Computational dissociation of dopaminergic and cholinergic effects on voluntary behavior and inhibitory control

Eduardo A. Aponte[1], Dario Schöbi[1], Klaas E. Stephan[1,2,3], Jakob Heinzle[1]

[1]Translational Neuromodeling Unit, Institute for Biomedical Engineering, University of Zurich & ETH Zurich, Wilfriedstrasse 6, 8002, Zurich, Switzerland.

[2]Wellcome Centre for Human Neuroimaging, University College London. 12 Queen Square, London, WC1N, 3AR, UK.

[3] Max Planck Institute for Metabolism Research, Gleueler Strasse 50, 50931 Cologne, Germany.

[*]**Corresponding authors:**

Eduardo A. Aponte; Address: Wilfriedstrasse 6, 8002, Zurich, Switzerland; Tel.: +41446349112; Email: aponte@biomed.ee.ethz.ch .

Jakob Heinzle; Address: Wilfriedstrasse 6, 8002, Zurich, Switzerland; Tel.: +41446349122; Email: heinzle@biomed.ee.ethz.ch

Abstract

Patients with schizophrenia make more errors than healthy subjects in the antisaccade task. In this paradigm, participants are required to inhibit a reflexive action (a saccade to a target) and to initiate a voluntary action (a saccade in the opposite direction). While the precise origin of this deficit is not clear, it has been connected to aberrant neuromodulation, specifically in relation to dopamine (DA) and acetylcholine (ACh).

To study how DA and ACh affect inhibitory control and voluntary action generation, we investigated two compounds (levodopa 200mg/galantamine 8mg) in healthy volunteers (N=100) performing the antisaccade task. Using a computational model of (anti)saccade generation (SERIA), we found that levodopa had no significant impact on inhibitory control. By contrast, galantamine reduced inhibition control at high doses, and this effect was reversed at lower doses. In addition, galantamine reduced the latency of voluntary saccades, whereas levodopa had the opposite effect. Our results challenge the hypothesis that increased DA has deleterious effects on inhibitory control. Instead, our findings suggest that levodopa improves the accuracy of voluntary actions at the cost of higher reaction times, while galantamine reduced the latency of voluntary actions, but negatively impacted inhibitory control at high doses.

Finally, using machine learning, we demonstrate that model-based estimates of dopaminergic and cholinergic effects on inhibition and voluntary action control allow for inferring which drug was administered to a given individual. This may provide a starting point for establishing practical computational assays for differentiating neuromodulatory abnormalities in heterogeneous diseases like schizophrenia.

Introduction

Schizophrenia is a heterogeneous clinical entity: patients with comparable symptoms show highly variable treatment response and clinical trajectories over time [1,2]. A key challenge is to devise procedures for differential diagnostics that disambiguate potential disease mechanisms and inform individualized treatment in single patients [3]. One proposal derives from the "dysconnection hypothesis" which posits that the schizophrenia spectrum consists of different abnormalities in dopaminergic and cholinergic modulation of NMDA receptor dependent plasticity [4-6]. This suggests the development of assays of neuromodulation that can operate on data obtained in clinical settings.

Eye movements are attractive targets in this regard [7]. They (i) can be measured easily in clinical settings, (ii) are sensitive to changes in neuromodulation, and (iii) are often abnormal in schizophrenia. For example, performance on the antisaccade task is robustly impaired in schizophrenia [8]. In this paradigm, subjects are required to saccade in the opposite direction of a visual cue. This is thought to probe participants' ability to inhibit a reflexive (pro)saccade towards the cue and to initiate a voluntary (anti)saccade in the opposite direction [9]. Since the first publication [10], it has been consistenly reported that patients with schizophrenia make more errors than control participants [11-13]. However, it remains unclear whether the elevated error rate (ER) in schizophrenia is caused by deficits in inhibitory control of reflexive prosaccades, in generating voluntary actions (antisaccades), or by a combination of these factors.

Notably, all of these options could be related to potential abnormalities of neuromodulation. Specifically, aberrant tonic dopamine (DA) levels in the basal ganglia (BG) could lead to abnormalities in the pathway from the BG to the motor layers of the superior colliculus [14,15] involved in the inhibition of saccades [16,17]. However, other DA-dependent mechanisms are conceivable. For example, the findings that (a) lesions in the BG do not affect antisaccade performance [18], but (b) prefrontal lesions critically impair it [19,20], challenge the view that higher ER in schizophrenia is caused exclusively by impaired inhibitory control [21,22]. Instead, higher ER rates may be caused by DA-dependent processes related to voluntary behaviour, e.g., aberrant prefrontal task set maintenance [22].

In contrast to the conjectured deleterious effect of high tonic DA, pro-cholinergic compounds targeting the $\alpha7$ and $\alpha4\beta2$ nicotine receptors have been postulated as possible treatments for negative symptoms and cognitive impairments in

schizophrenia [23-25]. While results from clinical studies have been mixed [26-29], several studies have specifically investigated whether nicotine impacts antisaccade performance [30-39]. These reports indicate that nicotine decreases antisaccade reaction time (RT) [30,32,34,38,39]. However, not all studies have replicated this result [40]. Similarly, several studies have found that nicotine reduces ER [31,34,35,38,41]; but see [39]. In summary, the effects of pro-cholinergic and pro-dopaminergic drugs on the antisaccade task are not fully understood.

The goal of the present study was twofold. First, we investigated the effects of pro-dopaminergic and pro-cholinergic drugs (levodopa/galantamine) on inhibitory control and voluntary action selection in the antisaccade task. Second, we asked whether these effects were specific enough to infer which drug had been administered to a subject based only on antisaccade performance.

In order to address these questions, we performed two twin experiments following a double-blind, placebo-controlled, between-group design. To uncover the effects of levodopa and galantamine on antisaccades, we used the *Stochastic Early Reaction, Inhibition and late Action* (SERIA) model [42,43], a recent computational model of antisaccade mechanisms that quantifies the contribution of inhibitory control and voluntary action generation to mean ER and RT. In addition, we investigated whether the parameters inferred by the model were predictive of the drug administered to individual participants. For this, we combined SERIA with a machine learning algorithm to predict the drug applied on a subject-by-subject basis. A successful prediction would speak to the clinical potential of SERIA as a computational assay of dopaminergic and cholinergic neuromodulation. This would constitute a step towards practically useful computational assays that could serve as differential diagnostic tools of aberrant neuromodulation [44].

Methods

Experiment and Apparatus

All procedures described here were approved by the Cantonal Ethics Committee Zurich (KEK-ZH-Nr.2014-0246). The placebo data from Exp. 1 were used in a previous study [42].

Participants

Participants were approached through the recruitment system of the University of Zurich. During the first visit, subjects provided written informed consent, and medical and demographic information. Only male participants were recruited due to interactions between the menstrual cycle and dopaminergic medication [45]. Exclusion criteria were: age outside the range $18 - 40$, resting pulse rate outside the range $55 - 100bps$, abnormal electrocardiogram, regular smoking, recreational drug consumption in the past 6 months, serious mental or neurological illness, current use of psychiatric medication, use of medication that could interact with levodopa, benserazide or galantamine, and lactose intolerance. Subjects who fulfilled all inclusion criteria were invited to two experimental sessions separated by one to eight weeks.

Pharmacology

We used two drugs: levodopa and galantamine. Levodopa is a precursor of DA that crosses the blood-brain barrier and increases the presynaptic availability of DA [46]. Galantamine is an acetylcholinesterase inhibitor (and thus increases availability of ACh at the synaptic cleft) and an allosteric potentiating ligand of the $\alpha 7$ [47] and $\alpha 4\beta 2$ ACh nicotinic receptors [48-50].

Experimental procedure

At the beginning of each session, participants were administered either Madopar® DR 250g (200mg levodopa, 50mg benserazide) or lactose (Exp. 1), or Reminyl® (8mg galantamine) or lactose (Exp. 2). Experimenters and participants were blind to the drug administered. Subsequently, participants received written instructions regarding the experiment and participated in a training that lasted 20 to 30 minutes.

Testing started 70 minutes after drug administration. At the end of each session, participants were asked whether they had received placebo or the active substance.

Task design

The task design has been described in detail previously (see Fig. 1A and [42]). Here we provide a brief summary.

During the experiment, two red circles (0.25°) were presented at a horizontal eccentricity of $\pm 12°$. A trial started when a central fixation cross was presented. Once participants fixated the cross, it remained on the screen 500 to 1000ms, after which a green bar ($3.48° \times 0.8°$) centered on one of the circles was displayed. The bar was presented in either vertical or horizontal orientation for $500ms$. Subjects were instructed to saccade to the circle cued by a horizontal bar (prosaccade trials) and to saccade to the non-cued circle if the bar was oriented vertically (antisaccade trials). The next trial started 1000ms after the bar was removed.

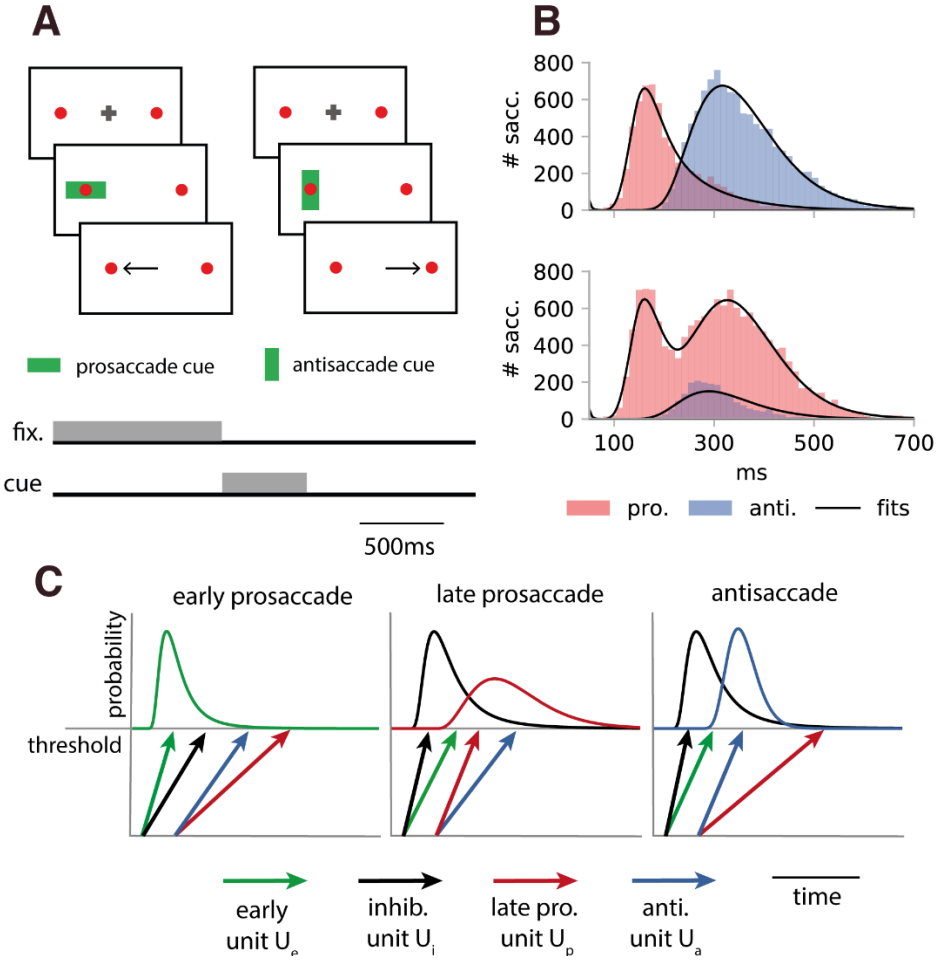

Figure 1: A. Task design. Participants were required to saccade to a cued red circle (prosaccade trials) or to saccade in the uncued direction (antisaccade trials). **B.** RT histogram and model fits of all subjects in a subset of the data (PP50 condition). Prosaccades are displayed in red, and antisaccades in blue. Top panel: Antisaccade trials. Red bars indicate error prosaccades. Bottom panel: Prosaccade trials. Blue bars indicate error antisaccades. Note that prosaccades were bimodally distributed. The first peak corresponds to early prosaccades, whereas the second peak corresponds to late prosaccades. The RT distributions predicted by the model are displayed in black. **C.** Schematic presentation of the model. SERIA uses four race-to-threshold units. The early unit (green) triggers fast prosaccades. If the inhibitory unit (black) hits threshold before the early unit, voluntary prosaccades (red) or antisaccades (blue) can be generated. Modified with permission from [43].

The main experiment consisted of three blocks of 192 trials. Every block contained randomly interleaved pro- and antisaccade trials, of which 20, 50 or 80% were prosaccade trials (conditions PP20, PP50, PP80 respectively). The order of the blocks was identical in both sessions, but pseudo-randomized across subjects.

Both experiments were conducted in a dimly illuminated room. Participants sat $60cm$ in front of a computer screen. Eye movements were measured with an Eyelink 1000 (SR Research) and stored at $500Hz$. Saccades were detected with the algorithm provided by the eye-tracker manufacturer.

Modeling

The SERIA model (Fig. 1B-C) was fitted to individual RT distributions. SERIA asserts that saccades are the result of the competition between four race-to-threshold processes or units [42,43]: an early response unit U_e associated with fast prosaccades, an inhibitory unit U_i whose function is to stop fast prosaccades, and two late response units that represent voluntary (late) prosaccades (U_p) and antisaccades (U_a). Conceptually, SERIA postulates that early or reflexive prosaccades are generated when the early unit is not stopped by the inhibitory unit. In addition, when a fast prosaccade is stopped, a voluntary eye movement is generated. The voluntary action (antisaccade or late prosaccade) is determined by the late unit that hits threshold first. For example, a late prosaccade is generated when the late unit hits threshold before the antisaccade unit.

The model can be used to infer on several quantities that are not directly measurable. First, SERIA's parameters capture the probability of an inhibition failure, i.e., the probability that the early unit hits threshold before all other units. Inhibition failures are reflexive reactions that comprise correct fast responses on prosaccade trials and short latency errors on antisaccades trials. Second, it is possible to quantify the mean hit time of the voluntary units. For antisaccades, this quantity is similar to the mean RT. For prosaccades, this quantity represents the RT of late actions. Finally, the parameters of the model determine the probability of late errors. On an antisaccade trial, a late error is a voluntary prosaccade. By contrast, on a prosaccade trial, an error antisaccade is generated when the antisaccade unit hits threshold before the late prosaccade unit.

Based on previous studies [42,43,51], the data from each block were split into switch and repeat pro- and antisaccade trials. We assumed that the early unit had the same parameters across all trial types, but the inhibitory and late units varied across all conditions. Other secondary parameters were equal across trial types but were allowed to differ between blocks and subjects. We have previously shown that this model best explains RT and ER in this version of the antisaccade task [51].

Statistical analysis

Statistical analyses were conducted using generalized linear mixed effect models (GLME) implemented in *R* (3.4.3*)*. Subjects were entered as a random effect, whereas the factors SWITCH, *prosaccade trial probability* (PP), SESSION, DRUG, *experiment* (EXP), and DOSE defined as *drug(mg)/weight(kg)*, were treated as fixed effects. In addition, we considered the following interactions PP*SESSION, PP*SWITCH, PP*DRUG, DOSE*DRUG. When both experiments were analyzed together, we also included the interactions DRUG*EXP, DRUG*DOSE*EXP and DRUG*PP*EXP. ER were analyzed with binomial regression models, whereas probabilities were analyzed with Beta regression models. Statistical inference about RT were based on *F*-tests. For ER and probabilities, Wald tests were employed. Significance was asserted at $\alpha = 0.05$.

Model estimation and fitting

SERIA was fitted with methods previously described [43]. Briefly, the model was fitted using the Metropolis-Hastings algorithm. For regularization, we used a hierarchical model [52] in which the prior distribution of the parameters associated with a run depended on the population distribution, which was simultaneously estimated using the data from all participants (see Supp. 1).

Classification

To test whether parameter estimates were predictive of the drug administered on a subject-by-subject basis, we used a classification algorithm. The goal was to determine whether a participant received levodopa or galantamine based on the difference between the drug and placebo conditions. Hence, the features used to train the classifier were subject-specific differences in parameter estimates between the two conditions. Classification was performed using *gradient boosting* [53] as implemented in *xgboost* [54].

Classification accuracy was assessed using leave-one-out cross validation. Briefly, each cross-fold consisted of the following steps (see Fig. 5). First, the data of one (test) subject was set apart. A hierarchical SERIA model was fitted to the data from the remaining N-1 subjects. Then, the classifier was trained on the difference between the SERIA parameter estimates from the drug and placebo conditions. Next, we computed the features of the test subject. To ensure similar regularization in the training and test phases, we included all N subjects in a hierarchical model, and used the parameter estimates of each subject as predictors of the corresponding drug label. This procedure was repeated once for each subject. We report the mean leave-one-out predictive accuracy across all subjects.

To test statistical significance, two permutation tests were conducted. First, we randomly shuffled the drug labels (levodopa/galantamine) 5000 times and reevaluated the analysis. Second, to rule out that the results were driven by any difference between Exp. 1 and 2 not related to the drug treatment, we implemented a permutation test in which the drug and placebo labels were randomly swapped. This represents the distribution of classification accuracies when experiment but not drug labels are used to predict the compound administered.

Results

Participants

In Exp. 1, 46 subjects (mean age 23.6, std. 2.9) were included in the final analysis. Four participants were excluded because their data were incomplete. No subject experienced side effects. Participants were not significantly better than chance in guessing the substance administered after the first ($\chi^2(1, N = 44) = 3.2, p = 0.07$) and second sessions ($\chi^2(1, N = 42) = 0.9, p = 0.75$). In total, 52993 trials were analyzed, from which 1303 trials were excluded (Supp. Table. S1) using criteria specified previously [42].

In Exp. 2, 44 subjects were included in the final analysis (mean age 22.4, std. 2.3). Four subjects reported side effects and were excluded from the study. Two subjects were excluded because of incomplete data. Again, participants could not discriminate galantamine from placebo (first session $\chi^2(1, N = 44) = 0.8, p = 0.54$; second session $\chi^2(1, N = 44) = 0.8, p = 0.36$). 50688 trials were analyzed, from which 1416 were excluded (Supp. Table. S1).

Error rate and reaction time

Error rate

The mean ER on pro- and antisaccade trials is displayed in Fig. 2 top row and Sup. Table S2. High congruent trial type probability was associated with fewer errors in pro- ($\chi^2(2, N = 1080) = 871.7, p < 10^{-5}$) and antisaccade trials ($\chi^2(2, N = 1080) = 901.2, p < 10^{-5}$). Subjects made fewer errors in the second session (pro.: $\chi^2(1, N = 1080) = 13.9, p = 10^{-3}$, anti.: $\chi^2(1, N = 1080) = 7.6, p = 0.005$). There were fewer errors on prosaccade trials in Exp. 1 compared to Exp. 2 ($\chi^2(2, N = 1080) = 6.1, p = 0.0129$).

Error rate: Drug effects

On prosaccade trials, there was a significant interaction between DRUG and EXP (Fig. 2B; $\chi^2(1, N = 1080) = 6.8, p = 0.008$). We proceeded to investigate Exp. 1 (levodopa) and 2 (galantamine) independently for drug related effects. Levodopa reduced the ER on prosaccade trials ($\chi^2(1, N = 552) = 6.5, p = 0.010$), and this effect was DOSE dependent ($\chi^2(1, N = 552) = 8.0, p = 0.004$). On antisaccade trials, we found no significant main effect of DRUG in Exp. 1 or 2, but there was a significant interaction between DRUG and DOSE in Exp. 2 ($\chi^2(1, N = 528) = 29.6, p = 10^{-5}$). Galantamine increased antisaccade ER at high doses, while it reduced it at more moderate levels.

Reaction time

RT on correct trials were analyzed similarly to ER (Fig. 2 bottom row and Sup. Table S3). Higher congruent trial type probability led to lower RT in both pro- ($F_{2,972} = 30.3, p < 10^{-5}$) and antisaccade trials ($F_{2,968} = 35.1, p < 10^{-5}$). RTs were lower in the second session (pro.: $F_{1,972} = 31.5, p < 10^{-5}$, anti: $F_{1,968} = 75.0, p < 10^{-5}$). RT in Exp. 2 were significantly lower than in Exp. 1 (pro: $F_{1,86} = 8.4, p = 0.004$; anti: $F_{1,86} = 12.5, p < 10^{-3}$).

Reaction times - drug effects

When Exp. 1 and 2 were analyzed together, we found a significant main effect of DRUG on prosaccade trials (Fig. 2F; $F_{2,972} = 4.0, p = 0.022$). In addition, levodopa increased the latency of antisaccades compared to galantamine (Fig. 2H; $F_{2,968} = 12.2, p = 10^{-3}$). When the two experiments were analyzed independently, we found that galantamine decreased antisaccade RT ($F_{2,250} = 11.1, p = 10^{-3}$). No other effect was significant.

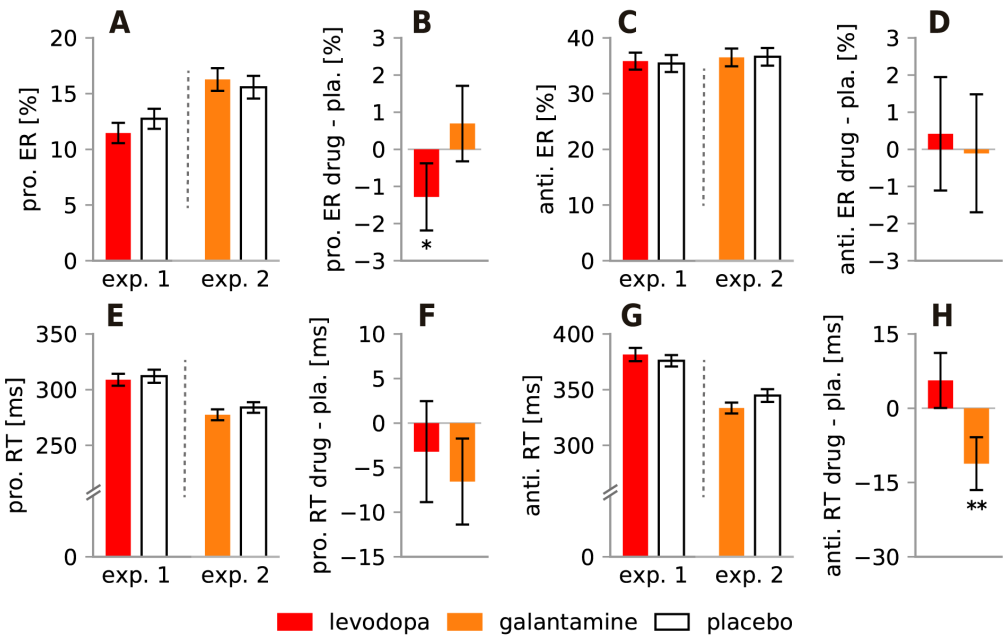

Figure 2: **A.** Mean prosaccade ER in Exp. 1 and 2. **B.** Difference in prosaccade ER between the drug and placebo conditions. Levodopa significantly reduced prosaccade ER ($\chi^2(1, N = 552) = 6.5, p = 0.010$). **C.** Mean antisaccade ER. **D.** Difference in antisaccade ER between the drug and placebo conditions. **E.** Mean prosaccade RT in Exp. 1 and 2. **F.** Difference in prosaccade RT between the drug and placebo conditions. **G.** Mean antisaccade RT. **H.** Difference in antisaccade RT between the drug and placebo conditions. Galantamine decreased antisaccade RT ($F_{2,250} = 11.1, p = 10^{-3}$). Error bars depicts the SEM. PP: prosaccade trial probability; $*: p < 0.05$; $**: p < 0.01$.

Modeling

Our main interest was to determine whether levodopa and galantamine affected (*i*) the hit times of the inhibitory and late units, (*ii*) the probability of inhibition failures, and (*iii*) the probability of late errors.

Threshold hit times

The hit times of the inhibitory, and late pro- and antisaccade units were analyzed as in the previous section. For the late units, we only report the hit times on correct trials. In the case of the inhibitory unit, pro- and antisaccade trials were analyzed together and the factor *trial-type* (TT) was included in the analysis.

Prosaccade trial probability (PP) had a significant effect on all units. In agreement with [42,43], we found that the hit time of the inhibitory unit increased with the frequency of prosaccade trials ($F_{1,972} = 309.6, p < 10^{-3}$), indicating reduced inhibition when prosaccade trials were more common. On

average, hit times were lower (faster saccades) in the second session. Furthermore, hit times were higher in Exp. 1 (late pro.: $F_{1,86} = 20.0, p < 10^{-3}$, anti: $F_{1,86} = 16.2, p < 10^{-3}$).

Threshold hit times - Drug effects

Levodopa increased the latency of voluntary actions (Fig. 3A-B; late pro. $F_{1,494} = 8.2, p = 0.004$; anti. $F_{1,494} = 6.5, p = 0.010$). On average, voluntary saccades were 5ms slower under levodopa than under placebo. However, levodopa had no significant effect on the inhibitory unit ($F_{1,494} = 3.0, p = 0.079$).

Galantamine had the opposite effect of levodopa, reducing the latency of voluntary actions. Specifically, it reduced the hit time of late pro- ($F_{1,472} = 15.7, p < 10^{-3}$) and antisaccades ($F_{1,472} = 10.9, p = 0.001$). On average, the hit times were 6ms lower under galantamine compared to placebo. Again, there was no main effect of DRUG on the inhibitory unit ($F_{1,972} = 0.7, p = 0.382$).

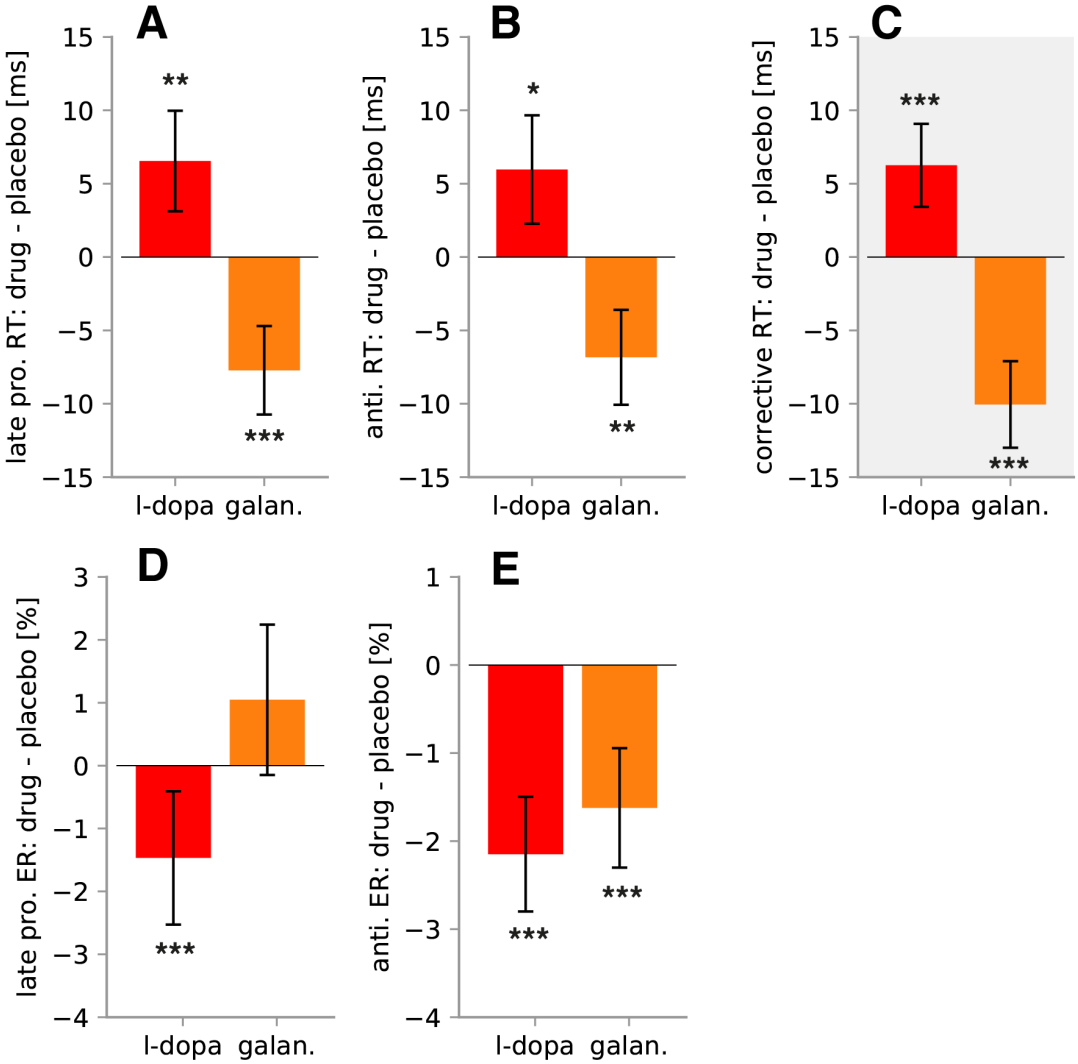

Figure 3: **A.** Difference in the RT of late prosaccades between drug and placebo conditions ($F_{1,972} = 20.2, p < 10^{-3}$). **B.** Difference in RT of antisaccades ($F_{1,972} = 14.1, p < 10^{-3}$). **C.** Difference in RT of corrective antisaccades ($F_{1,10620} = 24.4, p < 10^{-3}$). Note: The data in C (in gray) are completely independent of the modeling that led to the results in A and B. Corrective antisaccade display the same drug effects as voluntary saccades. **D.** Difference in ER in late prosaccades between the drug and placebo conditions ($\chi^2(1, N = 1080) = 24.0, p < 10^{-5}$). **E.** Difference in late ER on antisaccade trials ($\chi^2(2, N = 1080) = 19.6, p < 10^{-3}$). Error bars represent the SEM. $*: p < 0.05$; $**: p < 0.01$, $***: p < 0.001$.

Corrective antisaccades

In [42,43], we showed that corrective antisaccades that follow errors on antisaccade trials are distributed like late responses up to a fixed delay. Hence, SERIA predicts that corrective antisaccades should display the same drug effects

as antisaccades, i.e., slower corrective antisaccades in the levodopa condition, and faster antisaccades in the galantamine condition.

We analyzed 5696 corrective saccades in Exp. 1 and 4996 in Exp. 2. Because the frequency of corrective antisaccades varied widely over subjects and conditions, we accounted for the inhomogeneous number of trials by analyzing trial-by-trial RT as opposed to mean RT, using a strategy similar as [55].

When analyzed together, the interaction between DRUG and EXP ($F_{1,10620} = 24.4, p < 10^{-3}$, Fig. 3C) was significant. Supporting our hypothesis, levodopa increased the RT of corrective antisaccades ($\Delta RT = 8ms$; $F_{1,5654} = 10.8, p < 10^{-3}$), whereas galantamine had the opposite effect ($\Delta RT = -10ms$; $F_{1,4960} = 14.6, p < 10^{-3}$).

Inhibition failures and late errors

We proceeded to investigate the probability of late errors and inhibition failures. Late errors occur when the incongruent voluntary action (e.g., a late prosaccade on an antisaccade trial) hits threshold before the congruent action. An inhibition failure occurs when the early unit hits threshold before all other units.

Late errors were anticorrelated with congruent trial type probability (late pro: $\chi^2(2, N = 1080) = 1652.3, p < 10^{-5}$; anti: $\chi^2(2, N = 1080) = 402.5, p < 10^{-5}$). For example, late errors on antisaccade trials were most common when 80% of trials were prosaccade trials. The probability of an inhibition failure was positively correlated with prosaccade trial probability ($\chi^2(2, N = 1080) = 279.2, p < 10^{-5}$).

Inhibition failures and late errors – drug effects

Levodopa significantly reduced the late ER on pro- and antisaccade trials (Fig. 3D-E; pro.: $\chi^2(1, N = 552) = 11.7, p < 10^{-3}$; anti.: $\chi^2(1, N = 552) = 48.3, p < 10^{-5}$). However, levodopa had no significant effect on inhibition failures ($\chi^2(1, N = 1104) = 3.0, p = 0.082$). Therefore, levodopa increased the accuracy of voluntary actions at the cost of higher RT.

In Exp. 2, galantamine decreased the probability of late errors on antisaccade trials ($\chi^2(2, N = 528) = 22.4, p < 10^{-5}$), but not on prosaccade trials ($\chi^2(2, N = 528) = 2.7, p = 0.095$). There was no significant main effect of DRUG on the number of inhibition failures ($\chi^2(2, N = 528) = 0.2, p = 0.590$).

Dose dependent effects

At low doses, levodopa reduced the late ER on prosaccade trials. This effect was reversed at higher doses (Fig. 4A; interaction DRUG*DOSE $\chi^2(1, N = 552) =$

31.8, $p < 10^{-5}$). While the main effect of DRUG was not significant in Exp. 2, galantamine had a highly significant dose dependent effect on the latency of the inhibitory unit (Fig. 4B; $F_{1,471} = 16.0, p < 10^{-3}$). This was reflected by a linear effect on inhibition failure probability ($\chi^2(2, N = 528) = 14.3, p < 10^{-3}$). At a low dose, galantamine reduced the hit time of the inhibitory unit and the inhibition failure probability, and this effect was reversed at higher doses.

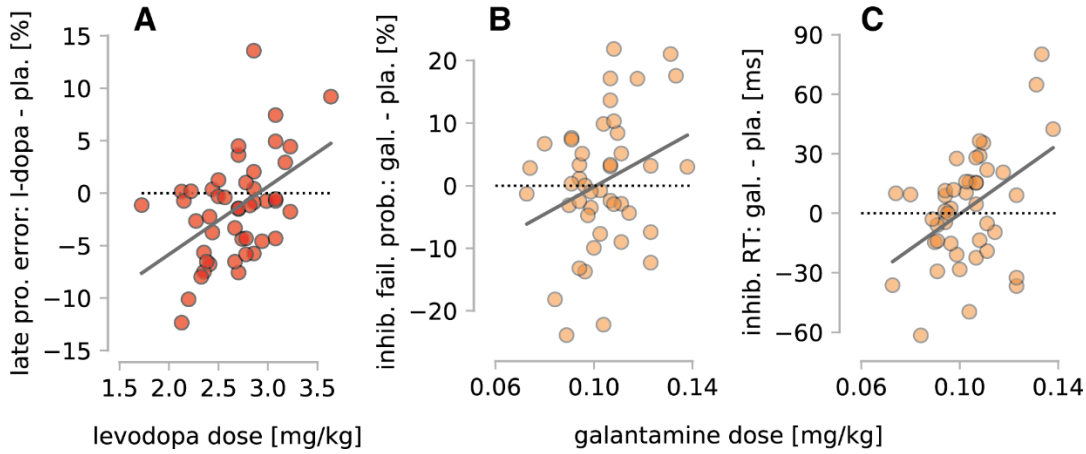

Figure 4: Dose dependent effects. A. Difference (levodopa-placebo) in late ER on prosaccade trials as a function of dose in Exp. 1 ($\chi^2(1, N = 552) = 31.8, p < 10^{-5}$). At a high dose, levodopa increased the number of errors, whereas at more moderate levels, it had the opposite effect. **B.** Difference (galantamine-placebo) in the percentage of inhibition failures averaged across all conditions in Exp. 2. Galantamine increased the number of inhibition failures as a function of dose ($\chi^2(2, N = 528) = 14.3, p < 10^{-3}$). **C.** Difference (galantamine-placebo) in the RT of the inhibitory unit averaged across all conditions. Galantamine increased the latency of the inhibitory unit as a function of dose ($F_{1,997} = 16.0, p < 10^{-3}$).

Classification of drug effects

Finally, we tested whether the effects of DA and ACh on computational parameters could be used to predict which of the two compounds was administered (Fig. 5). Leave-one-out cross-validation resulted in 0.70 predictive accuracy (95% CI [0.61, 0.79]). A permutation test, in which the levodopa and galantamine labels were randomly swapped, showed that this predictive accuracy was highly significant ($p<0.001$). A second permutation test (in which the drug and placebo labels were randomly swapped) yielded a similar result ($p=0.001$; Fig. 5). Because drug/placebo labels (but not experiment labels) were permuted, this second test rules out that the accuracy of the classifier depended on any difference between experiments not related to the drug administered.

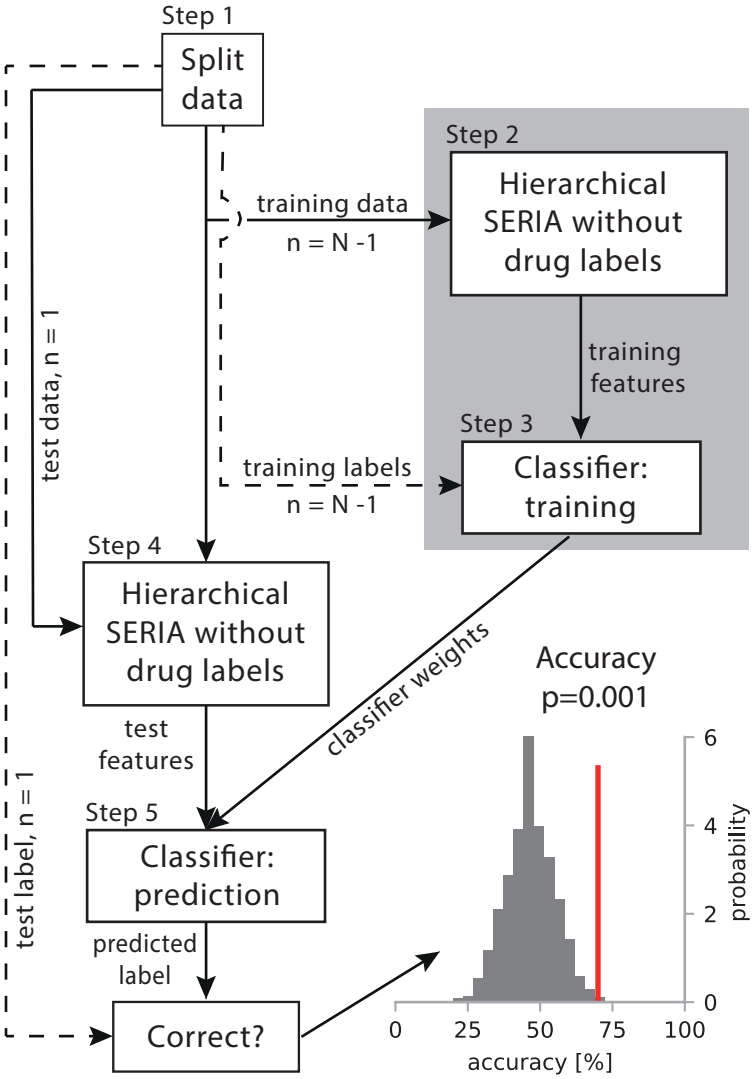

Figure 5: ***Prediction of drug labels with SERIA.*** This figures summarizes the classification procedure. **Step 1**. Data from N=90 subjects were split into test and training sets leaving one subject out at each iteration. **Step 2**. To generate training features, the SERIA model was fitted to data from N-1 subjects. **Step 3.** A gradient boosting classifier was trained on the SERIA parameters using the drug labels from the previous step. **Step 4**. Test features were generated by fitting SERIA to data from all N subjects. **Step 5**. Weights from classifiers trained on N-1 subjects were used to predict the drug label of the left-out subjects. This resulted in a predictive accuracy of 70% (95% CI[61,79]), *p=0.001*. The histogram in the bottom right shows the accuracies using randomly permuted drug labels. The red line illustrates the true accuracy.

374

Discussion

Using pharmacological challenges combined with computational modeling, our study demonstrated that pro-dopaminergic and pro-cholinergic compounds have largely opposite effects on antisaccades: Levodopa slowed down voluntary saccades and decreased voluntary saccade ER, whereas galantamine reduced voluntary saccade RT, and decreased late prosaccade ER. Moreover, galantamine, but not levodopa, affected the inhibition of reflexive prosaccades in a dose-dependent fashion. At low doses, galantamine reduced the probability of inhibition failures, but at higher doses, it had the opposite effect. Finally, we demonstrated that differences in model parameter estimates between placebo and drug conditions are compound-specific and can be used to predict the drug administered on a subject-by-subject basis.

Effects of levodopa

Even though widely-used in translational research [56], levodopa has not been studied systematically in the antisaccade task (but see [57,58]). In our study, levodopa did not impact ER on antisaccade trials. According to SERIA, this is explained by the weak effect of levodopa on the inhibition of reflexive prosaccades. Similarly, previous studies have not found changes in stop-signal response time under levodopa [59,60].

Intriguingly, we found that levodopa increased the RT of voluntary and corrective saccades. In addition, levodopa reduced the probability of late errors that occur when the wrong voluntary action is generated. These effects were not restricted to antisaccades but extended to voluntary prosaccades.

Prefrontal areas represent voluntary cue-action mappings in the antisaccade task [61,62] and possibly implement the late decision processes responsible for them [22,63]. In these regions, low-dose DA1 receptor mediated inhibition might induce stronger network stability [64] reducing late ER and RT, while not affecting inhibitory control. This possibility is also supported by our finding that levodopa reduced ‘late errors’ on prosaccade trials at lower doses, while it increased the ER at higher doses (Fig. 4A), suggesting that excessive DA impairs voluntary action control.

In summary, the main effect of levodopa was to slow down voluntary saccades, which led to fewer late errors. By contrast, there was no effect on the inhibition of reflexive saccades as suggested by the hypothesis that high tonic DA causes more inhibition failures. Rather, our findings support the notion that DA

predominantly affects voluntary action control, an executive, prefrontal function [22].

Effects of galantamine

While the effects of nicotine on antisaccades have been investigated previously, to our knowledge, this is the first antisaccade study applying a more general pro-cholinergic drug. We replicated previous studies in which nicotine reduced antisaccade RT [30,32,33,35,38]. This effect was concentrated on the generation of voluntary and corrective saccades.

Besides the effect on late responses, galantamine also affected the inhibition failure probability in a dose-dependent fashion. A comparable effect was reported previously [65], and it agrees with in-vitro [50] and in-vivo studies in rodents [66]. In patients with schizophrenia, galantamine at high doses (32mg/day) reduces inhibitory control and working memory [67]. In our study, model-based analysis revealed that galantamine affected ER mostly through its influence on response inhibition. At a high dose, galantamine had a deleterious effect, whereas at more moderate levels, it improved performance.

Opposite effects of levodopa and galantamine: Predictive classification

One promising application of mathematical models in translational psychiatry concerns the development of *computational assays* that can provide single-subject predictions [44]. With this goal in mind, we tested whether a computational model of (anti)saccade generation would allow us to infer on experimentally controlled neuromodulatory changes in individual subjects.

Our results indicate that perturbations by galantamine and levodopa could indeed be discriminated based purely on observed eye movements during the antisaccade task. To our knowledge, this constitutes the first demonstration that antisaccade behavior can be used to make statements about neuromodulation on an individual level. Because antisaccade performance can be easily measured in clinical settings and is robustly impaired in schizophrenia, the combination of SERIA with machine learning has promising potential for translational applications in schizophrenia research. Specifically, it is conceivable that this approach could help identify clinically relevant subgroups with different abnormalities in neuromodulation, as postulated by the dysconnection hypothesis of schizophrenia [4-6]. If successful, a computational assay of this sort could help establish procedures for differential diagnostics and aid individual treatment recommendations in schizophrenia. The prospects and limitations of this approach need to be evaluated in future studies.

Funding and disclosure:

This work was supported by the René and Susanne Braginsky Foundation (KES) and the University of Zurich (KES). The authors report no conflict of interest.

References

1. Buckley PF, Miller BJ. Personalized medicine for schizophrenia. NPJ Schizophr. 2017;3: 2.

2. Case M, Stauffer VL, Ascher-Svanum H, Conley R, Kapur S, Kane JM, et al. The heterogeneity of antipsychotic response in the treatment of schizophrenia. Psychol Med. 2011;41: 1291–1300.

3. Stephan KE, Bach DR, Fletcher, P. C., Flint J, Frank MJ, Friston KJ, et al. Charting the landscape of priority problems in psychiatry, part 1: classification and diagnosis. Lancet Psychiatry. 2016;3: 77–83.

4. Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and dysconnection in schizophrenia. Biol Psychiatry. 2006;59: 929–939.

5. Stephan KE, Friston KJ, Frith CD. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull. 2009;35: 509–527.

6. Friston K, Brown HR, Siemerkus J, Stephan KE. The dysconnection hypothesis (2016). Schizophr Res. 2016;176: 83–94.

7. Heinzle J, Aponte EA, Stephan KE. Computational models of eye movements and their application to schizophrenia. Current Opinion in Behavioral Sciences. Elsevier; 2016;11: 21–29.

8. Hutton SB, Ettinger U. The antisaccade task as a research tool in psychopathology: a critical review. Psychophysiology. 2006;43: 302–313.

9. Munoz DP, Everling S. Look away: the anti-saccade task and the voluntary control of eye movement. Nat Rev Neurosci. 2004;5: 218–228.

10. Fukushima J, Fukushima K, Chiba T, Tanaka S, Yamashita I, Kato M. Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. Biol Psychiatry. 1988;23: 670–677.

11. Myles JB, Rossell SL, Phillipou A, Thomas E, Gurvich C. Insights to the schizophrenia continuum: A systematic review of saccadic eye movements in schizotypy and biological relatives of schizophrenia patients. Neurosci Biobehav Rev. 2017;72: 278–300.

12. Radant AD, Millard SP, Braff DL, Calkins ME, Dobie DJ, Freedman R, et al. Robust differences in antisaccade performance exist between COGS schizophrenia cases and controls regardless of recruitment strategies. Schizophr Res. 2015;163: 47–52.

13. Reilly JL, Frankovich K, Hill S, Gershon ES, Keefe RS, Keshavan MS, et al. Elevated antisaccade error rate as an intermediate phenotype for

psychosis across diagnostic categories. Schizophr Bull. 2014;40: 1011–1021.

14. Matsuda T, Matsuura M, Ohkubo T, Ohkubo H, Matsushima E, Inoue K, et al. Functional MRI mapping of brain activation during visually guided saccades and antisaccades: cortical and subcortical networks. Psychiatry Res. 2004;131: 147–155.

15. Wiecki TV, Frank MJ. A computational model of inhibitory control in frontal cortex and basal ganglia. Psychol Rev. 2013;120: 329–355.

16. Hikosaka O, Takikawa Y, Kawagoe R. Role of the basal ganglia in the control of purposive saccadic eye movements. Physiol Rev. 2000;80: 953–978.

17. Isoda M, Hikosaka O. Role for subthalamic nucleus neurons in switching from automatic to controlled eye movement. J Neurosci. 2008;28: 7209–7218.

18. Condy C, Rivaud-Pechoux S, Ostendorf F, Ploner CJ, Gaymard B. Neural substrate of antisaccades: role of subcortical structures. Neurology. 2004;63: 1571–1578.

19. Guitton D, Buchtel HA, Douglas RM. Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. Exp Brain Res. 1985;58: 455–472.

20. Pierrot-Deseilligny C, Rivaud S, Gaymard B, Agid Y. Cortical control of reflexive visually-guided saccades. Brain. 1991;114 (Pt 3): 1473–1485.

21. Reuter B, Rakusan L, Kathmanna N. Poor antisaccade performance in schizophrenia: an inhibition deficit? Psychiatry Res. 2005;135: 1–10.

22. Everling S, Johnston K. Control of the superior colliculus by the lateral prefrontal cortex. Philos Trans R Soc Lond, B, Biol Sci. 2013;368: 20130068.

23. Arango C, Garibaldi G, Marder SR. Pharmacological approaches to treating negative symptoms: a review of clinical trials. Schizophr Res. 2013;150: 346–352.

24. Buchanan RW, Conley RR, Dickinson D, Ball MP, Feldman S, Gold JM, et al. Galantamine for the treatment of cognitive impairments in people with schizophrenia. Am J Psychiatry. 2008;165: 82–89.

25. Lieberman JA, Dunbar G, Segreti AC, Girgis RR, Seoane F, Beaver JS, et al. A randomized exploratory trial of an Î±-7 nicotinic receptor agonist (TC-5619) for cognitive enhancement in schizophrenia. Neuropsychopharmacology. 2013;38: 968–975.

26. Conley RR, Boggs DL, Kelly DL, McMahon RP, Dickinson D, Feldman S, et al. The effects of galantamine on psychopathology in chronic stable schizophrenia. Clin Neuropharmacol. 2009;32: 69–74.

27. Lindenmayer JP, Khan A. Galantamine augmentation of long-acting injectable risperidone for cognitive impairments in chronic schizophrenia. Schizophr Res. 2011;125: 267–277.

28. Umbricht D, Keefe RS, Murray S, Lowe DA, Porter R, Garibaldi G, et al. A randomized, placebo-controlled study investigating the nicotinic Î±7 agonist, RG3487, for cognitive deficits in schizophrenia. Neuropsychopharmacology. 2014;39: 1568–1577.

29. Walling D, Marder SR, Kane J, Fleischhacker WW, Keefe RS, Hosford DA, et al. Phase 2 Trial of an Alpha-7 Nicotinic Receptor Agonist (TC-5619) in Negative and Cognitive Symptoms of Schizophrenia. Schizophr Bull. 2016;42: 335–343.

30. Bowling AC, Donnelly JF. Effect of nicotine on saccadic eye movement latencies in non-smokers. Hum Psychopharmacol. 2010;25: 410–418.

31. Depatie L, O'Driscoll GA, Holahan AL, Atkinson V, Thavundayil JX, Kin NN, et al. Nicotine and behavioral markers of risk for schizophrenia: a double-blind, placebo-controlled, cross-over study. Neuropsychopharmacology. 2002;27: 1056–1070.

32. Ettinger U, Williams SC, Patel D, Michel TM, Nwaigwe A, Caceres A, et al. Effects of acute nicotine on brain function in healthy smokers and non-smokers: estimation of inter-individual response heterogeneity. Neuroimage. 2009;45: 549–561.

33. Larrison AL, Briand KA, Sereno AB. Nicotine improves antisaccade task performance without affecting prosaccades. Hum Psychopharmacol. 2004;19: 409–419.

34. Petrovsky N, Ettinger U, Quednow BB, Walter H, Schnell K, Kessler H, et al. Nicotine differentially modulates antisaccade performance in healthy male non-smoking volunteers stratified for low and high accuracy. Psychopharmacology (Berl). 2012;221: 27–38.

35. Petrovsky N, Ettinger U, Quednow BB, Landsberg MW, Drees J, Lennertz L, et al. Nicotine enhances antisaccade performance in schizophrenia patients and healthy controls. Int J Neuropsychopharmacol. 2013;16: 1473–1481.

36. Powell J, Dawkins L, Davis RE. Smoking, reward responsiveness, and response inhibition: tests of an incentive motivational model. Biol Psychiatry. 2002;51: 151–163.

37. Roos YBWEM, de Jongh FE, Crevits L. The effects of smoking on anti-saccades: A study in regular smokers. Neuro-Ophthalmology. 1995;15: 3–8. doi:10.3109/01658109509044587

38. Rycroft N, Hutton SB, Rusted JM. The antisaccade task as an index of sustained goal activation in working memory: modulation by nicotine. Psychopharmacology (Berl). 2006;188: 521–529.

39. Rycroft N, Hutton SB, Clowry O, Groomsbridge C, Sierakowski A, Rusted JM. Non-cholinergic modulation of antisaccade performance: a modafinil-nicotine comparison. Psychopharmacology (Berl). 2007;195: 245–253.

40. Ettinger U, Faiola E, Kasparbauer AM, Petrovsky N, Chan RC, Liepelt R, et al. Effects of nicotine on response inhibition and interference control. Psychopharmacology (Berl). 2017;234: 1093–1111.

41. Schmechtig A, Lees J, Grayson L, Craig KJ, Dadhiwala R, Dawson GR, et al. Effects of risperidone, amisulpride and nicotine on eye movement control and their modulation by schizotypy. Psychopharmacology (Berl). 2013;227: 331–345.

42. Aponte EA, Schobi D, Stephan KE, Heinzle J. The Stochastic Early Reaction, Inhibition, and late Action (SERIA) model for antisaccades. PLoS Comput Biol. 2017;13: e1005692.

43. Aponte EA, Tschan DG, Heinzle J, Stephan KE. Inhibition and late errors in the antisaccade task: Influence of task design. Journal of Neurophysiology. Cold Spring Harbor Laboratory; 2018;: 270165. doi:10.1101/270165

44. Stephan KE, Schlagenhauf F, Huys QJ, Raman S, Aponte EA, Brodersen KH, et al. Computational neuroimaging strategies for single patient predictions. Neuroimage. 2017;145: 180–199.

45. Caldu X, Dreher JC. Hormonal and genetic influences on processing reward and social information. Ann N Y Acad Sci. 2007;1118: 43–73.

46. Koller WC, Rueda MG. Mechanism of action of dopaminergic agents in Parkinson's disease. Neurology. 1998;50: S11–14.

47. Texido L, Ros E, Martin-Satue M, Lopez S, Aleu J, Marsal J, et al. Effect of galantamine on the human alpha7 neuronal nicotinic acetylcholine receptor, the Torpedo nicotinic acetylcholine receptor and spontaneous cholinergic synaptic activity. Br J Pharmacol. 2005;145: 672–678.

48. Maelicke A, Samochocki M, Jostock R, Fehrenbacher A, Ludwig J, Albuquerque EX, et al. Allosteric sensitization of nicotinic receptors by galantamine, a new treatment strategy for Alzheimer's disease. Biol Psychiatry. 2001;49: 279–288.

49. Santos MD, Alkondon M, Pereira EF, Aracava Y, Eisenberg HM, Maelicke A, et al. The nicotinic allosteric potentiating ligand galantamine facilitates synaptic transmission in the mammalian central nervous system. Mol Pharmacol. 2002;61: 1222–1234.

50. Samochocki M, Hoffle A, Fehrenbacher A, Jostock R, Ludwig J, Christner C, et al. Galantamine is an allosterically potentiating ligand of neuronal nicotinic but not of muscarinic acetylcholine receptors. J Pharmacol Exp Ther. 2003;305: 1024–1036.

51. Aponte EA, Stephan KE, Heinzle J. Switch costs in inhibitory control and voluntary behavior: A computational study of the antisaccade task. European Journal of Neuroscience. 2019. doi:https://doi.org/10.1111/ejn.14435

52. Gelman A, B CJ, S SH, B RD. Bayesian Data Analysis. Chapman and Hall/CRC; 2003.

53. Friedman JH. Greedy function approximation: a gradient boosting machine. Annals of statistics. JSTOR; 2001;: 1189–1232.

54. Chen T, Guestrin C. Xgboost: A scalable tree boosting system. 2016. pp. 785–794.

55. Tatler BW, Hutton SB. Trial by trial effects in the antisaccade task. Exp Brain Res. 2007;179: 387–396.

56. Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev. 2006;30: 1–23.

57. Duka T, Lupp A. The effects of incentive on antisaccades: is a dopaminergic mechanism involved? Behav Pharmacol. 1997;8: 373–382.

58. Hood AJ, Amador SC, Cain AE, Briand KA, Al-Refai AH, Schiess MC, et al. Levodopa slows prosaccades and improves antisaccades: an eye movement study in Parkinson's disease. J Neurol Neurosurg Psychiatr. 2007;78: 565–570.

59. Obeso I, Wilkinson L, Jahanshahi M. Levodopa medication does not influence motor inhibition or conflict resolution in a conditional stop-signal task in Parkinson's disease. Exp Brain Res. 2011;213: 435–445.

60. Overtoom CC, Verbaten MN, Kemner C, Kenemans JL, van Engeland H, Buitelaar JK, et al. Effects of methylphenidate, desipramine, and L-dopa on attention and inhibition in children with Attention Deficit Hyperactivity Disorder. Behav Brain Res. 2003;145: 7–15.

61. Everling S, DeSouza JF. Rule-dependent activity for prosaccades and antisaccades in the primate prefrontal cortex. J Cogn Neurosci. 2005;17: 1483–1496.

62. Amemori K, Sawaguchi T. Rule-dependent shifting of sensorimotor representation in the primate prefrontal cortex. Eur J Neurosci. 2006;23: 1895–1909.

63. Lo CC, Wang XJ. Conflict Resolution as Near-Threshold Decision-Making: A Spiking Neural Circuit Model with Two-Stage Competition for Antisaccadic Task. PLoS Comput Biol. 2016;12: e1005081.

64. Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat Neurosci. 2007;10: 376–384.

65. Vossel S, Bauer M, Mathys C, Adams RA, Dolan RJ, Stephan KE, et al. Cholinergic stimulation enhances Bayesian belief updating in the deployment of spatial attention. J Neurosci. 2014;34: 15735–15742.

66. Woodruff-Pak DS, Vogel RW, Wenk GL. Galantamine: effect on nicotinic receptor binding, acetylcholinesterase inhibition, and learning. Proc Natl Acad Sci USA. 2001;98: 2089–2094.

67. Dyer MA, Freudenreich O, Culhane MA, Pachas GN, Deckersbach T, Murphy E, et al. High-dose galantamine augmentation inferior to placebo on attention, inhibitory control and working memory performance in nonsmokers with schizophrenia. Schizophr Res. 2008;102: 88–95.

68. Bishop CM. Pattern Recognition and Machine Learning (Information Science and Statistics). Secaucus, NJ, USA: Springer-Verlag New York, Inc; 2006.

Supplementary materials

Supplementary 1

This section describes the modeling procedures. It is based on the previous publications and, in particular, includes passages from the supplementary materials of [51]. To infer the model parameters of all subjects, we used the SERIA model [42]. The likelihood function of SERIA is the joint probability of an action $A \in \{pro, anti\}$ and the associated RT $\in [0, \infty[$. According to this model, saccades are the product of the competition between four units that race to threshold: the early prosaccade unit u_e, the inhibitory unit u_i, the antisaccade unit u_a, and the late prosaccade u_p. Their hit times are treated as random variables (U_e, U_i, U_a, U_p respectively). A prosaccade is generated when either *(i)* the early unit hits threshold before all other units, *(ii)* the late prosaccade unit hits threshold before all other units, or *(iii)* the early unit is blocked by the inhibitory unit, and the late prosaccade unit is faster than the antisaccade unit. Formally, we express these three cases with the following equation, which represents the probability p of a prosaccade at time *t:*

$$\begin{aligned} p(A = pro, RT = t) = {} & p(U_e = t)p(U_a > t)p(U_i > t)p\big(U_p > t\big) + \\ & p\big(U_p = t\big)p(U_a > t)p(U_i > t)p(U_e > t) + \\ & p\big(U_p = t\big)p(U_a > t)\int_0^t p(U_i = \tau)p(U_e > \tau)d\tau\,. \end{aligned} \tag{S1}$$

An antisaccade at time t occurs when the antisaccade unit hits threshold before all other units, or the inhibitory unit hits threshold before the early unit, and the antisaccade unit hits threshold before the late prosaccade unit.

$$\begin{aligned} p(A = anti, RT = t) = {} & p(U_a = t)p\big(U_p > t\big)p(U_e > t)p(U_i > t) + \\ & p(U_a = t)p\big(U_p > t\big)\int_0^t p(U_i = \tau)p(U_e > \tau)d\tau\,. \end{aligned} \tag{S2}$$

This constitutes the likelihood function of the SERIA model. A more detailed treatment can be found in [42]. The code is openly available in https://github.com/translationalneuromodeling/tapas.

To fit SERIA to trial-by-trial RT and actions from each subject, we used a hierarchical model. In other words, we used an empirical prior that models the population distribution. Figure S1 presents the model in graphical notation following [68].

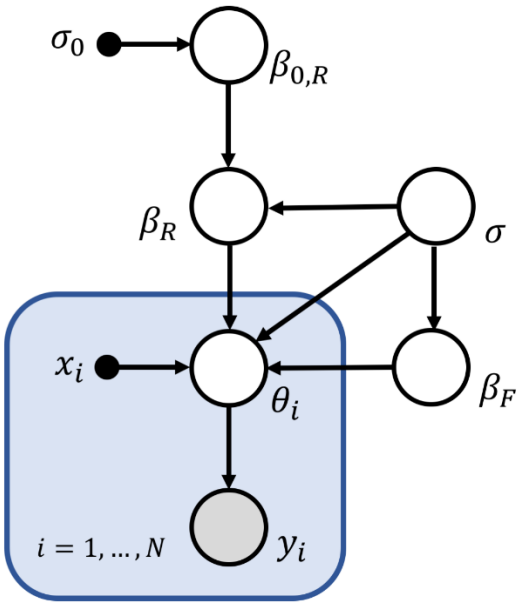

Figure S1: Graphical representation of the hierarchical model. Graphical summary of the statistical model using the convention in [68]. Briefly, each circle represents a probability distribution and arrows indicate conditional dependence. Black dots represent fixed parameters. The equations describing the distributions of each node are given below. The most important feature of the model is that the prior distribution of each set of parameters $\boldsymbol{\theta_i}$ is parametrically defined by a set of explanatory variables $\boldsymbol{x_i}$ and coefficients $\boldsymbol{\beta}$ with variance $\boldsymbol{\sigma^2}$. These coefficients are estimated from the population distribution. We partition parameters $\boldsymbol{\beta}$ into fixed ($\boldsymbol{\beta_F}$) and random effects ($\boldsymbol{\beta_R}$), such that the latter have a prior mean estimated again from the population distribution. For the present study, random effects represent subject specific intercepts, while their mean (or global intercept) is modeled by $\boldsymbol{\beta_{0,R}}$, whose prior distribution is assumed to be centered at zero with variance $\boldsymbol{\sigma_0^2}$.

In the following, we present the mathematical description of the model depicted in Figure S1. We will write down the conditional probabilities that specify individual nodes of the graphical model, starting from the likelihood and then moving up the hierarchy. To simplify notation, we assume that the data in each run i, i.e., the RT and actions in a single block of each subject, are represented by a vector y_i and a parameter θ_i. The extension to a multivariate model is straightforward under the assumption that different parameters are conditionally independent. This assumption facilitates the construction of a hierarchical extension of SERIA.

The likelihood of the model (represented by the gray shaded circle in Figure S1) is given by the product of the likelihood of all runs, i.e. all sessions in all subjects:

$$p(y_1, \dots, y_N | \theta_1, \dots, \theta_N) = \Pi_{i=1}^{N} p(y_i | \theta_i). \qquad (S3)$$

The prior distribution of parameters θ_i is given by

$$p(\theta_i|x_i, \beta, \sigma) = \mathcal{N}(\theta_i; x_i \cdot \beta, \sigma^2). \tag{S4}$$

$X = (x_1, \dots, x_N)$ is a design matrix of size $M \times N$ that codes M explanatory variables, such as SUBJECT, PP, etc., and β is a vector of dimension $M \times 1$ that represents the effect of each explanatory variable. The prior distribution of β is given by

$$p(\beta|\beta_0, \sigma) = \mathcal{N}(\beta; \beta_0, \sigma^2) \tag{S5}$$

and the prior probability of σ is

$$p(\sigma^{-2}) = \Gamma(\sigma^{-2}; a, b). \tag{S6}$$

We distinguish between two types of β coefficients in analogy to the concepts of fixed and random effects. For fixed effects β_F, we assumed that the coefficients have a fixed prior mean $\beta_{0,F} = 0$. For random effects β_R, we assume that the prior mean $\beta_{0,R}$ is a random variable drawn from a distribution that represents the sample population, i.e. all subjects,

$$p(\beta_{0,R}|\beta_R, \sigma, \sigma_0) \propto p(\beta_R|\beta_{0,R}, \sigma) p(\beta_{0,R}|0, \sigma_0) \tag{S7}$$

$$\propto \mathcal{N}(\beta_R; \beta_{0,R}, \sigma^2) \mathcal{N}(\beta_{0,R}; 0, \sigma_0^2) \tag{S8}$$

The conditional posterior of $\beta_{0,R}$ can be computed analytically and is given by

$$p(\beta_{0,R}|\beta_R, \sigma, \sigma_0) = \mathcal{N}(\beta_{0,R}; \mu_R, \pi_R^{-1}), \tag{S9}$$

where

$$\mu_R = \frac{\sigma^{-2} \sum_{i=1}^{N} \beta_{i,R}}{N\sigma^{-2} + \sigma_0^{-2}}, \tag{S10}$$

$$\pi_R = (N\sigma^{-2} + \sigma_0^{-2}). \tag{S11}$$

The rationale for including a random effect is to account for the idiosyncrasies of each subject with the parameters β_R while modeling a population wide intercept $\beta_{0,R}$.

All equations defined above are linear and rely on conjugate priors. Hence, it is possible to derive Gibbs steps to sample from the conditional posterior distributions of all parameters with the exception of $\theta_{1,..,N}$, which are sampled from a Gaussian kernel centered at the previous sample.

Supplementary 2

Table S1: Mean number of invalid trials per subject

	Mean # invalid trials							
	Experiment 1							
	Valid	Blink	Missing	Aborted	FE	Late	Early	NS
Placebo	563(10)	4(5)	1(3)	1(2)	5(5)	0(0)	1(1)	0(0)
L-dopa	562(14)	5(7)	1(3)	1(2)	5(6)	0(0)	1(2)	0(0)
	Experiment 2							
	Valid	Blink	Missing	Aborted	FE	Late	Early	NS
Placebo	558(24)	10(17)	3(6)	1(1)	3(7)	0(0)	1(1)	0(0)
Galan.	562(18)	9(14)	1(3)	1(2)	3(5)	0(0)	0(1)	0(0)

std. is displayed in brackets. Late = saccades with latency above 800ms. Early = saccades with latency below 90ms. FE = fixation errors, NS = No saccade.

Supplementary 3

Table S2: Mean error rate

	Error rate (%)					
	Experiment 1					
	Placebo			Levodopa		
	PP20	PP50	PP80	PP20	PP50	PP80
Anti.	23(17)	36(22)	52(20)	23(16)	36(21)	52(24)
Pro.	26(15)	11(8)	4(3)	25(18)	10(8)	3(4)
	Experiment 2					
	Placebo			Galantamine		
	PP20	PP50	PP80	PP20	PP50	PP80
Anti.	23(17)	36(22)	55(19)	22(17)	36(21)	53(22)
Pro.	31(17)	14(10)	5(3)	32(16)	15(9)	5(4)

std. is displayed in brackets.

Supplementary 4

Table S3: Mean reaction time.

Mean reaction times (ms)							
		Experiment 1					
		Placebo			Levodopa		
Trial	Action	PP20	PP50	PP80	PP20	PP50	PP80
Anti.	Anti.	355	381	391	367	380	396
		(59)	(55)	(60)	(73)	(65)	(70)
Anti.	Pro.	234	231	226	231	228	222
		(51)	(48)	(31)	(56)	(43)	(39)
Pro.	Pro.	332	320	285	329	319	279
		(72)	(68)	(59)	(65)	(60)	(51)
Pro.	Anti.	327	330	338	338	351	342
		(68)	(45)	(56)	(70)	(82)	(65)
		Experiment 2					
		Placebo			Galantamine		
Trial	Action	PP20	PP50	PP80	PP20	PP50	PP80
Anti.	Anti.	323	348	363	313	335	353
		(50)	(66)	(72)	(49)	(52)	(60)
Anti.	Pro.	218	225	215	220	220	211
		(35)	(41)	(30)	(44)	(39)	(34)
Pro.	Pro.	299	293	261	285	286	262
		(55)	(58)	(41)	(59)	(52)	(52)
Pro.	Anti.	300	307	305	293	301	314
		(42)	(52)	(62)	(50)	(42)	(59)

std. is displayed in brackets.