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Decision-making, impulsivity and addictions: Do Parkinson's disease patients jump to conclusions?

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Abstract

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Links between impulsive compulsive behaviors in treated Parkinson's disease, behavioral addictions and substance abuse have been postulated, but no direct comparisons have been carried out so far.

We directly compared patients with Parkinson's disease with and without impulsive compulsive behaviors with illicit drug abusers, pathological gamblers and age-matched healthy controls using the beads task, a test of reflection impulsivity and a working memory task.

We found that all patients with Parkinson's disease made more impulsive and irrational choices than the control group. Parkinson's disease patients who had an impulsive compulsive behavior showed similar behavior to illicit substance abusers whereas patients without impulsive compulsive behaviors more closely resembled pathological gamblers. In contrast we found no difference in working memory performance within the Parkinson's disease groups. However Parkinson's disease patients without impulsive compulsive behaviors remembered distractors significantly less than all other patients during working memory tests.

We were able to correctly classify 96% of the Parkinson's disease patients with respect to whether or not they had an impulsive compulsive behavior by analyzing 3 trials of the 80/20 loss condition of the beads task with a negative prediction value of 92.3% and we propose that this task may prove to be a powerful screening tool to detect an impulsive compulsive behavior in Parkinson's disease. Our results also suggest that intact cortical processing and less distractibility in Parkinson's disease patients without impulsive compulsive behaviors may protect them from developing behavioral addictions.

Keywords

Impulsive compulsive behavior; Parkinson's disease; reflection impulsivity; pathological gambling; substance abuse; beads task

Introduction

Although not necessarily maladaptive impulsive decision making is often linked with addiction and has been reported in patients with substance abuse and pathological gambling[1, 2]. It is also seen in a subgroup of patients with Parkinson's disease (PD) who develop impulsive compulsive behaviors (ICBs) on dopaminergic medication[3]. About 14% of PD patients treated with dopamine receptor agonists alone develop ICBs, such as pathological gambling, compulsive sexual behavior, binge eating, excessive shopping and punding[4].

It remains unclear why some PD patients are predisposed to ICBs, but risk factors include younger age of disease onset, male gender and a premorbid or family history of substance abuse[5]. ICBs have also been associated with 'behavioral addictions'[6] sharing clinical withdrawal symptoms of dysphoria, depression and anxiety[7, 8] with substance abuse. Functional imaging studies have demonstrated aberrant striatal dopaminergic "reward pathways" and altered function in frontal cortical regions in PD patients with ICBs (PD +ICB) and non-PD patients with addictive behaviors[7, 9, 10].

We have used the 'beads task'[11] to compare decision making in PD patients with and without ICBs, pathological gamblers and substance abusers. In addition to the Mini-Mental state examination (MMSE)[12] we also included a working memory (WM) task to assess whether impairments in decision making reflected a more generalized cognitive deficit. The beads task assesses how much information participants gather before making a decision that has been referred to as "*reflection impulsivity*"[13, 14]. This differs from 'motor' impulsivity, the inability to stop an ongoing process and from 'waiting' impulsivity, the inability to delay

an action[15]. Early decision on the beads task or 'jumping to conclusions' has been also seen in patients with schizophrenia[16–18]. In a modified version of this task a positive association between impulsivity and problem gambling has been reported[19]. Reflection impulsivity has been also described in opioid abusers previously[14] and has been shown not to correlate with scores on the Barratt impulsiveness scale[20].

We predicted that all impulsive patients would jump to conclusions and speculated that PD +ICB patients would show behavior similar to substance abusers and pathological gamblers and make choices which were more impulsive than PD patients without ICBs (PD−ICB). We also speculated that both PD groups would perform worse than matched controls, given recent studies showing that even PD−ICB patients show increased risk taking and temporal discounting[21, 22]. Negative effects of task irrelevant stimuli (=distractors) on WM performance have been reported[23]. Given our previous results on WM performance[21] we hypothesized that PD+ICB patients would perform significantly worse than controls and PD −ICB patients on the WM task and might have a performance similar to that seen in pathological gamblers and substance abusers. We also speculated that all patients with addictions would remember distractors significantly better than controls and PD−ICB patients.

Methods

All participants provided written informed consent according to the declaration of Helsinki and the study was approved by the UCLH Trust and the University of Lvov ethics committee.

PD and elderly control groups

Twenty seven PD−ICB and 26 PD+ICB patients were recruited from the National Hospital for Neurology and Neurosurgery London. All patients fulfilled the Queen Square Brain Bank criteria for the diagnosis of PD[24] and were taking L-dopa. Twenty-one/27 PD−ICB patients were taking a dopamine agonist, whereas only 13/26 PD+ICB patients were still on a dopamine agonist. Eighteen healthy matched elderly volunteers were recruited. Patients who scored under 26/30 points on the MMSE were excluded. All participants were screened for sub-classes of ICBs in a semi-structured interview, using accepted diagnostic criteria for pathological gambling[25], compulsive shopping[26], compulsive sexual behavior[27] and punding[28]. We also used a self-rated validated questionnaire for impulsive compulsive disorders in PD (QUIP)[29].

Patients were tested only "on" medication with the beads test to minimize "off" dysphoria and anxiety[30], which was however not specifically measured.

For the working memory task, patients were tested both off and on medication, in a counterbalanced order. Patients who were tested "off medication" did not take their anti-Parkinson medication, for at least 12 hours and performed the task between 8.00am and 9.00am. They were then retested "on medication" the following day. Those patients who were tested "on medication" first performed this task usually in mid-morning when their motor symptoms were well controlled. They were re-visited on the following day prior to their medication for the second test. Controls were tested in the same way but did not take any anti-Parkinson medication. All PD patients had an excellent L-dopa response assessed by UPDRS Part III scores during "off" and "on" state. L-dopa equivalent units (LEU-Table 1) were calculated as described previously[28](See supplementary material).

Pathological gamblers, substance abusers and matched controls

These participants were tested once usually mid-morning. Twenty-three patients with pathological gambling, according to DSM-IV criteria[25] were recruited from the National Problem Gambling Clinic, UK. Most gamblers only stopped gambling following financial ruin recently. All were help-seeking and awaiting treatment. None had a current history of substance abuse. Thirteen patients with a recent history of illicit substance abuse, meeting DSM-IV criteria for substance dependence[25] were also tested. Patients were recruited from the Replacement Therapy Unit of Lviv and were receiving buprenorphine. None fulfilled DSM-IV criteria for dementia. Twelve out of 13 patients had a long standing history of intravenous opioid abuse (see Table 1).

All pathological gamblers and 12/13 of the substance abusers were males. Results were compared with 18 age matched male controls.

Beads task

The beads task[11] was performed on a laptop computer, usually in the participant's home or in a quiet room to minimize distractions. Participants were required to guess from which of two cups colored beads were being drawn. The cups differed in the proportion of blue and green beads they contained. For example, one of the cups may have contained 80% blue beads and 20% green beads, whereas the other cup may have contained 80% green beads and 20% blue beads. Participants were first shown a bead draw, which was either blue or green. They could then draw another bead, or guess that the bead was being drawn from the predominantly green or blue cup. This was repeated until they chose to guess one of the cups. We were interested in the number of beads drawn before the participant guessed a cup and whether the urn choice represented a rational (e.g. if more blue beads were drawn the participant guessed blue) or irrational (i.e. the cup color guessed was not most probably correct, given the beads drawn) choice. This is referred to as opposite color choice.

Participants completed 4 blocks of 3 trials each. Two blocks contained an 80/20 ratio of beads and 2 blocks a 60/40 ratio of beads in each cup. (See supplementary material).

Working memory task

PD patients were tested prior and after their usual anti-Parkinson medication in a counterbalanced sequence to account for order effects. Twenty four trials of a WM task were completed on a laptop computer (Fig. S1). Participants were asked to memorize either 2 or 3 geometric figures which were shown for 3 seconds, followed by a delay of 2 seconds. During the delay, distractor images were shown. Then another geometric figure was presented and participants were asked whether this figure was within the set that they had to remember before. In half of the trials 2 geometric figures and in the other half 3 had to be remembered. Distractors could be positive, neutral or negative images taken from the validated International Affective Picture System[31].

At the end participants were shown 24 distractor images and were asked whether they thought they had seen the images before. Half of the distractors were shown during the WM task. (See supplementary material).

Results

Demographic and clinical features

Demographic variables (Table 1) were analysed using ANOVA, t-test or χ^2 tests where appropriate. There were no differences between the control groups and the matched patient groups on any demographic variables. Significantly more PD−ICB (21/27) than PD+ICB

(13/26) patients were taking a dopamine agonist (p=0.024), which is in line with accepted clinical guidelines of managing an ICB in PD. Consistent with the literature[4] PD+ICB patients showed a trend to be younger than PD−ICB patients and had a significantly younger disease onset relative to PD−ICB patients (t_{52}=3.28, p=0.002). (See supplementary material).

Beads task

We examined the number of draws each participant made in the different conditions (Fig. 1a). (For total numbers draws per group see Table 1). We found significant effects of group (Wald χ^2=191.0, p<0.001), beads ratio (Wald χ^2=167.9, p<0.001) and a significant beads ratio by loss condition interaction (Wald χ^2=9.4, p=0.002). There was no difference between the 2 control groups on number of draws (Wald χ^2=1.0, p>0.3). There was also no correlation between age and number of draws in the control groups (r=−0.15, p>0.37). We then combined the 2 control groups and performed pairwise comparisons between the PD +ICB group and the other groups to examine whether or not the PD+ICB group would perform similar to the other groups (Table 2).

We found that PD+ICBs were drawing significantly fewer than PD−ICBs (Wald χ^2=27.1, p<0.001), pathological gamblers (Wald χ^2=13.9, p<0.001) and controls (Wald χ^2=75.1, p<0.001). For completeness we also report comparisons between the other groups (Table 2). All pair-wise comparisons showed main effects of beads ratio. Only the PD−ICB vs. control pair-wise comparison additionally showed an interaction between group and beads ratio (Wald χ^2=8.0, p=0.005).

Opposite color choice

Next we examined the number of times participants made an irrational choice, summed across all conditions (Fig. 1b). We found a main effect of group (Wald χ^2=72.1, p<0.001) and examined effects pair-wise, between groups. Again there was no difference between the two control groups (Wald χ^2=0.07, p=0.8), so they were combined (Table 2). Pair-wise comparisons showed that substance abusers chose the opposite color significantly more often than all other groups (all p values<0.001). Further all patients chose the opposite color significantly more often than controls (p<0.001). There was no difference between PD+ICB and PD−ICB patients or pathological gamblers.

Classification of PD+ICBs on the basis of drawing behavior

We used the drawing behavior of individual participants in the 80/20 loss condition to try to predict group membership between the PD+ICB and PD−ICB groups. We used an unblended, supervised classification technique, which required labeled data and found that we correctly classified 25 out of 26 (>96%) PD+ICB patients. We also correctly classified 44% of PD−ICB patients as not having an ICB, giving a positive predictive value of 62.5% and a negative predictive value of 92.3%.

Working memory task

Detailed results are reported in supplemental material. For the WM performance pairwise comparison showed all groups performed better than substance abusers (Table 3), but there were no differences between all the other groups (Fig. 2a). For remembering distractors in the WM task we found a main effect of group (Wald χ^2=59.7, p<0.001) and pairwise comparisons showed that PD+ICB patients (Wald χ^2=7.2, p=0.007) and pathological gamblers (Wald χ^2=15.4, p<0.001) remembered distractors significantly better than PD −ICB patients (Table 3, Fig. 2b).

QUIP questionnaires

Consistent with previous studies[29, 32] we found a high sensitivity to detect an ICB (96.1%) for both the patient and caregiver rated QUIP. 40.7% of PD−ICB patients, who did not meet the diagnostic criteria for having an ICB, had at least 1 ICB symptom either self-rated or by their caregiver, consistent with a previous study[32]. There was no correlation of the QUIP and drawing behavior (see supplementary material).

Discussion

We have examined 'reflection impulsivity' using the beads task, an information gathering paradigm in which participants controlled the amount of information they gathered before making a decision[11]. We compared PD patients with and without ICBs, pathological gamblers and substance abusers and found evidence for impairment even in treated PD patients without clinically apparent ICBs. Across groups we found an effect of the beads ratios, such that participants drew more when the beads ratios were closer to chance (60/40) than when the ratio was greater between the cups (80/20). Further, the loss condition interacted with the beads ratio condition, such that subjects drew relatively more in the higher loss conditions.

Despite all groups showing behavior adaptive to the specific condition, the PD+ICB group drew significantly fewer beads than controls, PD−ICBs and pathological gamblers before making a decision. Significantly less PD+ICB than PD−ICB patients were taking a dopamine agonist and yet they still gathered less information. The fact that the PD+ICB group drew fewer beads than pathological gamblers is intriguing, given that half of the PD +ICB patients had clinically defined pathological gambling. Slot machines, scratch cards and bingo were the most commonly played gambles in PD, pathological gamblers preferred skilled games, such as spread betting and electronic casino games (see Table 1)[33–35], which may be of relevance in the interpretation of the results.

Direct comparison between groups on the beads task suggests greater similarities between PD+ICB patients and substance abusers, compared to the pathological gamblers or PD−ICB patients. Positron emission tomography studies have shown sensitization of the ventral striatum in PD+ICB patients[36, 37] and also in patients with substance abuse[10, 38]. Furthermore *'reflection impulsivity'* does not recover even after prolonged abstinence in substance abusers[14]. This is consistent with the fact that dopamine agonists have often been withdrawn for a long period in the PD+ICB group leading to alleviation of impulsive symptoms, and yet they still make impulsive choices in the beads task. PD+ICB patients also become irritable when their addictive behavior is restricted[28, 39], reminiscent of withdrawal symptoms in drug abusers.

Analysis of the QUIP revealed that 41% of PD−ICB patients had at least 1 symptom of an ICB, either self-rated or rated by their caregiver consistent with previous studies[32]. Using the beads tasks we classified 56% of PD−ICB patients as having tendencies towards impulsivity, suggesting that this task may be a more sensitive screening tool to detect hidden impulsive traits. Consistent with this, there was no difference in the behavioral pattern between PD−ICB patients and pathological gamblers. This is particularly interesting since none of the gamblers had received any treatment for their impulsivity and none of the PD −ICB patients had clinically defined ICBs. We also found that PD−ICB patients drew significantly less than matched controls.

Several studies have demonstrated increased impulsivity and changes on behavioral tasks in PD−ICB patients after starting dopaminergic medication[40–42] in contrast to treatment naive PD patients who perform similarly to controls[43]. Whether impulsivity arises as a result of

increased impulsive drive, decreased inhibitory control or a combination of both is still unclear. However, the results in the PD−ICB group could reflect an underlying increased impulsivity driven by excessive dopamine levels in the ventral striatum. In PD there is much less dopamine loss in the ventral than the dorsal striatum[44]. Therefore, treatment with dopaminergic medication to increase dopamine levels in the dorsal striatum may lead to excessive levels in the ventral striatum. This may result in a tendency in all treated patients to increased impulsivity, which however does not manifest as clinically significant impulsiveness due to intact inhibitory corticostriatal pathways. Hypoactivation of the orbitofrontal cortex is seen in pathological gamblers, illicit substance abusers[45, 46] and in treated PD+ICB patients, but not in PD−ICB patients[8]. The ventromedial plus the orbitofrontal part of the prefrontal cortex is important for impulse control[8, 47, 48] and is associated with 'jumping to conclusions' on the beads task[49]. Thus, intact inhibitory control driven by these cortical areas might prevent PD−ICB patients from clinical impulsivity[8].

Jumping to conclusions can also occur in psychosis[18]. Consistent with this, previous work has shown that PD+ICB participants score highly on measures of schizotypy, a personality trait related to psychosis[50]. Delusional thinking, defined as a belief based on incorrect inference[25], has been reported in PD+ICB patients[35, 51] and has been positively correlated with fewer draws on the beads task in delusional patients with and without schizophrenia[17]. Both PD groups also guessed the opposite color more often than controls and anecdotally some stated that they *"anticipated"* that the opposite color was more likely and therefore chose the less likely cup. In fact there was no group difference between PD patients and pathological gamblers. However substance abusers chose the opposite color significantly more often than the other groups.

There are important differences between risk taking behaviour, temporal discounting and the beads task. Previous studies have found no[21] or restricted[52] group differences in risk taking between PD+ICB and PD−ICB patients. In contrast, results on the beads task in the two PD groups were highly significant. The standard temporal discounting task[3] is more closely related to self-report questionnaires than metric tasks, and measures sensitivity to rewards delayed by weeks or months. In contrast, drawing more beads only delayed possible rewards by seconds. Not drawing often leads to not winning, or losing in the loss blocks which contrasts with waiting for a larger reward, as occurs with temporal discounting.

Since memory plays an important role in reward learning[53], we examined whether the results on the beads task could have been confounded by poor WM. In this WM task we examined the role of distractibility during the delay intervals. There was no correlation between the beads task and WM capacity, which suggests that early decisions relating to the beads were not driven by poor cognitive capacity. We also found that substance abusers had a significantly worse WM capacity than the other groups. This is consistent with previous studies demonstrating poorer attention in substance abusers when required to ignore salient stimuli during WM tasks[54]. However this finding has to be interpreted with caution since the substance abusers were taking opioid replacement therapy which is known to interfere with WM function[55].

Many patients with ICBs conceal their behavior due to shame or denial[56]. By analyzing data from the 80/20 loss condition we were able to correctly identify ICB patients with a sensitivity of 96%. The beads task might therefore provide a simple screening tool to detect patients at greater risk of ICBs or confirm a clinically suspected but concealed ICB. These results also suggest that a significant proportion of PD−ICB patients is at risk of developing impulsive behavior and thus over time may develop ICBs[57]. Poor performance on this task suggests that these patients should be monitored frequently by their treating physician and the results taken into consideration when deciding on the use of dopamine agonist treatment.

This study is free from the limitations of an indirect study design[58] and contains a large number of different groups. Further our results also might have clinical implications, since they imply that PD+ICB patients should be treated like substance abusers rather than patients with behavioral addictions. Additional studies comparing PD−ICB patients on and off dopamine agonists will be necessary to explore the role of dopaminergic medication in cognitive impulsivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosure

	Stock Ownership in medically-related fields	Consultancies	Advisory Boards	Partnerships	Honoraria	Grants	Intellectual Property Rights	Expert Testimony	Employment	Contracts	Royalties	Other
AD	none	none	none	none	none	none	none	none	none	none	none	none
SOS	none	none	none	none	Britannia Pharmaceuticals	none	none	none	none	none	none	none
YS	none	none	none	none	none	none	none	none	none	none	none	none
SS	none	none	none	none	none	none	none	none	none	none	none	none
YM	none	none	none	none	none	none	none	none	none	none	none	none
TF	none	none	none	none	Abbott, St Jude Medical, Data Monitoring Committee for Oxford Biomedical	Parkinson's UK, Cure Parkinson's Trust and European Union FP7	none	none	none	none	none	none
RM	none	none	none	none	none	none	none	none	none	none	none	none
IAO	none	none	none	none	none	none	none	none	none	none	none	none
LF	none	none	none	none	none	none	none	none	none	none	none	none
KMD	none	none	none	none	none	none	none	none	none	none	none	none
YF	none	none	none	none	none	none	none	none	none	none	none	none
MS	none	none	none	none	none	none	none	none	none	none	none	none
HBD	none	none	none	none	none	none	none	none	none	none	none	none
EJ	none	none	none	none	none	none	none	none	none	none	none	none
AJL	none	Genus	none	none	Novartis, Teva, Meda, Boehringer Ingelheim, GSK, Ipsen, Lundbeck, Allergan, Orion	PSP Association, Weston Trust – The Reta Lila Howard Foundation	none	none	none	none	none	none
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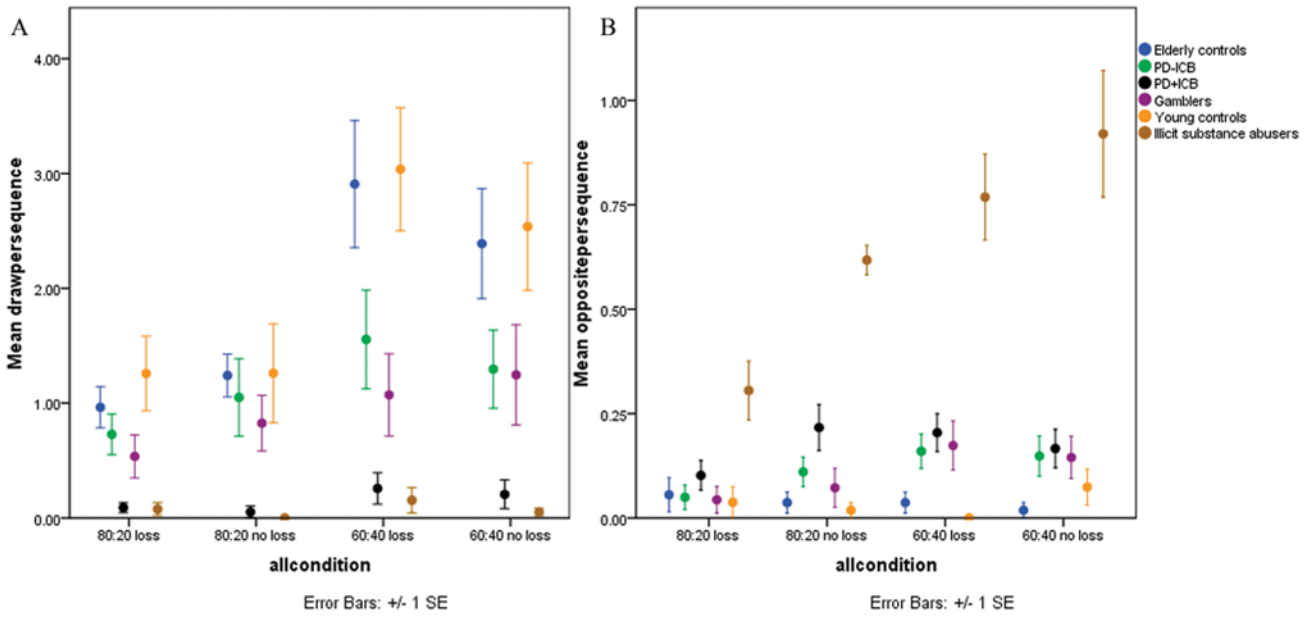

Figure 1.

Figure 1a. (left) Average number of draws per condition by group. 1b: (right) Number of times participants chose the opposite color.

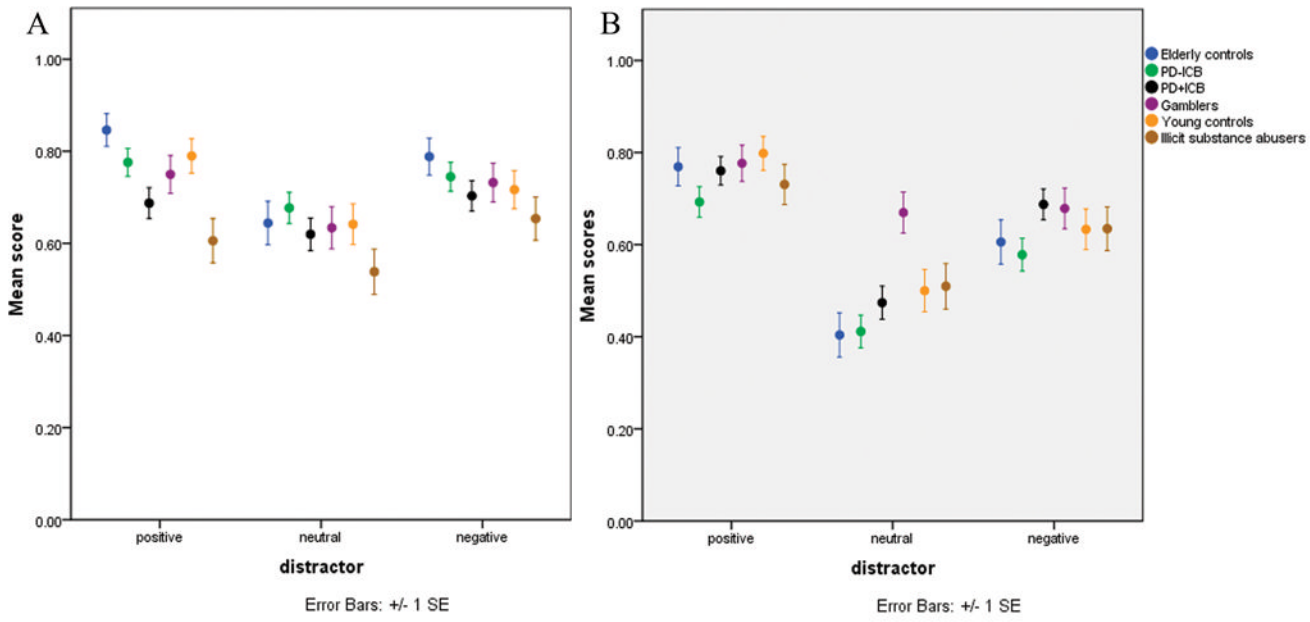

Figure 2.
Figure 2a. (left) WM performance. 2b: (right) recalling distractors (positive, neutral, negative).

Table 1

Demographic characteristics

	CO-O	CO-Y	PD+ICB	PD−ICB	Addicts	Gamblers	t value, χ^2 and F-value	p-value
Participants(no.)	18	18	26	27	13	23		
Age (yrs)	58.9±12.7	33.2±5.5	58.7±10.0	65.3±5.3	32.0±7.1	38.0±9.3	F=58.8	<0.001*
Gender (male)	15	18	22	24	12	23	χ^2=6.8	0.25
Average draws across all trials	1.9±0.1	2.0±0.1	0.15±0.1	1.2±0.1	0.07±0.1	0.9±0.1	χ^2=191	<0.001*
At PD onset			47.7±9.5	55.3±7.4			t=3.28	0.002*
PD Disease duration (yrs)			11.0±4.1	10.0±6.5			t=0.52	0.48
Education (yrs)	13.6±3.2	13.9±2.2	13.1±2.8	14.8±2.5	12.0±1.9	14.5±2.0	F=3.1	0.011*
ICB current			20					
ICB (>3–12months)			6					
Gambling (yrs)						12.1±7.4		
Gambling stopped (months)						1.8±2.7		
Drug abuse (yrs)					12.0±5.1			
Replacement therapy (yrs)					1.4±1.3			
LEU dose(mg/day)			934.2±407	740.1±369			t=1.8	0.072
PD patients currently using DA (N)			13/26	21/27			χ^2=5.1	0.024*
UPDRS on			16.2±10.6	21.1±9.0			t=1.7	0.09
UPDRS off			31.0±11.3	32.1±10.6			t=0.5	0.6
Improvement in UPRDS (%)			47.7	34.2				
Hypersexuality			12					
PG			13		3	23		
Casino games			-			15		
Sport betting			2			12		

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	CO-O	CO-Y	PD+ICB	PD−ICB	Addicts	Gamblers	t value, χ^2 and F-value	p-value
Stock markets			-			2		
Slot machines			8			3		
Bingo			4			-		
Scratch cards			2			-		
Punding			7					
Shopping			5					
Substance abuse			3(past)		13	1 (past)		
i.v. opiods					12			
i.v. heroin					4			
cannabis					3			
cocaine					1			
morphine					1			

UPDRS = Unified Parkinson's Disease Rating Scale; LEU = L-dopa equivalent units; DA = dopamine agonists. All values are mean ±SD. Significant differences are labeled with "*". Controls (CO-O, elderly controls; CO-Y, young controls), PD patients with (PD+ICB) and without (PD−ICB) impulsive compulsive behaviors, addicts (=illicit substance abusers) and pathological gamblers.

Table 2

Pair-wise comparisons between groups for number of draws (above) and for opposite color choices (below)

Group (χ^2, p-value)	PD−ICB	Illicit substance abusers	Gamblers	Controls
PD+ICB				
Draws	**27.1, p < 0.001**	0.38, p = 0.53	**13.9, p < 0.001**	**75.1, p < 0.001**
Opposite color	4.0, p = 0.044	**12.2, p < 0.001**	3.6, p = 0.055	**30.3, p < 0.001**
PD−ICB				
Draws		13.4, p < 0.001	0.45, p = 0.8	65.1, p < 0.001
Opposite color		29.4, p < 0.001	0.001, p > 0.97	15.0, p < 0.001
Addicts				
Draws			8.3, p=0.004	34.8, p < 0.001
Opposite color			24.0, p < 0.001	60.8, p < 0.001
Gamblers				
Draws				34.0, p < 0.001
Opposite color				13.9, p < 0.001

All p-values shown are uncorrected. Values less than 0.0125 (highlighted in bold) for the PD+ICB group are significant. All p-values in this and subsequent tables are for main effect of group.

Table 3

Pair-wise comparisons for WM performance(above) and for recalling the distractors (below)

Group (χ^2, p-value)	PD−ICB	Illicit substance abusers	Gamblers	Controls Old	Controls Young
PD+ICB					
WM	2.05, p = 0.15	**7.2, p= 0.007**	0.3, p > 0.58	4.3, p=0.038	0.74, p=0.38
Distractor	**22.8, p < 0.001**	0.6, p > 0.4	**12.2, p<0.001**	5.1, p = 0.023	0.002, p>0.9
PD−ICB					
WM		17.0, p< 0.001	0.44, p > 0.5	0.86, p > 0.35	0.1, p > 0.74
Distractor		10.1, p=0.001	59.8, p=0.001	2.4, p = 0.1	15.8, p<0.001
Addicts					
WM			9.3, p = 0.002	18.8, p< 0.001	10.1, p=0.001
Distractor			13.8, p < 0.001	1.6, p = 0.2	0.46, p=0.5
Gamblers					
WM				1.9, p = 0.16	0.78, p > 0.7
Distractor				24.3, p=0.001	8.2, p=0.004
Control Old					
WM					1.1, p > 0.28
Distractor					3.7, p=0.055

All p-values shown are uncorrected. Values less than 0.0125 are significant.