ventromedial prefrontal cortex (VM-PC) and the corticobasal-ganglionic-thalamic circuit in PD patients. Single-photon emission computed tomography (SPECT) studies found a dysfunction of the mesolimbic regions in PD with PG,[10–12] and alteration of these pathways were shown in non-PD patients with PG, showing a reduced activity during rewarding events and monetary-reward tasks.[13–15] Furthermore, the Stroop color word task[16] showed reduced activity in VM-PC in poor PG patients. Stroop and memory task alterations were shown in PD patients with hypersexuality. PD patients with ICDs were impaired on spatial planning and set-shifting tests compared with healthy controls.[17] The involvement of the prefrontal cortex (PC) suggests that tasks to assess executive functions are the best method to study PG and ICD in patients.

Recent studies hypothesize that levodopa-induced dyskinesias (LIDs) and behavioral alterations observed in dopamine dysregulation syndrome and ICD[2,18] depend on common mechanisms involving alterations of glutamate homeostasis with combined activation of sensitized dopamine and NMDA glutamatergic receptors.[19] Pre- and postsynaptic mechanisms are implicated in the devolvement of LIDs and ICDs, the first based on alterations in dopamine transmission after chronic administrations and the second because of excessive expression and sensitization of D1 receptors in striatonigral neurons.[2,20] The neuronal adaption underlying the imbalance between synaptic and nonsynaptic glutamate might result in failure of PC control.

Yet no treatments are at present validated for ICDs or dopamine dysregulation syndrome; reduction or withdrawal of DA are considered possible options, but may induce severe worsening of motor control and DA withdrawal syndrome.[21,22]

Amantadine (Ama) is L-amino-adamantanamine, a salt of the symmetric 10-carbon primary amine. Its mechanism of action is based on interaction with dopamine, by enhancing release and inhibiting its reuptake and by changing dopamine receptor affinity, and on NMDA glutamate receptor blockade, normalizing the activity of the glutamatergic corticostriatal and subthalamic-pallidal pathways. As shown for other antiglutamatergic drugs, Ama reduces LIDs to the point that its effect on LIDs is considered by Cochrane reviews and a recent treatment guideline[23] as having the only class I level A evidence of efficacy[23,24] for Ama.

In a recent study, we investigated the possible efficacy of Ama in the control of PG associated with PD.[9] The study was conducted in a double-blind cross-over manner with Ama 200 mg/day versus placebo and an open follow-up. Assessments included PG specific scales (Yale–Brown obsessive compulsive scale, South Oaks Gambling Screen [SOGS]) as well as assessment of expenditures and time spent gambling. Ama abolished or reduced PG in all treated patients, as confirmed by scale score and daily-expenditures reduction.

Also, the antiglutamatergic drug acamprosate ([Aca] Ca-acetyl homotaurine), a drug clinically used to reduce alcohol dependence and craving, attenuates glutamate release within the nucleus accumbens by binding to GluR5 AMPA receptors and interacting with NMDA receptors. A recent study showed that acamprosate significantly reduced obsessive-compulsive behavior in binge eating and food craving, and improved quality of life in patients affected by binge eating disorder.

Therefore, a possible option for ICDs and LIDs treatment might be to consider antiglutamatergic drugs.[23] However, few molecules are characterized by efficient antiglutamatergic activity;[25] for example, memantine,[26,27] Dextrometrophan,[28] and budipine are considered antiglutamatergic drugs, yet only anecdotal reports showed LIDs or ICDs reduction. Lamotrigine, oxcarbazepine, and topiramate represent a class of anticonvulsant compounds with glutamate-release-inhibiting properties that shows encouraging evidence as novel medications for alcoholism.[29,30] However, their potential in ICDs still needs to be demonstrated.

In our study, which considers a subsample of PD patients with ICDs previously described elsewhere,[9,31] we tested before (T0) and after (T1) Ama add-on medication (200 mg/day) to assess its effect on executive functions, emotion, and reward and loss processing. The color word Stroop task, emotional Stroop task (EST), and monetary reward/loss task slot machine-like game, respectively, were used to test the effect of Ama in PD patients with PG (PD-PG) and PD patients with ICDs (PD-ICD).

Materials and methods

Study population

A cohort of 1,096 patient with diagnosis of idiopathic PD according to UK-BBC[32] were regularly followed and treated from January 2011 to March 2012 in our Movement Disorder Clinic; they were asked to participate in the study. Inclusion criteria were: idiopathic PD; aged between 18 and 80 years; ascertained dopaminergic response; patients willing and able to give written informed consent; patients willing and able to comply to the study procedures; stable dose of dopaminomimetic drugs for at last 28 days; diagnosis of PD-PG for group A, and diagnosis of PD-ICD for group B (diagnosis according to DSM, 4th edition [DSM-IV] text revision, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, a rating scale designed to measure severity of symptoms and support a diagnosis of impulse control disorders and related disorders in PD).[33] Group C was PD control (PD-CTR) without PG or ICD.

Exclusion criteria were: history or signs suggesting atypical or secondary parkinsonism; history of stereotactic brain surgery for PD; mini–mental state examination (MMSE) score less than 24 at screening; any medical or psychiatric condition (other than ICD) that may compromise the patient's participation in the study; women with child-bearing potential; history of antipsychotics or anticholinergics medication and previous treatment with Ama.

Thirty-three patients (six females) with idiopathic PD met the inclusion/exclusion criteria. PG was identified according to DSM-IV (rule of five of nine items) and SOGS criteria.[34] PD patients were grouped on the basis of DSM-IV text revision criteria for ICDs and PG. PD patients were divided into three different groups: group A consisted of ten PD patients affected by pathological gambling (PD-PG; mean age 60.6±6.8 years); group B consisted of nine PD patients with other ICDs such as compulsive shopping, hypersexuality, and binge eating (ICD-PD; mean age 59.3±6.8 years); and group C consisted of 14 PD patients without PG or ICD (PD-CTR; mean age 59.0±9.5 years). Patients were matched for age, education, disease stage and duration, and dopaminomimetic therapy according to their need. None of the patients presented with LID.

According to our clinical procedures, all patients were evaluated with the Unified Parkinson's Disease Rating Scale,[35] PD stage was assessed with the Hoehn/Yahr scale,[36] and all patients underwent MMSE neuropsychiatric evaluation.[37] The study was approved by the University of Chieti ethics committee and was carried out according to the declaration of Helsinki and subsequent revisions. Patients (or caregivers) signed a written informed consent.

In order to understand whether the effect of antiglutamatergic drugs in ICD is dependent on modulation of executive functions or on processing of emotions and reward/loss, we assessed the effect of Ama as add-on therapy with the color word Stroop task, EST, and monetary reward/loss task slot machine-like game in PD-PG, ICD-PD, and PD-CRT. The patients were evaluated at T0 and T1, add-on medication (200 mg/day), following an opportune up and down titration. The neuropsychological tasks were performed at T0 and T1, also at the same time when the patients presented optimal motor performance and in "on" phase.

Tasks and stimuli

Tasks were given to all participants in a randomized order and performed at T0 and T1. Each participant performed tasks after the task had been explained in-depth. Task stimuli were presented on a computer by using MATLAB software.

Monetary reward/loss risk-taking task

Given the participants, we chose to make the task very simple to avoid stress derived from difficult instructions. Based on previous studies on PG,[14,15] we chose a non-realist gambling task. The task, is able to observe processes underlying addictive behavior and to measure indirectly the functioning of the front-striatal pathway in PD-PG.[38]

The task we used was a version of a slot-machine game where participants were asked to bet 50€ (high reward) or 5€ (low reward) on a random drawn square. There were two squares: a red square representing a winning bet and a black square representing a losing bet. The goal of the game was to win as much money as possible. The task was divided in three within-subjects randomized subsessions, the first with a 75% probability of winning, the second with a 50% probability of winning, and the third with a 25% probability of winning. For data analysis, we considered risky choices the bet of 50€ on losing squares. Choices and reaction times were collected.

Stroop task

The classic Stroop test relies on the observation that color naming can be slowed by the concomitant presence of a color word (competing information). The task requires participants to respond to the ink color and suppress the more familiar word identity. Whilst responses in congruent settings are relatively automatic, incongruence between the letters and ink color requires keen attention and leads to slower responses.[39,40]

Each trial consisted of a fixation cross at the center of a grey screen (500 ms), followed by word stimulus (500 ms), and then by an interstimulus interval ([ISI] 3,000 ms). During ISI, participants were instructed to press a key corresponding to the color (red or green) of the word that appeared on the screen with both speed and accuracy. The task comprised four blocks (100 trials), with half of the trials being incongruent (eg, the word "red" printed in the color green) and half being congruent (eg, the word "red" printed in the color red). Color words and ink colors selected for use in this study included red, green, and black. Presented trial type was randomized, though each participant completed 40 of each possible trial type (both congruent and incongruent trials using each of the three possible colors) until the end of the task. Participants were initially exposed to a 20-trial practice block.

Emotional Stroop task

EST is widely used to investigate attentional bias and interference caused by emotionally salient stimuli.[40] The task presented neutral and emotionally charged stimuli (neutral and emotionally-negative/-positive words) with three different colors (black, red, and green), and the patients were asked to press the button corresponding to the color of the word as quickly as possible.

Color naming EST was designed based on previous studies.[41–43] Neutral, negative, and positive words were selected on the basis of norms in the Italian language, ie, emotionality, familiarity, and statistical frequency. The task contained 111 trials presented in three blocks of 37 words each (three different words for each word type). The word stimuli were presented for 500 ms and the ISI was 3,000 ms. The color-identification response latency for each stimulus was recorded (Figure 1).

Data analysis

Statistical analysis was performed using Statistica®, Version 6.0 (StatSoft, Inc., Tulsa, OK, USA). Results of the Stroop task were analyzed as follows: the mean reaction times and percentage of correct responses (accuracy) for each stimulus (congruent and incongruent, respectively) was computed; then, three different two-tailed *t*-tests were computed for each group for the T0 and T1 to assess the effect of add-on therapy.

Results for EST Task were analyzed, computing mean reaction times and accuracy for positive and negative words. Two tailed *t*-tests were computed for each PD group at T0 and T1.

Results for the monetary reward/loss task were analyzed by computing the percentage of risky and non-risky choices. Three different two-tailed *t*-tests were performed to assess the effect of add-on therapy.

Between-group comparison was performed for T0 and T1 separately for each task. Where possible, Bonferroni correction was applied to *t*-test results.

Results

Thirty-three patients (six females) with idiopathic PD met the inclusion/exclusion criteria. PD patients were divided into three different groups: ten PD-PG (mean age: 60.6±6.8 years); nine PD-ICD (mean age 59.3±6.8 years) ; and 14 PD patients without PG or ICD (PD-CTR) (mean age 59.0±9.5). As shown in Table 1, patients were not different in age, education, disease stage and duration, and dopaminomimetic therapy according to their need. UPDRS III scores were not different between groups. MMSE evaluation did not show a significant cognitive decline (MMSE >24). SOGS scores indicated the presence of pathological gambling in group A, while in the other group the scores were under the cut-off for pathological gambling. On the YBOCS, scores indicating the presence of obsessive-compulsive behaviors were reported in the PD-PG and PD-ICD groups. On the QUIP-R scale, scores showed impulse-control behavior in the PD-PG and PD-ICD groups.

No significant between- and within-group differences were observed in mean reaction times for the three different tasks. Data for within-group results are shown in Table 2.

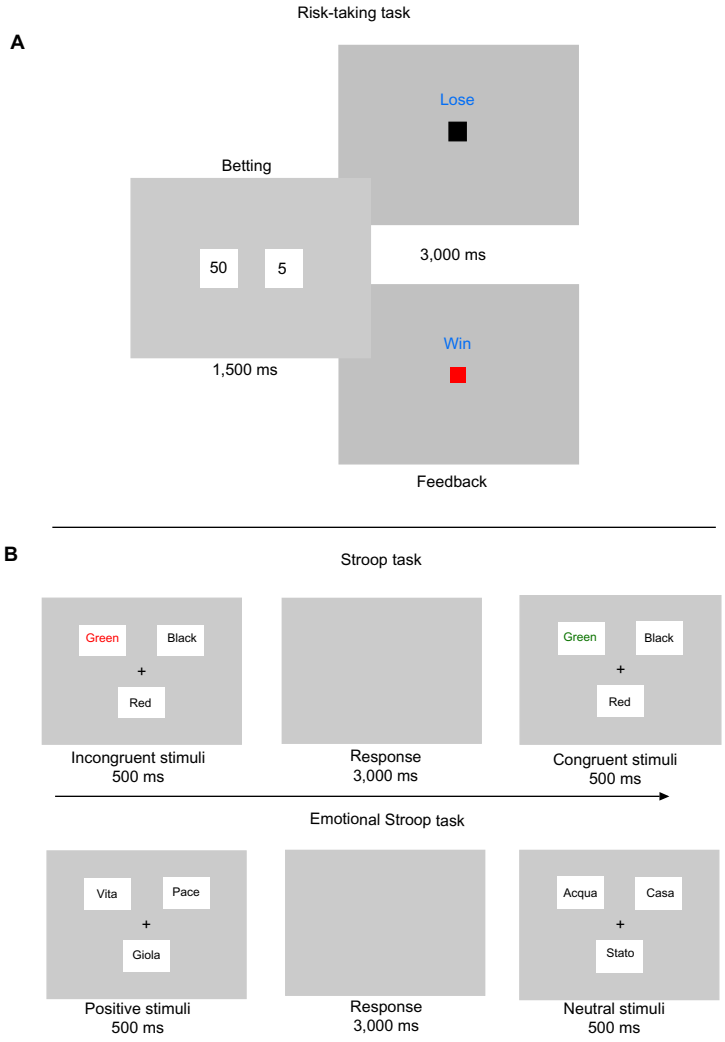

Figure 1 Psychological tasks.
Notes: (**A**) Detailed procedure of a risk-taking task. (**B**) Detailed procedure of the Stroop task and the emotional Stroop task.

At T0, results from the risk-taking task, Stroop task, and EST were not different between groups.

At T1, results from the risk-taking task showed a decrease in risky choices and increase in non-risky choices ($t(9)=-2.40$, $P<0.05$ and $t(9)=2.67$, $P<0.05$ uncorrected, respectively) in PD-PG patients. Between-group comparison of PD-PG versus PD-CRT showed a significant decrease in risky choices for the PD-PG group ($t(22)=-4.16$, $P<0.01$).

At T1, results from the Stroop task did not show within- and between-group differences. Interestingly, we did not observe modifications in the accuracy.

At T1, our results for the EST showed a significant decrease in accuracy for positive words in the PD-PG and PD-ICD groups ($t(9)=-15.83$, $P<0.05$ corrected and $t(8)=-2.7$, $P<0.05$ uncorrected, respectively), while a significant increase was observed to negative words in the PD-ICD group ($t(9)=-2.40$,

Table 1 Patient demographics

	Group A PD-PG (n=10)	Group B PD-ICD (n=9)	Group C PD-CTR (n=14)
Age (years)/male sex	60.6±6.8/7	59.3±6.8/6	59.0±9.5/7
Education (years)	11.7±2.6	10.3±3.2	11.7±1.9
Disease duration (months)	28.2±12.3	29.0±8.5	27.2±8.4
UPDRS III	20.5±6.8	21.4±4.2	21.6±6.9
Hoehn/Yahr stage	1.9±0.2	1.7±–0.3	1.7±0.02
MMSE	28.5±2.1	28.4±1.9	28.6±2.0
SOGS	13±2.5	4±0.5	0.8±0.3
YBOCS	9.3±3.8	8.3±7.8	2.1±0.9
Quip-RS	37.5±15.1	51.0±11.1	5.00±3.5
L-dopa equivalent dose (mg)	294.5±123.1	283.3±132.9	307±96.3

Abbreviations: CTR, control; ICD, impulse control disorder; L-dopa, L-3,4-dihydroxyphenylalanine; MMSE, mini–mental state examination; PD, Parkinson's disease; PG, pathological gambling; Quip-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; SOGS, South Oaks Gambling Screen; UPDRS III, unified Parkinson's disease rating scale motor part; YBOCS, Yale–Brown obsessive compulsive scale.

$P<0.03$ uncorrected). PD-PG patients showed a decrease in accuracy for positive words compared to the PD-ICD group ($t(17)=-7.49$, $P<0.01$) and PD-CTR group ($t(22)=-4.29$, $P<0.01$). Results are shown in detail in Figure 2.

Discussion

The purpose of our study was to assess the effect of Ama add-on therapy on executive functions, emotions, and processes underlying reward and loss in PD-PG and PD-ICD. Ama is one of the possible pharmacological treatments for PD and non-PD patients with PG as has been shown in recent studies.[9,44] The main outcome of the present study was to evaluated the efficacy of Ama in improving ICDs in PD-PG and PD-ICD patients using neuropsychological tasks at time T0 and T1 in the three patient groups.

The main outcome of this study was to assess the efficacy of Ama in improving the selection of non-risky choices in the risk-taking task in PD-PG patients and the increase in accuracy to negative words in the PG-ICD group.

The significant reduction of risky choices after treatment observed in this study may represent a protective factor that is able to reduce the number of relapses in subjects with PG.

Table 2 Within-subjects task results

Group	Condition	Time	Mean	SD	t-value	*df*	*P*-value
Risk taking task							
PD-PG	Risk	T0	42.8	16.4			
		T1	28.7	16.2	2.40	9	0.039
	No risk	T0	40.6	13.8			
		T1	56.4	21.6	−2.67	9	0.025
PD-ICD	Risk	T0	46.3	5. 6			
		T1	40.2	12.3	1.46	8	0.181
	No risk	T0	40.7	5.7			
		T1	49.7	18.2	−1.30	8	0.229
PD-CTR	Risk	T0	42.5	18.4			
		T1	46.3	0.9	−0.84	13	0.413
	No risk	T0	43.9	16.6			
		T1	52.4	1.8	−1.84	13	0.088
Stroop task							
PD-PG	Congruent	T0	85.7	15.5			
		T1	83.1	14.3	0.32	9	0.75
	Incongruent	T0	88.9	7.1			
		T1	91.6	8.1	−0.80	9	0.442
PD-ICD	Congruent	T0	88.3	6.6			
		T1	88.3	16.6	0.00	8	1
	Incongruent	T0	93.9	3.1			
		T1	90	17.4	0.72	8	0.489
PD-CTR	Congruent	T0	85.7	15.5			
		T1	81.4	21.4	1	13	0.33
	Incongruent	T0	84.3	14.2			
		T1	82.8	14.1	1	13	0.33
Emotional stroop task							
PD-PG	Negative	T0	65.6	7.3			
		T1	68.8	3.7	−1.92	9	0.086
	Positive	T0	64	8			
		T1	29.3	3.9	15.83	9	0.000
PD-ICD	Negative	T0	67.1	3.3			
		T1	70.8	1.7	−2.78	8	0.023
	Positive	T0	70.7	2.8			
		T1	40	1.9	25.03	8	0.000
PD-CTR	Negative	T0	64	10.2			
		T1	66.8	6.5	−1.11	13	0.28
	Positive	T0	66	5.4			
		T1	56.8	19.8	−1.12	13	0.28

Abbreviations: CTR, control; ICD, impulse control disorder; PD, Parkinson's disease; PG, pathological gambling; SD, standard deviation; T0, before amantadine add-on medication; T1, after amantadine add-on medication; df, degrees of freedom.

Reduction of risky choices could be considered the focal process responsible for the efficacy of Ama in PD-PG, previously described in other studies.[9,44]

Our data highlight a modified behavior in PD-PG patients after introduction of Ama; in other PD patients (PD-ICD/PD-CTR), performance was unchanged and executive function, specifically inhibition processing, was not affected.

In all PD patients, the Stroop task we performed did not show changes in accuracy, indicating that there is no deficiency in inhibition of interference, as shown by Kertzman.[45] Previous literature shows contradictory results regarding executive functions, PD-PG and PD-ICD patients data, and the relationship between executive functions and PG or other ICDs in PD patients.[46,47]

The differences observed in the Stroop task and EST at T1 indicate the involvement of different inhibitory processes during the execution of the task.[48] For the EST, we found at T1 in PD-ICD a decrease in accuracy for positive words and an increase in accuracy for negative words, while PD-PG showed a decrease in accuracy for positive words.

Previous studies where EST was used indicated that the level of activation or performance for emotional words was higher than for neutral words, resulting in a decreased ability to inhibit the processing of emotional meaning.[49,50] The higher performance relative to negative words may depend on the automatic vigilance effect.[51] The automatic vigilance effect is an innate mechanism that normally allows a person to direct attention to negative or dangerous stimuli, having a high adaptive value. Automatic vigilance seems to be more active during experimental tasks like EST in healthy subjects.[51]

Between-group comparison for the post-treatment period showed decreased accuracy in recognizing positive words in PD-PG and PD-ICD patients. The possible effect of Ama may be the enhancement of the automatic vigilance effect in PD-PG and PD-ICD patients. This is in line with our results.

A relevant limitation of this study is the small sample size and the consequent low statistical power, but levels of significance have been found, confirming the strength of the data.

A theoretical limitation is represented by two previous studies using a cross-sectional or retrospective design,[8,52] which did not evidence a statistical reduction of PG in patients treated with Ama. Yet, cross-sectional or retrospective studies are subject to treatment and recall bias, and can only identify the prevalence and clinical correlates of

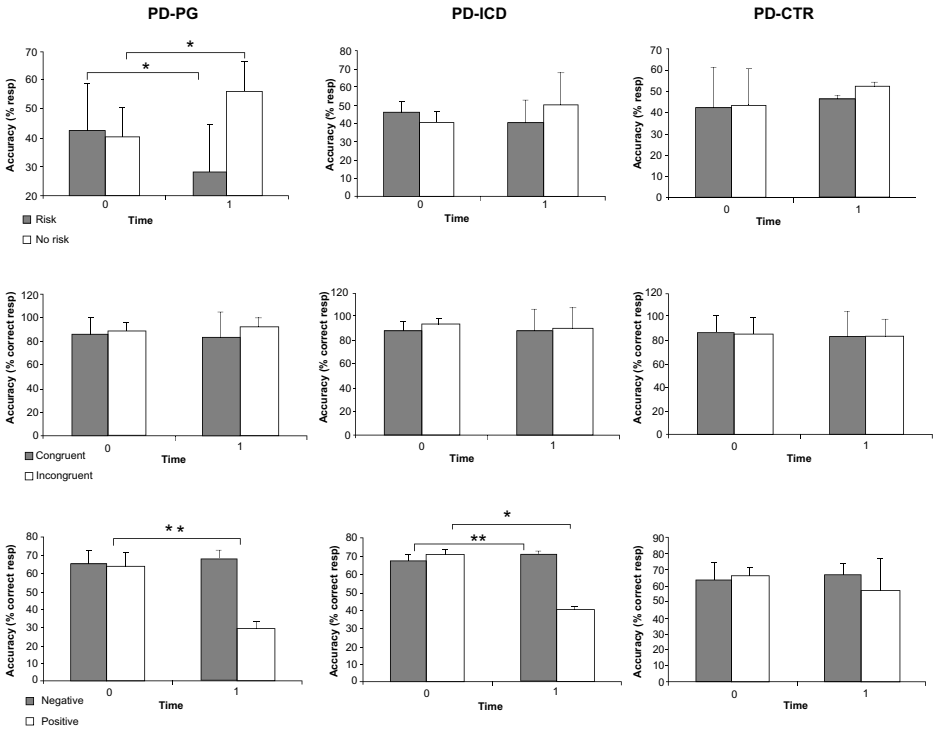

Figure 2 Within-group results.
Notes: Graphs show percentage of risky and non-risky choices in risk-taking task, and accuracy in Stroop task and emotional Stroop task, respectively, before (0) and after (1) amantadine add-on therapy. Vertical bars indicate standard deviations. *$P<0.05$; **$P<0.0001$.
Abbreviations: CTR, control; ICD, impulse control disorder; PD, Parkinson's disease; PG, pathological gambling; resp, response.

ICDs, but not their incidence or risk factors; as such these are not sufficient evidence of efficacy or lack of efficacy of a drug.[53]

Any new treatment calls for validations and further study designs. Taking as an example the history of L-3,4-dihydroxyphenylalanine treatment, the initial evidence of L-3,4-dihydroxyphenylalanine benefits in PD were challenged by reports showing its inefficacy or side effects; the key to efficacy was patient selection and dose finding.[54] The lack of studies due to inappropriate patient selection is misleading and represents one of the major problems in clinical/pharmacological research,[8,55,56] particularly in PD, where the clinical presentation and the variety of symptoms – ranging from hallucinations to motor and sleep-behavior problems – is large.[31,57] In our recent study,[9] the obvious prerequisite was the absence of prior exposure to Ama, whereas in cross-sectional observational studies, the history of Ama intake, of psychosis and tachyphylaxis are well known effects of Ama, were not considered.

Further research with larger clinical trials are needed to assess the role of antiglutamatergic drugs in the treatment of ICDs in PD.

Disclosure

The authors report no conflicts of interest in this work.

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