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Neural correlates and role of medication in reactive motor impulsivity in Tourette disorder

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Abstract

Abnormality of inhibitory control is considered to be a potential cognitive marker of tics in Tourette disorder (TD), attention deficit hyperactivity disorder (ADHD), and impulse control disorders. The results of the studies on inhibitory control in TD showed discrepant results. The aim of the present study was to assess reactive inhibitory control in adult TD patients with and without antipsychotic medication, and under emotional stimulation (visual images with positive, neutral and negative content).

We assessed 31 unmedicated and 19 medicated TD patients and 26 matched healthy controls using the stop signal task as an index of reactive motor impulsivity and emotional stimulation with the aim to increase impulsivity. We performed a multimodal neuroimaging analysis using a regions of interest approach on grey matter signal, resting-state spontaneous brain activity and functional connectivity analyses.

We found a higher reactive motor impulsivity in TD patients medicated with antipsychotics compared to unmedicated TD patients and controls. This propensity for reactive motor impulsivity in medicated TD patients was not influenced by ADHD or emotional stimulation. Neuroimaging results in medicated TD patients suggested that reactive motor impulsivity was underpinned by an increased grey matter signal from the right supplementary motor area and inferior frontal gyrus; decreased resting-state spontaneous activity of the left putamen; higher functional connectivity between the inferior frontal gyrus and the superior temporal gyri (bilaterally); lower functional connectivity between the cerebellum and the right subthalamic nucleus.

Taken together, our data suggested (i) a deficit in reactive motor impulsivity in TD patients medicated with atypical antipsychotics that was unrelated to ADHD and (ii) that motor impulsivity was underpinned by structures and by functional connectivity of the fronto-temporo-basal ganglia-cerebellar pathway.

Keywords: Tourette disorder; Motor impulsivity; Motor inhibition; Aripiprazole; Stop signal task.

1. Introduction

Tourette disorder (TD), whose hallmark is tics, is also frequently associated with comorbidities such as attention deficit hyperactivity (ADHD), impulse control and obsessive-compulsive disorders (M. C. Frank, Piedad, Rickards, & Cavanna, 2011; Hirschtritt et al., 2015; Martino, Ganos, & Pringsheim, 2017; Morand-Beaulieu et al., 2017).

Identification of cognitive endo-phenotypes of this syndrome and associated psychiatric comorbidities has been a focus of research over the past few years. For instance, putative abnormality of inhibitory control is considered to be a promising marker of tics (Jackson, Draper, Dyke, P  p  s, & Jackson, 2015), ADHD (Ma, van Duijvenvoorde, & Scheres, 2016), and impulse control disorders (M. C. Frank et al., 2011). However, while the association between TD and impaired inhibitory control might be clinically relevant, this question remains a matter of debate (Jackson et al., 2015), as highlighted in the largest up-to-date meta-analysis on this topic: “*The puzzling question of inhibitory control in Tourette syndrome*” (Morand-Beaulieu et al., 2017). According to the results of this meta-analysis, TD seems to be associated with motor impulsivity with a small to medium size effect. This association was also task-dependent and influenced by psychiatric medication and comorbidities (especially ADHD). This latter effect, to the best of our knowledge, was directly assessed in only one study, which found that motor inhibition in TD was influenced by both comorbid ADHD and antipsychotic medication (Sallee, Sethuraman, & Rock, 1994). Notably, there has been no previous assessment on the effect Aripiprazole, one of the most widely used antipsychotics for the treatment of tics in TD (Pringsheim et al., 2019), has on motor impulsivity.

In TD, motor impulsivity has been studied using various tasks that measure inhibitory control such as GO/NO-GO, Stroop, and Continuous Performance tasks (for a review, see (Morand-Beaulieu et al., 2017)). However, these tasks mainly measure proactive inhibition processes (engaged before the response). A different way to assess motor impulsivity is to measure reactive inhibition processes, which requires a participant to stop an already initiated action. This is frequently assessed by using the Stop Signal Task (SST; Schall, Palmeri, & Logan, 2017). On the neural level, this task is underpinned by an interplay of the direct, indirect and hyper-direct cortico-basal ganglia pathways; dysfunction of which was also suggested to be present in TD (Martinez-Torres, Hariz, Zrinzo, Foltynie, & Limousin, 2009; Worbe et al., 2015; Yael, Vinner, & Bar-Gad, 2015).

Several studies were performed on reactive inhibition in TD using the SST and revealed that, on the neural level during motor inhibition, TD patients showed increased activity in the right inferior parietal cortex and supplementary motor area (SMA) and decreased activity in the dorsal premotor cortex (Fan et al., 2018; Ganos et al., 2014); decreased P300 amplitude and increased error processing, as well as increased error-related negativity amplitude and decreased error positivity amplitude were present in the left cerebellum, right mesencephalon, right insula and SMA (Schüller et al., 2018). Moreover, one study showed that SMA activity during successful stops trials also correlated with tics frequency, suggesting that this cortical area could mediate successful inhibition during the task, as well as the inhibition of tics (Ganos et al., 2014). However, none of these studies found significant behavioural differences in reactive inhibition between TD patients and controls. It should be noted that some of these studies did not account for patients taking antipsychotic medication (Fan et al., 2018; Ganos et al., 2014; Johannes et al., 2001; Ray Li, Chang, Hsu, Wang, & Ko, 2006), while others excluded medicated patients entirely (Mancini et al., 2018), or stopped medication only 24 hours prior to assessment (Schüller et al., 2018).

In addition, TD patients are highly sensitive to emotional context, which could increase tics manifestation (Conelea & Woods, 2008; Leckman, Bloch, Scahill, & King, 2006; Neuner et al., 2010; Rae et al., 2018). Some studies reported that TD patients have an impairment of emotional processing such as emotion attribution (Devinsky, Bear, Moya, & Benowitz, 1993; Drury et al., 2012), which could be explained by a higher sensitivity of several brain territories, especially the amygdala, to emotionally charged stimuli (Neuner et al., 2010). Interestingly, emotional context was shown to interfere with the efficacy of inhibitory control in both proactive and reactive inhibition behavioural paradigms (Rebetez, Rochat, Billieux, Gay, & Van der Linden, 2015).

Using a modified version of the SST, the aim of the present study was to assess reactive motor impulsivity in adult TD patients with and without antipsychotic medication. We also addressed the question of the role emotions play on inhibitory capacity, hypothesising that emotional context would impair the TD patients' capacity to inhibit their ongoing actions.

2. Material and methods

Here we report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, all manipulations, and all measures in the study.

2.1. Subjects

63 TD patients and 34 gender, age and educational level matched healthy controls (HC) were included in the study in an approximate 2:1 ratio. TD patients were recruited through the Tourette reference center at the Pitié-Salpêtrière Hospital in Paris. All participants gave their written consent to participate in the study, and obtained a financial compensation (50€ per subject plus transport compensation for patients). The study was approved by the ethics committee (CCP16163/C16-07) and preregistered prior to the research being conducted on ClinicalTrials at <https://clinicaltrials.gov/ct2/show/NCT02960698>. The study procedures did not deviate from the preregistered protocol. Following data quality inspection (i.e. incomplete or non-exploitable behavioural or neuroimaging data), 13 TD patients and 8 HC were excluded. The final sample was 26 HC and 50 TD patients, where 31 TD patients were unmedicated (TD-Unmed group) and 19 were taking antipsychotic medication (TD-Med group).

For all subjects, the exclusion criteria was an incapability or unwillingness to give consent for the study, evidence of either present or prior substance addiction (excluding nicotine; recreational cannabis use was allowed), a past or present history of psychosis, and a presence of neurological symptoms other than tics for TD, including childhood tics and known psychiatric disorders for healthy controls.

All participants were assessed for psychiatric disorders (Mini International Neuropsychiatric interview, MINI; Sheehan et al., 1998), impulse-control disorders (Minnesota Impulse Disorders Interview, MIDI; Grant, 2008), impulsivity (using the Barratt Impulsivity scale, BIS-11; Patton, Stanford, & Barratt, 1995), and anxiety with the State-Trait Anxiety Inventory (STAI; Hamilton, 1959). Yale Global Tics Severity Scale (YGTSS; Leckman et al., 1989) was used to assess tics severity, and the presence of psychiatric co-morbidities was evaluated using patient medical records and psychiatric evaluations prior to their inclusion in the study.

2.2. Emotional Stop Signal Task

We used the computerised emotional Stop Signal Task (ESST; **Fig.1** panel A; Hare, Tottenham, Davidson, Glover, & Casey, 2005; Logan, Cowan, & Davis, 1984) implemented in the e-prime software (Schneider, Eschman, & Zuccolotto, 2012). Each trial started with a fixation cross followed by the presentation of an image during 500msec. 135 previously used images (Mathieu et al., 2014) were selected from the international affective picture system

and divided into 3 groups: neutral, positive and, negative images. The images containing emotional content (positive or negative) were selected based on their moderate emotional intensity and arousal. For a total of 405 trials, each image was presented 3 times.

Following the image presentation, two categories of trials were performed, a GO-trial (67% of all the trials) or a STOP-trial (33% of all the trials). During the GO-trials, a GO-cue (a green circle) was presented after variable delay (1000msec – 2000msec), and participants were instructed to press the enter key of the keyboard as quickly as possible. During the STOP-trials, the GO-cue was also presented but was followed by the presentation of a STOP-cue (a red cross) after a specific delay (stop-signal delay, SSD) and participants were instructed to withhold their response. For the first STOP trial, the SSD was fixed at 250msec and then adjusted by increments or decrements of 25msec dependent on subject performance: increased if the subject successfully inhibited their response and diminished if the subject failed to inhibit their response.

This task allows to identify the time necessary for action inhibition, called the Stop-signal reaction time (SSRT). This ability to inhibit an already initiated action could be described as a race between the go and stop systems (Logan et al., 1984). The first of two systems reaching a specific threshold wins the race and performs (go winner) or inhibits (stop winner) an action. Indeed, the SSRT is a measure of reactive motor impulsivity. We estimated SSRT using the integration method (Logan et al., 1984), which was recently recommended (Verbruggen et al., 2019). Two different SSRT were calculated for each participant according to the emotional condition (low for neutral pictures and medium for both positive and negative images).

In addition, data inspection was performed to assess inhibition curves related to the SSD. Participants were excluded from analyses if the curves did not reach a proportion of 20% failed inhibition, and if they were incoherent (i.e. no increase of failed inhibition when the SSD increased).

Lastly, we performed 3 validation subtasks. Two subtasks were used to identify if images were correctly perceived according to their valence (i.e. positive, neutral and negative), and their intensity (i.e. weak to high) using 10 points Likert scales. One subtask was performed to assess whether participants correctly paid attention to the images using a presentation of viewed and non-viewed images. Participants were instructed to report whether or not they had seen the image during the task.

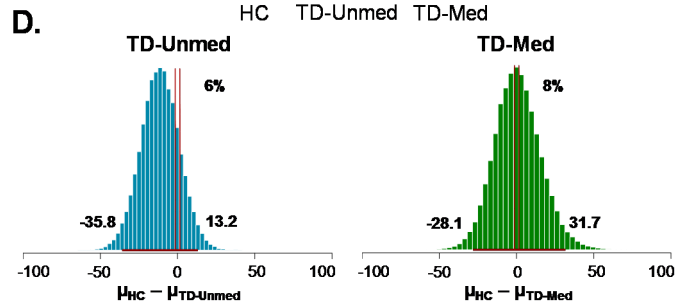
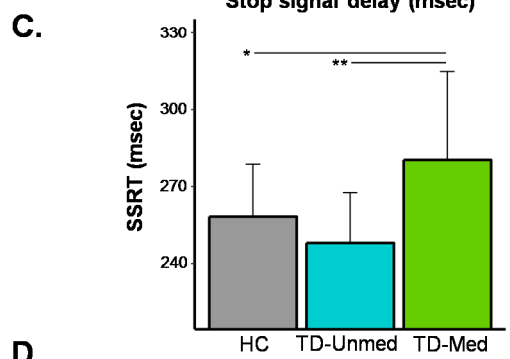
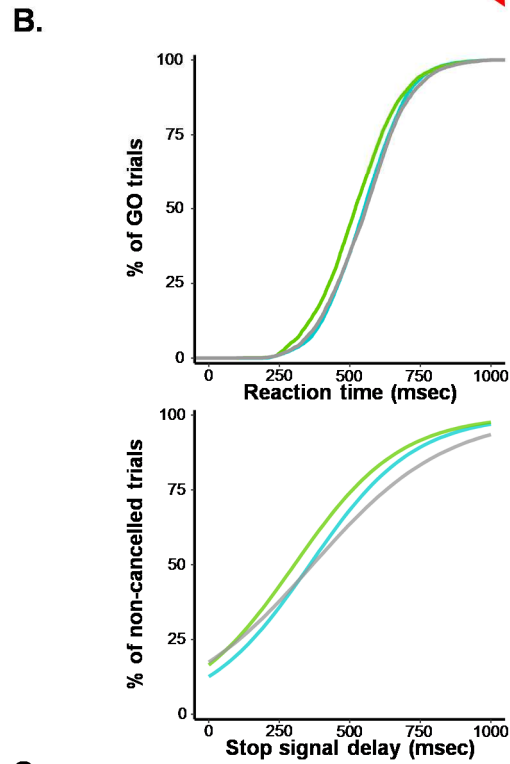
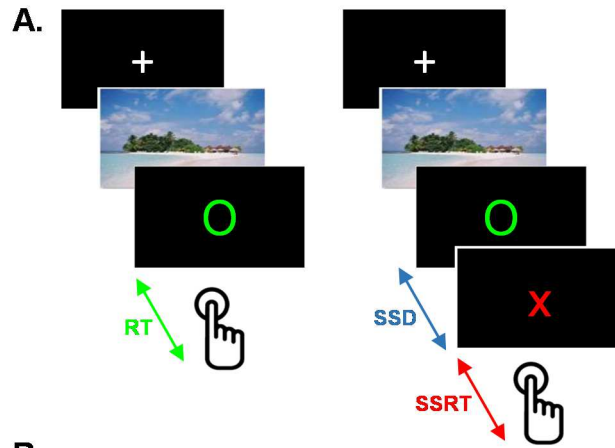


Fig.1. A) Emotional Stop Signal Task experimental paradigm for both GO and STOP trials; B) Behavioural outcomes for each group; C) Stop-signal reaction time comparisons for each group; D) Bayesian t-tests comparing SSRT between HC and TD patients for the emotional condition. The top percentages represent the results part in the ROPE; the bottom numbers represent the 95% HDI. The color-coding is the same for part B, C and D of the figure.

μ : Mean; HC: Healthy controls; HDI: Highest density interval; ROPE: Region of practical equivalence; RT: Reaction time; SSD: Stop-signal delay; SSRT: Stop-signal reaction time; TD-Med: Medicated patients; TD-Unmed: Unmedicated patients.

2.3. Behavioural statistical analyses

Behavioural analyses were conducted using the R software (R Core Team, 2013) as follows: i) Demographics and clinical data were analysed using two-samples t-tests or Anova for continuous variables and χ^2 for categorical variables; ii) ESST validation tasks (images valence, arousal and recognition) were analysed using repeated measures Anova followed by Bonferroni corrected post-hoc tests when appropriate; iii) eSST main task (i.e., SSRT) was analysed using repeated measures Anova followed by post-hoc tests when appropriate including effects of groups, comorbidities and images valence (neutral vs. emotional [positive and negative together]). In addition, we performed Bayesian t-test analyses to compute the posterior probability of the difference between HC and patients regarding the SSRT using a region of practical equivalence (ROPE) set at 3% (from -1.5% to +1.5%) and a 95% highest density interval (HDI); iv) Lastly, SSRT were correlated to demographics and clinical data using Pearson's correlation corrected by permutations (n=5000). Also, we added correlations using bootstrapping based on 10,000 replications, with and without one marginal value. No part of the analyses was preregistered prior to the research being undertaken. Lastly, we reported Cohen's *d* effect size for all results.

2.4. Neuroimaging data acquisition and analyses

Neuroimaging data were acquired on 3T MRI scans (Siemens Prisma, Germany) with a 64-channel head coil. Two sequences were acquired: a T1-weighted image (MP2RAGE, TR=5s, TI=700/2500ms, fov=256, 1mm isotropic, Ipat acceleration of 3) and a resting-state functional MRI (rs-fMRI) of 11min duration. Rs-fMRI data were acquired with the eyes opened: the subjects were asked to fixate on a cross during the sequence acquisition, which was monitored

by an eye tracker. Multi-echo echo-planar imaging (EPI) sequences were performed with a multi-slice, multi-echo acquisition scheme (TR=1.9s, TE=17/36/56ms, Ipat acceleration factor 2, Multi-band 2, isotropic voxel size 3mm, dimensions=66x66 in plane x 46 slices).

T1-weighted images were first denoised (O'Brien et al., 2014) and pre-processed (segmentation, normalisation to Montreal Neurological Institute space and smoothing at 10mm) using the Computational Anatomy Toolbox (<http://www.neuro.uni-jena.de/cat/>) extension from SPM12 (www.fil.ion.ucl.ac.uk/spm/).

EPIs were processed with the MEICA toolbox (www.github.com/ME-ICA/me-ica/). This toolbox implements standard pre-processing steps: slice timing correction and realignment to the first volume driven by the first echo, coregistration to the anatomic volume. A single warp was applied to combine realignment and coregistration. Then, we performed a principal component analysis to reduce the dimensionality of the dataset by removing thermal noise, and an independent component analysis decomposition to separate BOLD (blood-oxygen-level dependent) from non-BOLD components based on the echo time dependence of the BOLD component (Kundu et al., 2013; Kundu, Inati, Evans, Luh, & Bandettini, 2012). After the independent component analysis, we obtained a dataset where thermal noise and physiological noise such as movements, respiration artefacts, and cardiac artefacts were removed. Prior to analysis, to control for movements artefacts, we performed statistical analyses on movements metrics and found no group (HC vs. TD) difference for the mean framewise displacement ($p=0.89$), the standard deviation of the framewise displacement ($p=0.92$), the maximal value of framewise displacement ($p=0.93$) and the root mean square values ($p=0.97$). Finally, we normalized the dataset using the flow field generated by the T1 processing from CAT12.

We performed correlation analyses of behavioral performance only on the group of patients presenting motor inhibition impairment. For both T1 and rs-fMRI analyses, we generated regions of interest (ROI) using the WFU-Pick-Atlas toolbox implemented in SPM12. ROI were selected based on the previous literature on motor inhibition processes (Bari & Robbins, 2013; Jahanshahi, Obeso, Rothwell, & Obeso, 2015) and included, bilaterally, the primary motor cortex (M1), the supplementary motor area (SMA), the inferior part of the frontal gyrus (IFG), the putamen and the caudate, the pallidum, and the subthalamic nuclei (STN; **Fig.2** left panel).

For the ROI we extracted using the Marsbar toolbox (i) the grey matter mean signal from the T1; (ii) the mean Z-standardized fractional amplitude of low-frequency fluctuation, which represents the spontaneous brain activity, from the rs-fMRI. The extracted signal from both

MRI modalities was correlated with SSRT using permutations correlations ($n=5000$) and with a threshold for significance fixed at $p \leq 0.05$. In addition, we computed brain connectivity from the study ROI to all AAL atlas regions (120 predetermined brain regions (Tzourio-Mazoyer et al., 2002)). We extracted the mean connectivity among the ROI and AAL regions if the mean connectivity was significantly different from 0 (one sample permutations t-test [$n=5000$]; threshold at $p \leq 0.01$) and then performed correlation analysis with SSRT (threshold at $p \leq 0.01$ following permutations [$n=5000$]).

2.5. Data availability statement

The conditions of our ethics approval do not permit public archiving of individual anonymised raw data. Readers seeking access to the data should contact the lead author Dr. Worbe. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Specifically, requestors must obtain a specific authorization from the ethics committee. Regarding E-prime and R scripts for experimental task and statistical analyses, they are available at <https://osf.io/k48c9/>.

3. Results

3.1. Participants characteristics

As shown in Table.1, both patients groups had higher scores on MIDI and STAI scales ($p < 0.001$; MIDI: HC vs. TD-Med $d=1.53$ and HC vs. TD-Unmed $d=1.38$; STAI: HC vs. TD-Med $d=1.62$ and HC vs. TD-Unmed $d=0.73$) and TD-Meds had a higher STAI score than TD-Unmed ($p < 0.05$; $d=0.85$). In addition, **Table.2** highlights that the main part of our TD-Med patients was taking Aripiprazole (15/19).

Table.1. Demographics and clinical data.

	HC (n=26)	TD-Unmed (n=31)	TD-Med (n=19)	p-value
Gender (M/F)	18/8	26/5	14/5	0.41
Age (y)	32 ± 10.7	30.4 ± 11.4	31 ± 9.4	0.85
Years of education	14.1 ± 2.9	14.4 ± 2.5	14 ± 2.9	0.88
MIDI	0.2 ± 0.4	1.4 ± 1.2*	1.5 ± 1.3*	<0.001
BIS-11	59.3 ± 9.7	64.8 ± 10.4	66.6 ± 12.3	0.054
STAI	63.3 ± 15.7	75.3 ± 16.9**	89.7 ± 17.1**	<0.001
YGTSS (/50)	-	15.9 ± 7.7	17.1 ± 5.8	0.55
ADHD (%)	0	38.7	26.3	0.55
OCD (%)	0	12.9	10.5	1

ADHD + OCD (%)	0	9.7	5.2	0.98
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*: Significantly different from HC; [‡]: Significant differences between TD-Unmed and TD-Med; ADHD: Attention deficit hyperactivity disorder; BIS-11: Barratt Impulsivity scale; HC: Healthy controls; MIDI: Minnesota Impulse Disorders Interview; OCD: Obsessive-compulsive disorder; STAI: State-Trait Anxiety Inventory; TD-Med: Medicated patients; TD-Unmed: Unmedicated patients; YGTSS: Yale Global Tics Severity Scale.

Table.2. Medication of the TD-Med group.

Subject	Third generation neuroleptics	Second generation neuroleptics	Typical neuroleptics	Others
1			Pimozide (0.25mg/d)	
2	Aripiprazole (2.5mg/d)			
3	Aripiprazole (5mg/d)			
4	Aripiprazole (5mg/d)			
5		Risperidone (2mg/d)		Topiramate (100mg/d)
6	Aripiprazole (10mg/d)			
7	Aripiprazole (5mg/d)			
8	Aripiprazole (5mg/d)			
9	Aripiprazole (2.5mg/d)			
10	Aripiprazole (5mg/d)			
11	Aripiprazole (5mg/d)			Fluoxetine (20mg/d)
12	Aripiprazole (5mg/d)			
13	Aripiprazole (1.25mg/d)			
14			Haloperidol (0.5mg/d)	Escitalopram (10mg/d)
15	Aripiprazole (5mg/d)			
16	Aripiprazole (15mg/d)			Mianserin (60mg/d) Fluoxetine (40mg/d) Prazepam (10mg/d)
17	Aripiprazole (5mg/d)			
18		Risperidone (1mg/d)		
19	Aripiprazole (10mg/d)			

3.2. ESST results

Anova analysis showed a main effect of group ($F_{(2;144)}=4.37$; $p=0.014$; $d=0.49$) but no significant effect of emotions ($F_{(1;144)}=3.65$; $p=0.058$; $d=0.32$) and no significant interaction ($F_{(2;144)}=0.58$; $p=0.56$; $d=0.18$). Post-hoc analyses showed that TD-Med had a higher SSRT in comparison to both TD-Unmed ($p=0.005$; $d=0.83$) and HC ($p=0.039$; $d=0.63$), and no significant difference between TD-Unmed and HC ($p=0.37$; $d=0.24$) (**Fig.1** panel C). In a second and third Anova analyses that accounted for comorbidities, we found no significant effect of ADHD ($F_{(2;144)}=0.24$; $p=0.79$; $d=0.11$) nor OCD ($F_{(2;144)}=0.15$; $p=0.85$; $d=0.08$) on SSRT.

To confirm the absence of significant interaction in the emotion condition among the groups, we performed Bayesian t-tests and found no sufficient evidence to conclude that any of our patient groups were different to HC in the emotional condition (TD-Unmed: 95% HDI from -35.8 to 13.2msec; TD-Med: 95% HDI from -28.1 to 31.7msec; **Fig.1** panel D).

For TD-Med, we found no significant correlations between the SSRT and YGTSS, BIS-11, STAI and MIDI scales ($p>0.05$).

Based on behavioural results, we focused our neuroimaging analyses on TD-Med patients to determine the brain correlates of reactive motor impulsivity.

3.3. ESST images processing evaluation

To assure that the absence of the emotional effect was not related to the misidentification or inattention to images, we performed an analysis of valence, arousal and recognition.

Repeated Anova analysis confirmed that the valence of images were correctly identified ($F_{(2;233)}=528.55$; $p<0.001$; $d=4.26$; all post-hoc were significant: $p<0.001$) by all the participants ($F_{(2;233)}=2.41$; $p=0.09$; $d=0.29$), there was no interaction ($F_{(4;233)}=0.47$; $p<0.76$; $d=0.18$).

We found an effect of the valence ($F_{(2;233)}=83.8$; $p<0.001$; $d=1.69$) and the group ($F_{(2;233)}=4.4$; $p=0.01$; $d=0.39$) but no interaction ($F_{(4;233)}=0.19$; $p=0.94$; $d=0.12$). Post-hoc analysis revealed that both positive and negative images were perceived as more intense to neutral images ($p<0.001$; $d>1.6$), but with no difference between positive and negative images ($p=0.47$; $d=0.11$). TD-Med patients perceived the images as less intense than HC ($p=0.003$; $d=0.89$), but there was no significant difference between TD-Unmed and HC and between TD-Med and TD-Unmed ($p>0.05$; $d<0.3$).

Finally, for the attention to images effect, we found a main effect of the image valence ($F_{(2;239)}=9.54$; $p=0.0001$; $d=1.94$) but no effect of groups ($F_{(2;239)}=1.09$; $p=0.34$; $d=0.19$) and no interaction ($F_{(4;239)}=0.66$; $p=0.62$; $d=0.21$). Post-hoc analysis revealed that negative images were better recognised compared to neutral images ($p=0.03$; $d=0.32$), and neutral images were better recognised compared to positive images ($p=0.02$; $d=0.36$).

3.4. Brain correlates of ESST in medicated patients with Tourette disorder

We performed a correlation analysis of TD-Med performance in ESST task across selected ROI and image modalities (**Fig.2** right panel).

For structural imaging, we found a positive correlation with grey matter signal in the right SMA ($t_{(17)}=2.51$; $p=0.0226$; $r=0.52$; $d=1.15$; r value with bootstrapping on all data [$r=0.58\pm 0.28$] and without the marginal value [$r=0.36\pm 0.3$]) and one positive correlation between the SSRT and grey matter signal in the right IFG that was significant without permutations ($t_{(17)}=2.11$; $p=0.049$; $r=0.45$; $d=0.97$; r value with bootstrapping on all data [$r=0.49\pm 0.34$] and without the marginal value [$r=0.19\pm 0.23$]) and showed a trend following 5000 permutations corrections ($p=0.066$).

For rs-fMRI, we found a negative correlation with spontaneous brain activity in the left putamen ($t_{(17)}=-2.12$; $p=0.043$; $r=-0.46$; $d=0.97$; r value with bootstrapping on all data [$r=-0.49\pm 0.21$] and without the marginal value [$r=-0.32\pm 0.21$]).

None of these results were correlated with YGTSS, BIS-11 and MIDI scales, or were different among the 3 groups (minimal p -value= 0.11).

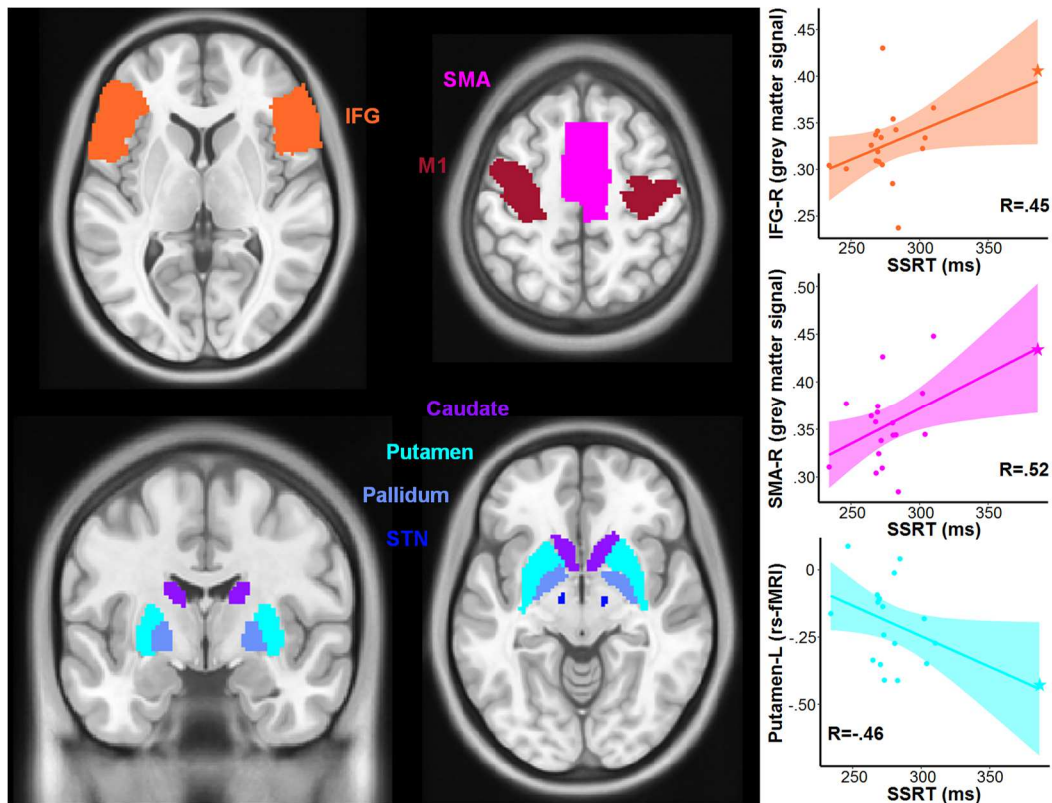


Fig.2. Left panel represents the selected regions of interest; right panel represents the significant correlations between these regions (using grey matter signal or resting-state activity) and the SSRT for medicated patients. rs-fMRI data refers to the exacted Z-standardized fractional amplitude of low-frequency fluctuation. The stars represent marginal' values.

IFG: Inferior frontal gyrus; L: Left; M1: Primary motor cortex; R: Right; SMA: Supplementary motor area; SSRT: Stop-signal reaction time; STN: Subthalamic nucleus.

For functional connectivity in TD-Med patients (**Fig.3**), our results showed an increased SSRT which was correlated with increased connectivity between the right IFG (opercular part) and the superior temporal gyrus (bilaterally), and decreased connectivity between the right IFG (opercular part) and the left cerebellum (crus I); the right subthalamic nucleus and the right cerebellum (crus I); and between the right IFG (triangularis part) and left cerebellum (part 10). We also found that the connectivity between the right IFG (opercular part) and the superior part of the temporal cortex bilaterally were negatively correlated to the MIDI scale (right: $t_{(17)}=6.08$; $p=0.004$; $r=-0.624$; $d=2.79$; left: $t_{(17)}=7.66$; $p=0.0007$; $r=-0.706$; $d=3.51$) while the connectivity between the right STN and the right cerebellum (crus I) was positively correlated to the MIDI scale ($t_{(17)}=3.638$; $p=0.04$; $r=0.47$; $d=1.67$). No significant correlations were found with the BIS-11 scale and tic severity ($p>0.05$). Group comparisons ($F_{(2,73)}=4.462$;

$p=0.0149$; $d=0.69$) showed that TD-Unmed had a decreased connectivity between the right IFG (triangularis part) and the left cerebellum (part 10) in comparison to HC ($p=0.015$; $d=0.77$), which was not significant between TD-Med and HC ($p>0.05$; $d\leq 0.5$).

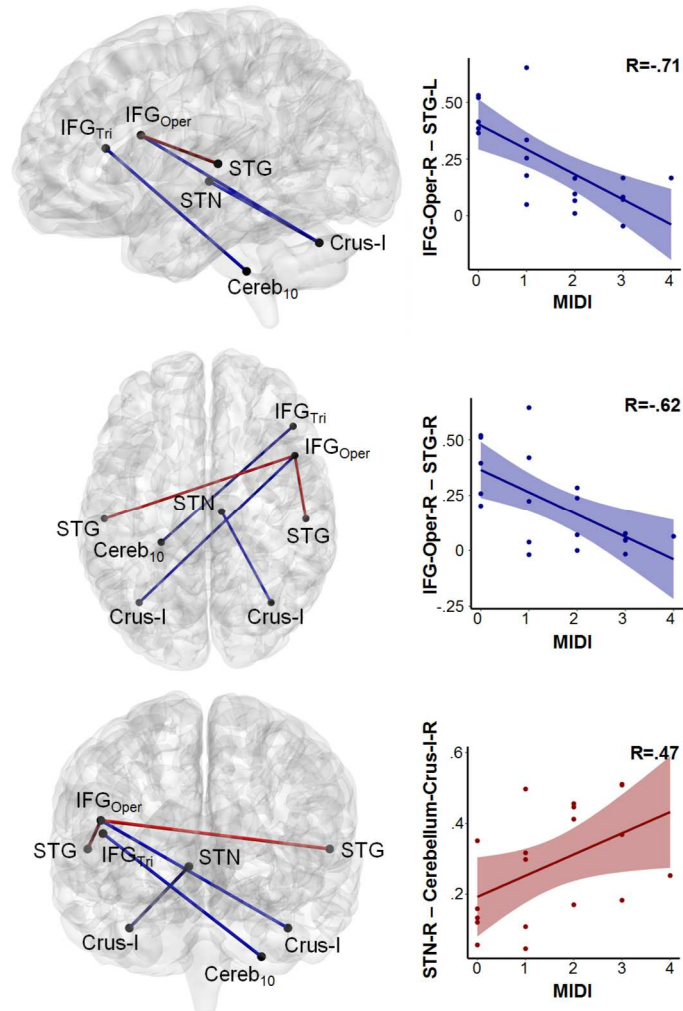


Fig.3. Correlation analysis with SSRT and functional connectivity: left panel – functional connectivity that positively (in red) and negatively (in blue) correlated with behavioural performance in TD-Med group of patients; right panel – the functional connections that correlated with both SSRT and MIDI scale in TD-Med group of patients.

IFG_{Tri/Oper}: Inferior frontal gyrus (Triangularis/Operculum parts); L: Left; MIDI: Minnesota Impulse Disorders Interview; R: Right; SSRT: Stop-signal reaction time; STG: Superior temporal gyrus; STN: Subthalamic nucleus.

4. Discussion

Using SSRT as index of reactive motor impulsivity, we showed that TD-Med patients had a higher impulsivity compared to TD-Unmed and to HC. Surprisingly, we found no effect of the emotional stimulation on motor impulsivity. Neuroimaging analyses suggested that higher reactive motor impulsivity in TD-Med patients correlated with (i) increased grey matter signal from the right SMA and, to some extent, the right IFG; (ii) decreased resting-state spontaneous activity of the left putamen, (iii) higher connectivity of the IFG with the superior temporal gyrus bilaterally and lower connectivity with the cerebellum (part 10 and crus I), and lower connectivity between the right STN and the right cerebellum (crus I).

Taken together, these results suggest that reactive motor impulsivity observed in TD could result from medication, and was underpinned by fronto-temporo-basal-ganglia-cerebellar pathway. Interestingly, a higher connectivity of the right IFG with bilateral temporal cortices predicted a lower score of MIDI, whereas lower connectivity of the right STN with the cerebellum predicted a higher score of MIDI.

4.1. Reactive motor impulsivity in TD and the role of antipsychotic medication

Our first result supported the conclusion of a recent meta-analysis of the studies on inhibitory control in TD and the role of medication (Morand-Beaulieu et al., 2017), as only TD-Med had a higher reactive motor impulsivity compared to both TD-Unmed and HC. These results are also in line with previous research that included only medicated patients and found group differences on Flanker task performance (Wylie, Claassen, Kanoff, Ridderinkhof, & van den Wildenberg, 2013), or included only unmedicated patients and did not observe group differences on SSRT (Mancini et al., 2018).

We found no significant effect of ADHD on SSRT in TD, which corroborated with some studies on pure ADHD showing no behavioural effect on this task (Congdon et al., 2014; Fosco et al., 2019; Keute, Krauel, Heinze, & Stenner, 2018). However, the previous meta-analysis on TD (Morand-Beaulieu et al., 2017) suggested a potential effect of association of TD with ADHD on inhibitory control deficit in this population. Moreover, in children with ADHD, reactive inhibitory control was shown to be a good clinical indicator for medication response (van der Oord, Geurts, Prins, Emmelkamp, & Oosterlaan, 2012). Discrepancies could arise from (i) the difference in ages in the populations studied, as differences in response inhibition were shown between adults and children with ADHD (Lei et al., 2015) and (ii) the ADHD medication status of the patients, as previous studies suggested that ADHD patients medicated with psychostimulants had impaired reactive inhibitory

performance (Congdon et al., 2014). In our study, none of the patients with both TD and ADHD were under psychostimulant medication.

In this study most of the TD patients were being treated with Aripiprazole, an atypical antipsychotic that has an effect on both dopaminergic (as a partial agonist) and serotonergic neurotransmission. The dysfunction of these neurotransmitter systems has been shown to considerably impact motor impulsivity. For instance, atypical antipsychotics have a partial agonistic effect on the dopaminergic pathways, particularly on D2 receptors in the dorsal striatum (Leysen, Janssen, Megens, & Schotte, 1994; Shapiro et al., 2003). Previous studies reported that D2 receptor availability in the striatum (both the putamen and caudate nucleus) were positively related to motor impulsivity (Ghahremani et al., 2012; Robertson et al., 2015). Additionally, the administration of a D2 agonist improved motor inhibition in humans (Nandam et al., 2013), while a D2 antagonist impaired motor impulsivity in other animals (Eagle et al., 2011; Pezze, Dalley, & Robbins, 2009). In accordance with these results, we can suggest that the putative hyperactivity of the dopamine system in TD (Maia & Conceição, 2017, 2018), does not contribute to motor inhibition impairment, whereas the antipsychotics would exert an antagonist effect on the dopaminergic system and impair performance on the task in TD-Med patients.

In addition, Aripiprazole also has an antagonistic effect of 5HT_{2A} receptors, which could induce motor impulsivity and attention impairment in humans (Wingen, Kuypers, & Ramaekers, 2007) and other animals (Carli, Baviera, Invernizzi, & Balducci, 2006; Robinson et al., 2008), even if the effect of serotonin antagonists on motor inhibition seemed to be less consistent (Clark et al., 2005; Eagle et al., 2009).

4.2. Brain correlates of reactive motor impulsivity in medicated patients with TD

In TD-Med, a higher reactive motor impulsivity (longer SSRT) was correlated with a higher grey matter signal in the right SMA and IFG, and lower spontaneous BOLD activity in the left putamen. The cortical areas were previously related to intentional motor inhibition and strongly lateralized in the right hemisphere (Aron, Robbins, & Poldrack, 2014; M. J. Frank, 2006; Jahanshahi et al., 2015). In TD, a higher SMA activity was associated with error processing during a motor inhibition task (Fan et al., 2018), and activity in the IFG was correlated with tic frequency during stop trials (Ganos et al., 2014). Interestingly, a positive correlation of grey matter in the IFG and SMA with SSRT was also shown in previous studies on healthy controls (Wang et al., 2016), suggesting, so far, that these findings could be related to the intrinsic propensity of these TD patients to reactive motor impulsivity.

Spontaneous activity of the left putamen negatively correlated with the SSRT, suggesting that a lower activity in this territory was linked to reactive motor impulsivity. The putamen was already reported to be involved in motor inhibition (Hermans et al., 2017; Hu & Li, 2012), via its putative role in the regulation of responses by modifying the activity of trans-striatal direct and indirect pathways (Wijeakumar et al., 2015). Taking into account that other studies pointed out a higher putaminal activity in drug-naïve TD patients (Cui et al., 2014), our present results likely reflect the effect of antipsychotic medication, mainly with Aripiprazole, which affected task performance.

Further, a single dose of 10mg of Aripiprazole in controls showed important changes in regional blood flow and, in particular, in temporal and prefrontal cortices, the striatum, and the cerebellum (Handley et al., 2013). Even if the exact relationship between cerebral blood flow and BOLD resting-state activity is unknown and likely nonlinear, the changes observed after Aripiprazole administration could explain the functional connectivity results of the present study.

Namely, functional connectivity in relation with SSRT in TD-Med, showed two major networks. First, reactive motor impulsivity was predicted by lower connectivity between the cerebellum (crus I and pars 10) and the IFG and STN. Second, reactive motor impulsivity was predicted by a higher connectivity of the IFG with temporal cortices bilaterally. Previous studies suggested that cerebellar damage impaired both executive control and movement monitoring and performance in SSRT (Brunamonti et al., 2014; Olivito et al., 2017). The connectivity of the right STN - right cerebellum is anatomically and functionally plausible as the STN is connected to the cerebellum by the pontine nuclei (Bostan & Strick, 2018). In addition, the STN and the cerebellum (among others, the crus I) recruited during cognitive tasks (Lehericy et al., 2005) are suggested to play a role (Jahanshahi et al., 2015) in both reactive (M. J. Frank, 2006) and proactive inhibition (Ballanger et al., 2009), as well as in high-level cognitive inhibition related to decision-making processes (Atkinson-Clement et al., 2019; Zénon et al., 2016). Similarly, the activity in fronto-temporal regions in HC predicted the stop accuracy in the SSRT (Chevrier, Cheyne, Graham, & Schachar, 2015). The temporal cortex was also found to be involved with mental preparation (Kounios et al., 2006; Tian et al., 2011) and proactive control (van Belle, Vink, Durston, & Zandbelt, 2014). Taken together, our imaging data suggests that structural changes in SMA and IFG associated with medication could contribute to the predisposition of reactive motor impulsivity in TD patients, and that the effect of antipsychotics on brain activity within the fronto-temporo-basal ganglia-cerebellar network likely resulted in altered SSRT performance.

4.3. Reactive motor impulsivity and impulse control disorders in TD patients medicated with antipsychotics

In addition to SSRT, we found significant correlations in our TD-Med group, between the functional connectivity of the right IFG and the superior temporal gyrus, and of the STN and the cerebellum with the MIDI scale so that (i) increased connectivity between the right IFG and the STG bilaterally predicted higher reactive motor impulsivity but lower impulse control disorders (ICDs); (ii) the increased connectivity between the right IFG and the superior temporal gyrus bilaterally correlated with lower reactive motor impulsivity but higher ICDs.

The dissociation between the SSRT performance and presence of ICDs has been previously shown in patients with Parkinson disease and ICDs, as they showed shorter SSRT in comparison to controls and patients without ICDs (Claassen et al., 2015). Interestingly, in our study, most of the connections related to the SSRT and ICDs were lateralised in the right hemisphere. One recent study pointed that during a gambling task in volunteers, the risk-taking bias and, consequently, gambling behaviour was related to the physiological activity within the right hemisphere (Sacré et al., 2019). Overall, our results question the neuronal correlates that underpin the inhibitory control and ICDs, as they suggest that atypical antipsychotics used in TD could potentially exert a different effect on complex impulsive behaviours and reactive motor impulsivity.

4.4. Limitations

Our study suffered from several limitations. First, we cannot exclude that medicated patients have greater tics severity compared to unmedicated patients, and that could impact our findings. However, we did not find any correlation with severity of tics measured by the YGTSS. Moreover, our analyses were performed on a relatively small group of TD patients (n=19), which could contribute to missing some results which did not reach the threshold for significance. Additionally, the findings are consistent with recent meta-analysis results (Morand-Beaulieu et al., 2017), which make us more confident in regards to our conclusions. Prospective studies with before and after treatment initiation assessments would be warranted to address this limitation.

In addition, we found no effect of emotional stimulation on reactive motor impulsivity. This unexpected result could be explained by a methodological choice. We only selected images with moderate emotional intensity, which, potentially, may not have exerted enough

emotional stimulation to impair motor inhibition in TD. Indeed, it was previously reported that moderate emotional stimulation could enhanced motor inhibition, while a higher emotional stimulation could impair this function (Pessoa, Padmala, Kenzer, & Bauer, 2012). So far, we cannot completely exclude that higher emotional stimulation may impair motor inhibition in TD.

5. Conclusion

Here we showed that reactive motor impulsivity measured by SSRT in TD (i) was present in patients medicated with mostly atypical antipsychotics, whereas performance of unmedicated patients was similar to that of controls, (ii) was not related to the presence of ADHD and (iii) was underpinned by structural dysfunctions and by functional connectivity of fronto-temporo-basal ganglia-cerebellar pathway.

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8. Declarations of interest

None of the authors declare any conflict of interest.

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