Title:

Specific effect of dopamine partial agonist on counterfactual learning: evidence from Gilles de la Tourette syndrome

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Acknowledgements

SP was supported by a Marie Sklodowska-Curie Individual European Fellowship (PIEF-GA-2012 Grant 328822). The study was supported by Association Francaise du Syndrome de Gilles de la Tourette.

Conflict of interest

SP declares no conflict of interest.

Abstract

The dopamine partial agonist aripiprazole is increasingly used to treat pathologies for which other antipsychotics are indicated, as it displays fewer side effects, such as sedation and depression-like symptoms, compared to other dopamine receptor antagonists.

Previously, we showed that aripiprazole may protect motivational function, by preserving reinforcement-related signals used to sustain reward-maximisation behaviour in a simple action-outcome learning task. However, the effect of aripripazole on more abstract facets of human reinforcement learning, such as learning from the hypothethical outcomes of alternative course of actions (counterfactual learning), is unknown.

To test the influence of aripripazole on counterfactual learning, we administrated to two groups of Gilles de la Tourette (GTS) patients (unmedicated and under aripiprazole mono-therapy) and to healthy subjects a reinforcement-learning task that involves both direct learning from obtained outcomes and indirect learning from previous outcomes.

We replicated a previous finding showing that aripiprazole does not affect direct learning. We also found that, whereas learning performance improved in presence of counterfactual feedback in both healthy controls and unmedicated GTS, this was not the case in aripiprazole-medicated GTS.

Our results suggest that, whereas aripiprazole preserves direct learning of action-outcome associations, it may impair more complex inferential processes such as counterfactual learning.

Introduction

Aripiprazole is a recently introduced antipsychotic medication with dopamine receptor partial agonist mechanisms (Potkin *et al*, 2003). In schizophrenia patients, it exhibited efficacy comparable to that of typical and atypical antipsychotics in the treatment of positive and negative symptoms, as well as in the prevention of relapse (Kane *et al*, 2002; Pigott *et al*, 2003). Its efficacy has also been demonstrated in other neurological disorders where antipsychotics are indicated, such as Gilles de la Tourette syndrome (GTS) (Kawohl *et al*, 2009; Neuner *et al*, 2012). Its tolerability is often considered superior compared to typical antipsychotics with fewer adverse side effects, such as extrapyramidal and metabolic syndromes (Citrome *et al*, 2014; Stroup *et al*, 2011). In GTS, Aripiprazole is effective for suppressing tics, while displaying a less severe side effect profile than dopamine receptor antagonists, with regard to motivational deficits, such as sedation and depressive reactions (Hartmann and Worbe, 2013). It is because of this advantageous cost-benefit trade-off, that it has become a widely prescribed treatment for schizophrenia and GTS.

Pharmacological studies in humans suggest that dopamine receptor antagonist-induced sedation and depressive states may be the consequence of blunting reward-related signals (Eisenegger *et al*, 2014; Frank *et al*, 2004). For instance, reward seeking behavior and reward prediction errors encoded in the ventral striatum were reduced by halopedidol administration in healthy volunteers (Pessiglione *et al*, 2006). In contrast, both functions were preserved in GTS patients medicated with aripiprazole (Worbe *et al*, 2011). These results are consistent with the idea that, distinctly from dopamine receptor antagonists, aripripazole preserves motivational functions via preserving reward-related signals.

However, in humans reinforcement learning (RL) is seldom solely based on learning from obtained outcomes (i.e. *factual* outcomes) (O'Doherty *et al*, 2015). In fact, human RL often makes use of more abstract inferential processes including learning from *counterfactual* outcomes (Coricelli and Rustichini, 2010; Coricelli *et al*, 2007). Previous neuroimaging studies demonstrated that, when available, subjects take into account counterfactual feedback and suggested that this form of learning could be underpinned by a dorsal prefrontal system (Boorman *et al*, 2011; Fischer and Ullsperger, 2013; Koechlin, 2014).

Here, to characterize the effect of aripiprazole on counterfactual learning, we administered a recently developed behavioural task that contrasts learning from obtained and hypothetical outcomes to aripiprazole-medicated and unmedicated GTS patients and matched healthy controls (Palminteri *et al*, 2015). GTS patients represented an ideal model for this investigation because in this population we have already shown the beneficial effects of aripiprazole, compared to a dopamine receptor antagonist, in *factual* learning, that is learning from obtained outcomes (as opposite to *counterfactual* leanring, which is learning from forgone outcomes) (Worbe *et al*, 2011). Futhermore, unlike many schizophrenic patients, GTS patients have relatively preserved cognitive efficiency (Leckman, 2002; Singer, 2005).

Material and methods

Participants

The ethics committee of the Pitié-Salpêtrière Hospital approved the study. All participants gave their written informed consent prior to the study, and the study was conducted in accordance to the Declaration of Helsinki (1964). Fifty-one consecutive patients were included in this study.

Patients were recruited from the GTS Reference Centre in Pitié-Salpêtrière, and were examined by a multidisciplinary team experienced in GTS (AH and YW). Tic severity was rated by the Yale Global Tic Severity Scale (Leckman *et al*, 1989). Inclusion criteria for the patients were as follows: age above 18, and confirmed diagnosis of GTS fulfilling the DSM-5 criteria. Aripiprazole-medicated GTS patients were on stable antipsychotic treatment for at least 4 weeks. Exclusion criteria were the co-occurrence of Axis I psychiatric disorders established by the Mini International Neuropsychiatry Inventory (Sheehan *et al*, 1998), including current major depressive episode, current or past diagnosis of psychotic disorder; autistic spectrum disorder; substance abuse aside from nicotine; or a neurologic or movement disorder other than tics.

Healthy volunteers were recruited by hospital-based advertisements. Inclusion criterion for healthy volunteers was an age over 18 years. Exclusion criteria were the same as for TS patients plus a personal history of tics and any concomitant treatment, except contraceptive pills for women.

Behavioral task

Subjects performed a probabilistic instrumental learning task adapted from previous imaging studies (Palminteri *et al*, 2009a, 2015). Subjects were first provided with written instructions, which were reformulated orally, if needed. Subjects first performed a short training session (16 trials), aimed at familiarizing them with the task's timing and responses. They then performed three learning sessions.

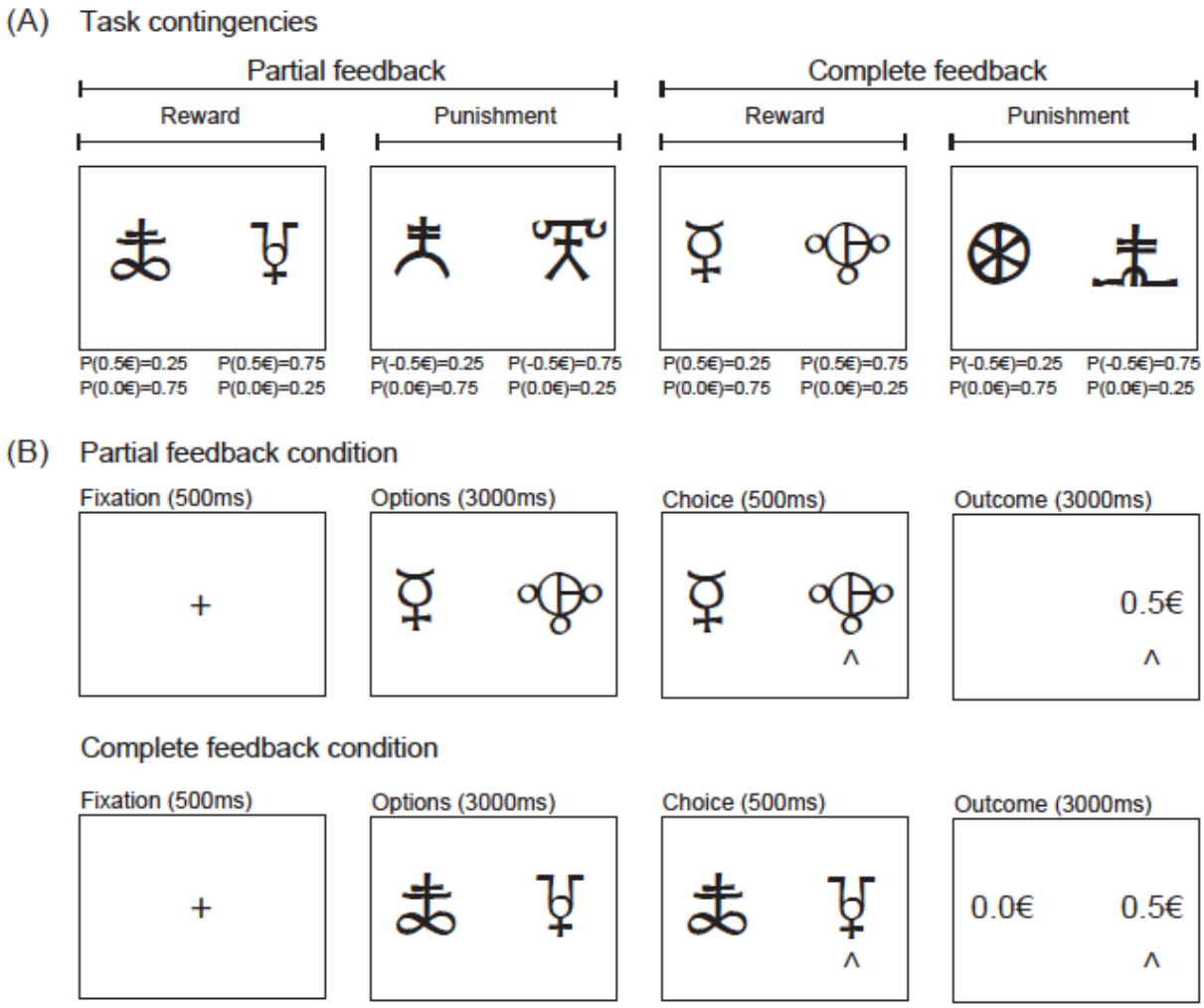

Figure 1: task. (A) Task contingencies and factoral design**.** The subolts to condition attribution was randomized across sujects. **(B)** Typical trials. A novel trial started after a fixation screen (500ms). Subjects were required to select between the two options by pressing one of the corresponding two buttons with their left or right index finger to select the leftmost or the rightmost option, respectively, within a 3000ms time window. After the choice window, a red pointer appeared below the selected option for 500ms. At the end of the trial the options disappeared and the selected one was replaced by the outcome ("+0.5€", "0.0€" or "-0.5€") for 3000ms. In the complete information contexts, the outcome corresponding to the unchosen option (counterfactual) was also displayed.

Options were abstract symbols taken from the Agathodaimon font. Each session contained eight novel options divided into four novel fixed pairs of options. The pairs of options were fixed so that a given option was always presented with the same other option. Thus, within each session, pairs of options represented stable choice contexts. Within sessions, each pair of options was presented 24 times for a total of 96 trials. The four option pairs corresponded to the four conditions (reward/partial, reward/complete, punishment/partial and punishment/complete), which were associated with different pairs of outcomes (reward contexts: winning 0.5€ versus nothing; punishment contexts: losing 0.5€ versus

nothing) and a different quantity of information being given at feedback (partial and complete). In the partial feedback contexts, only the outcome about the chosen option was provided, while in the complete feedback contexts both the outcome of the chosen and the unchosen option were provided (**Figure 1A**). Within each pair, the two options were associated to the two possible outcomes with reciprocal probabilities (0.75/0.25 and 0.25/0.75). Subjects were informed that the aim of the task was to maximize their payoff, and that only factual (and not counterfactual) outcomes counted. Between cues the outcome probability was independent on a trial-by-trial basis, even if it was anti-correlated on average. Thus, in a complete feedback trial, subjects could observe the same outcome from both cues on 37.5% of trials and different outcomes from each cue on 62.5% of trials.

Pairs of options were presented in a pseudo-randomized and unpredictable manner to the subject (intermixed design). During each trial, one option was randomly presented on the left and one on the right side of a central fixation cross (**Figure 1B**). The side in which a given option was presented was also pseudo-randomized, such that a given option was presented an equal number of times in the left and the right of the central cross. We also acquired post-learning assessmenf of option preference. Data from this post-learning test were lost due to technical problems in two subjects from the «aripiprazole » group and we therefore decided not to include this measure. Importantly, analysis of the post-learning test confirmed the conclusions derived from the learning test analysis (i.e. of a reduction of counterfactual learning, following dopamine partial agonist treatment).

Statistical analysis

From the learning task we extracted accuracy (i.e. the « correct » choice rate) as a dependent variable. A « correct» response was to choose the most rewarding option in the reward contexts, or the less punishing option in the « punishment » contexts. Statistical effects were assessed using repeated measures ANOVA with group (« Controls », « Unmedicated », and « Aripiprazole ») as between-subjects factor and trial (1:24), feedback valence (reward seeking vs. punishment avoidance) and feedback information (partial vs. complete feedback) as within-subject factors.

Post hoc comparisons were performed using Student's t-tests, two sample t-tests when comparing groups, one sample t-test when comparing group value to zero. These t-tests

were two-sided except when a clear assumption justified a one-sided test. A Welch-Satterthwaite approximation was used when variance was not equal across groups (Reference). Correlations, in particular the correlation between treatment dose and accuracy was computed using linear regression. Significativity of the slope of the linear regression compared to zero was assessed using a t-test. Significance level was set at 5%.

All statistical analyses were performed using the R statistical software.

Results

Demographic and psychometric data

As shown in **Table 1**, three groups of subjects did not differ in demographic properties or in any of the psychometric measures (all p>0.2).

Table 1: Demographic characteristics and psychometric scales for participants by treatment group. The p-values (two sample t-test) correspond to the comparison between Unmedicated and Aripiprazole patients (mean±s.e.m.).

	Controls	**Unmedicated**	**Aripiprazole**	
	mean	mean	mean	p
N	20	17	14	
Gender (F/M)	9 / 11	4 / 13	5 / 9	0.26
Age	32.35±13,36	30.76±10.33	32.07±11.52	0.23
Years of Study	14.40±1.70	13.24±1.95	12.79±2.26	0.30
AgeOnset	-	6.00±1.49	9.42±3.00	0.49
YGTSS	-	43.13±17.21	34.56±14.05	0.67

Behavioural results

A preliminary ANOVA evaluating accuracy as a function of trial, feedback information, feedback valence and group (Aripiprazole-medicated and Unmedicated GTS, controls) showed that there was a significant main effect of group ($F(2,4864)=14.5$. $p<0.001$) , a significant main effect of trial number ($F(1,4864)=46.4$. $p<0.001$), a significant main effect of feedback information ($F(1,4864)=23.7$. $p<0.001$), but no main effect of feedback valence ($F(1,4864)=0.8$. $p>0.3$). Valence was therefore excluded from the subsequent ANOVA analysis. Post-hoc tests confirmed that accuracy was not affected by valence in either of the groups (all p>0.4).

The final ANOVA evaluating accuracy as a function of trial, feedback information, and group showed that there was a significant main effect of trial number on correct choice rate ($F(1,2432)=41.1$. $p<0.001$), indicating that accuracy improved over learning (**Figure 2A**). In addition, there was a significant main effect of feedback information ($F(1,2432)=21.0$ $p<0.001$) and of group ($F(2,2432)=12.9$. $p<0.001$), with a significant interaction between group and feedback information ($F(2,2432)=13.6$. $p<0.001$), indicating that accuracy

counterfactual feedback did not positively modulate the accuracy similarly in the three groups.

We defined the « countrefactual gain » as the difference in accuracy between the complete and the partial feedback conditions. ANOVA evaluating Counterfactual gain as a function of group and trial showed a significant main effect of group ($F(2,1216)=17.9$, $p<0.001$) indicating that the groups benefited differently from counterfactual information. There was no main effect of trial ($F(1,1216)=1.00$, $p=0.3$), indicating that the benefit from counterfactual information was present along the whole duration of the experiment.

Post-hoc tests showed that accuracy in the complete condition was significantly higher than accuracy in the partial condition in both the Controls and the Unmedicated GTS ($t(19)=-2.6$, $p<0.05$, and $t(16)=-2.3$, $p<0.05$ respectively), but not in the Aripiprazole GTS group ($t(13)=0.151$, $p=0.882$) (**Figure 2B**). The average counterfactual gain was significantly higher in the Controls group and in the Unmedicated group than in the Aripiprazole group (8.3% Controls versus 0.3% Aripiprazole, $t(31.5)=2.2$, $p<0.05$; t-test 10.5% Unmedicated versus 0.3% Aripiprazole GTS, $t(23.3)=2.1$, $p<0.05$). There was no difference in counterfactual gain between the Controls and unmedicated patients ($t(29.3)=-0.4$, $p=0.70$) (**Figure 23**).

In addition, in the Aripiprazole GTS group, we found a signifiant correlation between treatment dose and accuracy in the complete information conditions, indicating that the higher the dose of atypical antipsychotic medication received, the lower the accuracy in the complete condition ($t(11)=-2.6$, $p<0.05$).

We performed a number of controls ensuring that accuracy and counterfactual gain was independent from other clinical factors. We found that the counterfactual gain was not explained by disease severity, assessed by the YGTSS scale, or by disease duration (all $p>0.6$). We also checked for differences in reaction times and we detected no significant difference when comparing aripiprazole treatment to the other groups (all $p> 0.3$; **Table 2**)

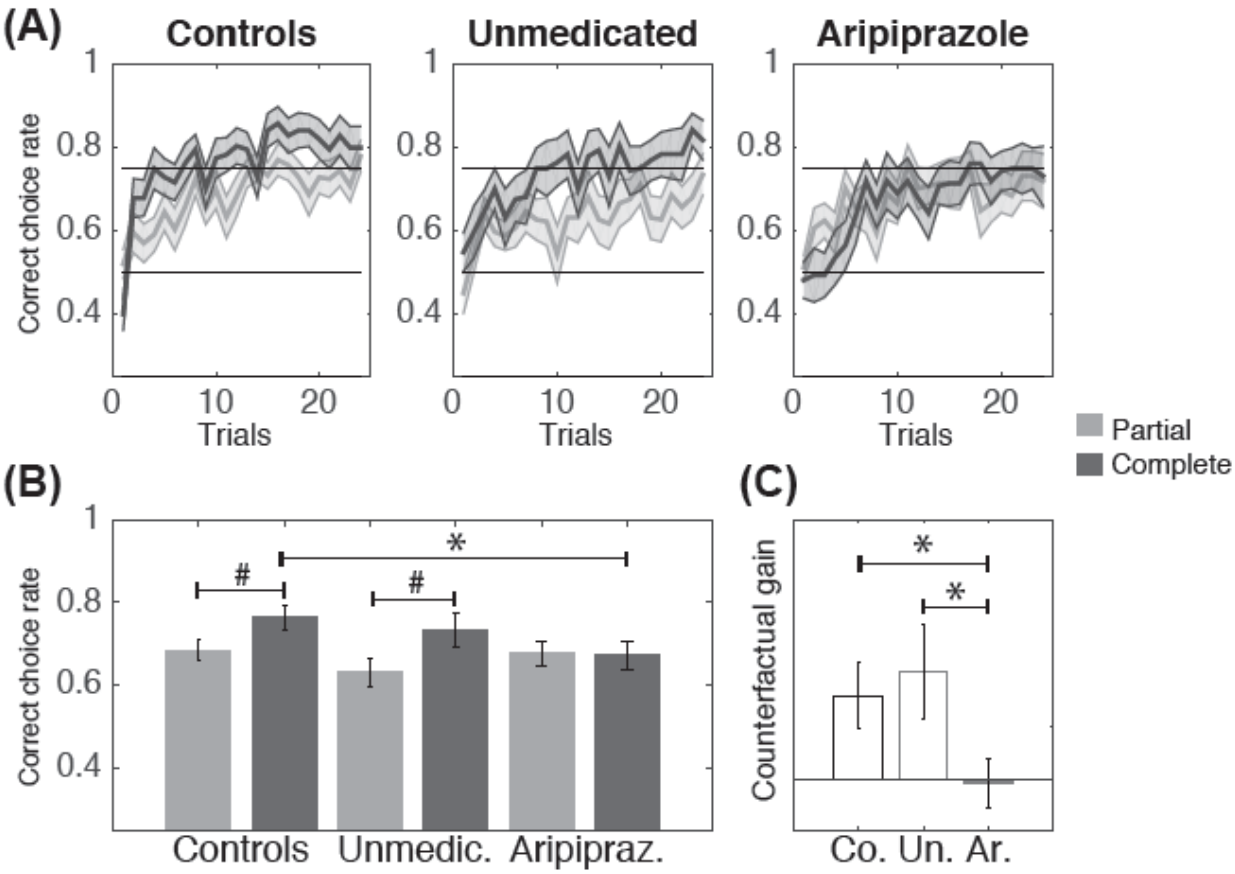

Figure 2: **(A)** Learning curve as a function of feedback information and group. The bold lines represent tha trial-by-trial averages. The shaded areas between the thin lines represent s.e.m. values. Light and dark grey represent partial and complte feedback conditions, respectively. (**B**) Average performance averaging across the 24 trials. (**C**) Average « counterfactual gain » (complete minus partial accuracy) (Co. = controls; Un. = Unmedicated; Ar. = Aripiprazole). #p<0.05 one-sample t-test. * p<0.05 two-sample t-test.

Table 2: average behavioral data (mean±s.e.m.).

	Accuracy (correct choice rate)				**Reaction times (seconds)**			
	Rew./Par.	**Pun./Com.**	**Pun./Par.**	**Pun./Com.**	**Rew./Par.**	**Pun./Com.**	**Pun./Par.**	**Pun./Com.**
Controls	0.68±0.04	0.76±0.04	0.68±0.03	0.77±0.04	1.16±0.04	1.21±0.06	1.37±0.06	1.27±0.06
Unmedic.	0.61±0.05	0.74±0.05	0.65±0.04	0.72±0.04	1.14±0.06	1.16±0.06	1.29±0.06	1.28±0.07
Aripipraz.	0.66±0.05	0.64±0.04	0.69±0.03	0.70±0.05	1.15±0.06	1.16±0.06	1.28±0.06	1.27±0.07

Discussion

Using a probabilistic learning paradigm, with factual (where subjects were informed only about the result of the chosen outcome) and counterfactual (where subjects were also informed about the result of the unchosen outcome) conditions in healthy controls and aripiprazole-medicated and unmedicated GTS, we showed a specific effect of aripiprazole on counterfactual learning in the absence of any effect on factual learning.

All subjects significantly performed above chance level in the partial feedback conditions and accuracy was not different across groups. As previously shown, control subjects had higher accuracy in the complete, compared to the partial, feedback condtions (Palminteri *et al*, 2015, 2016). However, in GTS patients, counterfactual learning was affected by medication status: unmedicated patients behaved similarly to healthy controls, whereas aripiprazole-medicated patients did not improve their performance in presence of counterfactual feedback.

Counterfactual learning, as implemented in our task, requires at least two component processes: a 'peripheral' process, which corresponds to the fact that complete feedback conditions mobilize additional attentional resources; and a 'central' process, which corresponds to integrating hypothetical prospects ('counterfactuals') in reinforcement learning (Baird and Fugelsang, 2004).

Was the effect of aripiprazole on counterfactual learning the hallmark of a specific impairment in counterfactual reasoning or the consequence of reduced attention? Against a non-specific 'peripheral' effect, our data show that baseline performance (as measured in the partial feedback conditions) was not different comparing the unmedicated and the aripiprazole groups. If anything, average accuracy in the partial feedback conditions was numerically higher in the aripiprazole, compared to the unmedicated group (67.5% vs. 63.0%). Also against the idea of a general attentional decrease, we found that reaction times were not different between groups.

The preserved ability to learn from factual outcomes replicates previous work by Worbe and colleagues showing that aripiprazole did not affect probabilistic reward learning in TS patients (Worbe *et al*, 2011). These findings strikingly contrast with the robust observation that dopamine antagonists blunt reward-related learning and performance (Eisenegger *et*

al, 2014; Frank *et al*, 2004; Pessiglione *et al*, 2006) and is consistent with a corpus of research indicating preserved motivation in subjects treated with aripiprazole. The reduction of counterfactual learning observed in the Aripiprazole GTS group is also consistent with previous studies indicating no improvement in cognitive function, as measured by the Brief Assessment of Cognition in Schizophrenia, as a result of dopamine partial agonist treatment (Désaméricq *et al*, 2014; Mishara and Goldberg, 2004; Yasui-Furukori *et al*, 2012). Reduced counterfactual learning has been reported in disorders characterised by higher impulsivity, such as nicotine addiction (Chiu *et al*, 2008). It may therefore be argued that this learning deficit may contribute to the increased likelihood of impulse control disorders, such as pathological gambling, in aripiprazole-medicated patients (Moore *et al*, 2014) as well as the observation that aripiprazole increases cigarette smoking (Lofwall *et al*, 2014).

Previous studies suggest that disrupted reinforcement learning may significantly contribute to GTS symptoms (Maia and Frank, 2011; Palminteri and Pessiglione, 2013). Assuming that positive and negative prediction errors are represented by phasic fluctuations of dopaminergic transmission, we previously found that unmedicated GTS reinforcement learning was consistent with a functional hyperdopaminergia, both in terms of enhanced reward (Palminteri *et al*, 2011) and reduced punishment learning (Palminteri *et al*, 2009b). These findings were obtained when reward-outcome contingencies were deterministic and unconscious, as measured by post-test assessments of cue visibility and stimulus reward associations, with a task shown to rely specifically on the ventral striatum (Pessiglione *et al*, 2008). On the contrary, our present results were obtained with a probabilistic instrumental learning task using perfectly visible (theredore conscicous) cues, with a task recruiting both cortex (namely the medial prefrontal cortices and the insula), as well as the ventral striatum) (Palminteri *et al*, 2015). In the present study we found that unmedicated GTS patients performed equally well in the reward-seeking compared to the punishment-avoidance conditions.

Taken together, our current and previous findings might suggest that in GTS the eccessive positive reinforcement occurs for implicit/unconscious, as opposite to explicit/conscious, learning process, which could therefore be supported by different neural substrates (subcortical vs. cortical). This idea is also consistent with recent findings that indicated enhanced habitual (implicit) to the detriment of goal-directed (explicit) learning and

decision-making, in GTS patients (Delorme *et al*, 2016).

We demonstrated a negative effect of aripiprazole on counterfactual learning in a population of medicated GTS patyients. At this stage it is unclear wheather this finding could be generalized to other clinical populations and most notably schizophrenic patients, in which the treatment with Aripiriprazole is becoming increasingly popular. Futher research is needed to address this question.

Aripiprazole has multiple affinities with both dopamine and serotonin receptors (Potkin *et al*, 2003). These neuromodulatory systems have been associated with both automatic/reflexive and deliberative/reflective reinforcement processesing, which in our task could be mapped into factual and counterfactual leanring (Doll *et al*, 2016; Sharp *et al*, 2016; Worbe *et al*, 2016; Wunderlich *et al*, 2012). A recent study investigating counterfactual learning under regimen of dieteray depletion of serotonine and dopamine/noradrenal precursors led to negative results (Tobia *et al*, 2014). Future studies with spefic pharmacological agents, including D2 antagonists, are required to determine if the effect of Aripiprazole on counterfactual learning is mediated by its dopaminergic or its serotonergic affinity (or a combination of both).

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