## Supporting Information

# Statistical Analyses

## Multiple Break-Point Test

We used a Bai-Perron multiple break point test (Bai and Perron, 1998) to identify breaks in the coefficients of a linear regression of average choices on trial numbers. The test showed that there arSe two breaks in the coefficients, in both the gain and loss domain. Figures S1 illustrates individuals´ choices, the fitted regression lines and the break points identified. The break points are in trials 9 and 25 in the gain domain and in trials 11 and 31 in the loss domain.

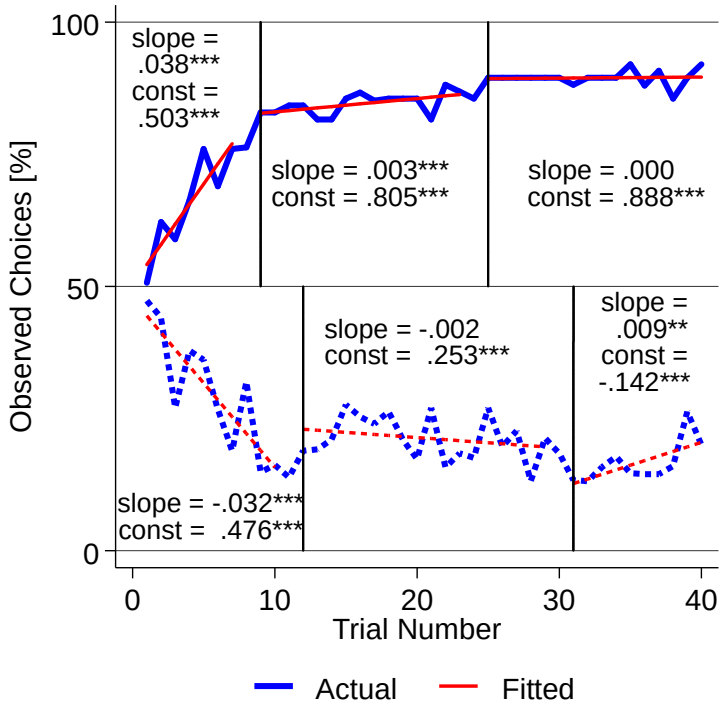


Figure S1. Bai-Perron multiple break-point test. The blue lines depict the actual ratio of volunteers that chose the "correct" stimulus in the gain domain (upper graph, solid lines), and the "incorrect" stimulus in the loss domain (lower graph, dashed lines). The red lines depict the fitted ratio of "correct" and "incorrect" choices based on linear regressions with trial numbers as the only explanatory variable. The linear regression is estimated separately in each phase and for the gain and loss domain. The size of the slope coefficients and the constant terms are reported in the graph. ***, **, * depict significance on the 1%, 5% and 10% level, respectively. Vertical lines at the break points indicate structural break points.

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## Logistic Growth Curve Model

The logistic growth curve approach is a non-linear approach suitable to model dynamics of learning data. This approach models learning by fitting a logistic function (sigmoid, $f(choice) = 1/\left(e^{-(m*trial+b)} + 1\right)$ to the data. The shape of the "upper part" of the S-shaped curve yield the best fit to our data as increments in correct choices are large in the early trials, but reduced as learning stabilizes. While parameter *m* determines the estimated curvature of the learning curve, parameter *b* determines the estimate of the choice in the first period (intercept). In our model we allow for different values of *m* in the placebo and sulpiride groups. We fix *b*, however, as testing for effects of sulpiride on *b* turned out to be non-significant. The fitting of a log growth curve to the data (Table S1) confirms that the volunteers in the sulpiride group chose less frequently the correct stimulus than volunteers in the placebo group (m * treatment dummy) and this decrease is specific to the gain domain (m * domain dummy * treatment dummy). The results also hold for serum level analysis and are only observed in A1+, but not in A1- allele carriers.

Table S1. Data analysis of the logistic growth curve model.

| Dependent variable:<br>Choice dummy (1=correct choice) | All | Only sulpiride | A1+ | A1- |
|---|---|---|---|---|
| Trial (m) | 0.07 | 0.11 | 0.13 | 0.05 |
| | (0.007)** | (0.015)** | (0.017)** | (0.007)** |
| m * treatment dummy (1=sulpiride) | -0.04 | | -0.09 | -0.00 |
| | (0.006)** | | (0.016)** | (0.008) |
| m * sulpiride serum level dummy (1=high) | | -0.10 | | |
| | | (0.014)** | | |
| m * domain dummy (1=loss) | -0.04 | -0.07 | -0.10 | -0.02 |
| | (0.006)** | (0.014)** | (0.016)** | (0.007)** |
| m * domain dummy * treatment dummy | 0.04 | | 0.10 | -0.00 |
| | (0.008)** | | (0.017)** | (0.010) |
| m * domain dummy * serum level dummy | | 0.08 | | |
| | | (0.015)** | | |
| Intercept (b) | 0.66 | 0.57 | 0.63 | 0.68 |
| | (0.065)** | (0.091)** | (0.094)** | (0.091)** |
| Observations | 6009 | 3083 | 3003 | 3006 |
| Adjusted-$R^2$ | 0.81 | 0.80 | 0.82 | 0.81 |

*Notes*. The table reports the coefficients of a non-linear regression. In parenthesis are White standard errors and asterisks denote the significance level: + 10%-level, * 5%-level, ** 1%-level.

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Rows labeled "m * treatment dummy (1=sulpiride)" and "m * sulpiride serum level dummy (1=high)" show sulpiride or serum level effects on learning. Rows labeled "m * domain dummy * treatment dummy" and "m * domain dummy * serum level dummy" show that sulpiride as well as sulpiride serum value effects were indeed specific for the gain domain. To test whether sulpiride had differential effects in the A1+ and A1- group on *m*, we perform a t-test on whether the difference in the coefficients is equal to zero (t-test, $t = 5.03 = (-0.10 - (-0.00))/\sqrt{(.016^2 + .008^2)}$, $p = 0.000$, n = 6009). The number of observation is based on 76 volunteers who each perform 40 trials in the gain domain and 40 trials in the loss domain. Missing observations occurred when volunteers pressed the buttons too late (33 in the sulpiride and 35 in the placebo group) or pressed the wrong button (1 in the sulpiride and 2 in the placebo group) out of 6080 responses.

## Q-Learning Model

Table S2 shows the detailed parameter estimates of the Q-learning model. This model uses two parameters that dissociate the learning rate and choice performance.

Table S2. Parameter estimates of the Q-learning model.

| | **All** | **Only sulpiride** | **A1+** | **A1-** |
|---|---|---|---|---|
| 1) Learning rate (α) | 0.06 | 0.05 | 0.07 | 0.04 |
| | (0.011)** | (0.013)** | (0.016)** | (0.016)** |
| 2) α * treatment dummy (1 = sulpiride) | 0.00 | | 0.01 | 0.00 |
| | (0.016) | | (0.025) | (0.021) |
| 3) α * sulpiride serum level dummy (1 = high) | | 0.00 | | |
| | | (0.025) | | |
| 4) α * domain dummy (1 = loss) | 0.10 | 0.05 | 0.14 | 0.06 |
| | (0.023)** | (0.026)* | (0.036)** | (0.030)+ |
| 5) α * domain dummy * treatment dummy | -0.03 | | -0.07 | 0.01 |
| | (0.032) | | (0.049) | (0.042) |
| 6) α * domain dummy * serum level dummy | | 0.05 | | |
| | | (0.045) | | |
| 7) Temperature (β) | 0.14 | 0.12 | 0.09 | 0.16 |
| | (0.016)** | (0.017)** | (0.013)** | (0.037)** |
| 8) β * Treatment dummy (1 = sulpiride) | 0.08 | | 0.19 | -0.01 |
| | (0.027)** | | (0.035)** | (0.047) |
| 9) β * Sulpiride serum level dummy (1 = high) | | 0.22 | | |
| | | (0.067)** | | |
| 10) β * domain dummy (1 = loss) | 0.18 | 0.16 | 0.25 | 0.14 |
| | (0.025)** | (0.029)** | (0.031)** | (0.048)** |
| 11) β * domain dummy * treatment dummy | -0.10 | | -0.24 | 0.03 |
| | (0.038)** | | (0.050)** | (0.063) |
| 12) β * domain dummy * serum level dummy | | -0.17 | | |
| | | (0.076)* | | |
| Observations | 6009 | 3083 | 3003 | 3006 |
| Log-likelihood | -2741.60 | -1437.71 | -1288.90 | -1405.09 |

| | | | | |
|---|---|---|---|---|
| Pseudo-$R^2$ | 0.34 | 0.33 | 0.38 | 0.33 |
| Bayesian Information Criteria (BIC) | 5552.8 | 2939.7 | 2641.9 | 2874.3 |

*Notes*. The table reports parameter estimates of the Q-learning model. In parenthesis are standard errors of the estimated parameters and asterisks denote significance level of z-tests (coefficients tested against zero): + 10%-level, * 5%-level, ** 1%-level. The first row shows the estimated learning rate α in the placebo group for the gain domain. The second row labeled "α * treatment dummy (1 = sulpiride)" reports whether the learning rate is significantly different between the sulpiride and placebo group in the gain domain. The third row labeled "α * sulpiride serum level dummy (1 = high)" shows whether the learning rate is different in the sulpiride group between people with high and low serum levels in the gain domain. The fourth row labeled "α * domain dummy (1 = loss)" reports whether the learning rate is different between the gain and loss domain in the placebo group. The fifth row labeled "α * domain dummy * treatment dummy" reports whether the effect of sulpiride on the learning rate is different between the gain and loss domain. The sixth row labeled „α * domain dummy * serum level dummy" indicates whether the effect of the serum level in the sulpiride group was different between the gain and loss domain. Rows 7 – 12 report the temperature (β) effects and can be interpreted in the same way as rows 1 – 6. To test whether sulpiride had differential effects in the A1+ and A1- group on β (row 8), we perform a t-test on whether the difference in the coefficients is equal to zero (t-test, $t = 3.41 = (0.19 - (-0.01))/\sqrt{(.035^2 + .047^2)}$, $p = 0.001$, $n = 6009$).

**Q-Learning Model Comparison.** We compare our model with alternative models to assess quality, using the Bayesian Information criteria (BIC) values (Table S3). The first comparison model is a naïve baseline model without parameters assuming that volunteers choose all stimuli with equal probability. A model that does not do better than the naïve baseline model should be considered an implausible model describing the observed learning process. We computed BIC values for further comparison models that constrain either $\alpha$, $\beta$, or both to be the same in the gain and loss domains. We also test specifications without a temperature parameter $\beta$. The model motivated by theoretical assumptions yields the lowest BIC values ("2 β and 2 α"). Alternative models, e.g. a model using only two estimates, irrespective of the gain and loss domain ("1 β and 1 α"), perform worse.

Table S3. Model comparisons.

| Models | BIC value |
|---|---|
| 2 β and 2 α (preferred model) | **5552.8** |
| 0 β and 0 α (naive model) | 8330.2 |
| 0 β and 1 α | 6806.7 |
| 0 β and 2 α | 6813.8 |
| 1 β and 1 α | 5601.3 |
| 1 β and 2 α | 5598.5 |
| 2 β and 1 α | 5565.9 |

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## Plasma Prolactin Levels

Sulpiride is well-known to induce an increase in prolactin serum concentrations by blocking DA D2 receptors which under normal conditions exert an inhibitory effect on prolactin secreting cells in the pituitary (Muller *et al*, 1983). In line with this, blood plasma prolactin levels increased significantly by 33.1 mg/ml (+ 350%) after sulpiride administration (Wilcoxon signed-ranks test, $p = 0.000$, n = 37), and this increase was significantly higher (Mann Whitney test, $p = 0.000$, n = 73) than the changes in the placebo group -0.91 mg/ml (-12%). The laboratory was not able to extract reliable prolactin data for three volunteers due to blood contamination.

## Side-Effects

We performed several measures of physiological side effects such as blood-pressure and heart-rate, but also assessed self-reported side-effects, using a drug effects questionnaire (neurovegetative list, NVL) (Rush *et al*, 2003) and visual analogue scales (VAS) of alertness, calmness and contentedness (Bond and Lader, 1974). Items in the scale were alert/drowsy, calm/excited, strong/feeble, muzzy/clear-headed, well coordinated/clumsy, lethargic/energetic, contented–discontented, troubled–tranquil, mentally slow/quick-witted, tense/relaxed, attentive/dreamy, incompetent/proficient, happy/sad, antagonistic/amicable, interested/bored and withdrawn/gregarious. These dimensions were presented as 10 cm lines on a computer screen and volunteers marked their current state on each line with a mouse click. In line with previous studies (Chamberlain *et al*, 2006; Eisenegger *et al*, 2010a), the factors “alertness”, “contentedness”, and “calmness” were calculated from these items.

Physiological measures as well as the VAS were measured at baseline and 3 hours after drug administration, NVL only after drug administration. Table S4 shows all side-effects measures, their changes over time, as well as the results of a Mann-Whitney test for differences across treatment groups. NVL and VAS data of one volunteer recorded at 3 hours were lost due to a technical problem. Significance levels are not above chance level if corrected for multiple testing (Holm-Bonferroni correction). Notably, a drug-group awareness check (Eisenegger *et al*, 2010b) shows that volunteers did not notice whether they got sulpiride or placebo. While 30% volunteers who received placebo believed to have received sulpiride, 34% of volunteers believed so in the sulpiride group (Mann-Whitney test, $p = 0.68$, n = 75).

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Table S4. Physiological and self-reported side effects following administration of 800 mg of sulpiride or placebo.

| side effects | time point | N | Plac. | Sulp. | Sign. (*p*) |
|---|---|---|---|---|---|
| Heart rate | base | 76 | 69.2 | 67.5 | 0.807 |
| | 3 h | 76 | 63.8 | 64.9 | 0.596 |
| | δ | 76 | -5.4 | -2.6 | 0.666 |
| Blood pressure systolic [mm hg] | base | 76 | 132.2 | 132.8 | 0.783 |
| | 3 h | 76 | 128.1 | 127.5 | 0.975 |
| | δ | 76 | -4.1 | -5.4 | 0.621 |
| Blood pressure diastolic [mm hg] | base | 76 | 76.1 | 76.9 | 0.856 |
| | 3 h | 76 | 72.0 | 70.9 | 0.629 |
| | δ | 76 | -4.1 | -6.0 | 0.240 |
| VAS: alertness (mean) | base | 76 | 22.6 | 23.4 | 0.880 |
| | 3 h | 75 | 28.5 | 28.8 | 0.945 |
| | δ | 75 | 5.9 | 5.7 | 0.719 |
| VAS: contentedness (mean) | base | 76 | 18.7 | 19.6 | 0.767 |
| | 3 h | 75 | 20.6 | 22.1 | 0.660 |
| | δ | 75 | 2.0 | 3.0 | 0.304 |
| VAS: calmness (mean) | base | 76 | 22.6 | 24.9 | 0.659 |
| | 3 h | 75 | 23.0 | 23.4 | 0.812 |
| | δ | 75 | 0.4 | -0.8 | 0.890 |
| NVL: any effect | 3h | 75 | -31.5 | -38.3 | 0.743 |
| NVL: bad effects | 3h | 75 | -42.4 | -43.1 | 0.439 |
| NVL: good effects | 3h | 75 | -40.2 | -40.7 | 0.570 |
| NVL: high | 3h | 75 | -43.3 | -41.6 | 0.204 |
| NVL: rush | 3h | 75 | -41.3 | -43.6 | 0.270 |
| NVL: like drug | 3h | 75 | -16.8 | -14.6 | 0.417 |
| NVL: stimulated | 3h | 75 | -39.4 | -36.7 | 0.100 |
| NVL: performance impaired | 3h | 75 | -38.2 | -35.6 | 0.152 |
| NVL: performance improved | 3h | 75 | -38.1 | -41.1 | 0.629 |
| NVL: willing to take again | 3h | 75 | 8.8 | 2.9 | 0.656 |
| NVL: willing to pay for | 3h | 75 | -39.3 | -40.8 | 0.402 |
| NVL: active-alert-energetic | 3h | 75 | -35.1 | -37.9 | 0.844 |
| NVL: shaky/jittery | 3h | 75 | -42.0 | -36.0 | 0.337 |
| NVL: euphoric | 3h | 75 | -43.3 | -38.7 | 0.158 |
| NVL: irregular or racing heart | 3h | 75 | -45.8 | -44.7 | 0.153 |
| NVL: talkative-friendly | 3h | 75 | -39.1 | -31.9 | 0.049 |
| NVL: nauseated, queasy or sick to stomach | 3h | 75 | -46.4 | -46.5 | 0.393 |
| NVL: nervous or anxious | 3h | 75 | -42.9 | -45.1 | 0.734 |
| NVL: restless | 3h | 75 | -36.2 | -30.8 | 0.085 |
| NVL: sluggish-lazy-fatigued | 3h | 75 | -25.7 | -23.6 | 0.487 |

Notes. Base = baseline; 3h = 3 hours after drug loading; δ = difference between the value 3 hours after drug loading and the baseline; N = number of observations; Plac. = Placebo group; Sulp. = Sulpiride group; Sign. = Significance of Mann-Whitney tests for differences.

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## Response Latencies

We calculated the average response latencies using all choices, i.e. the correct and incorrect choices. Choices that were not taken within the time limit (1700ms) are not included in the calculation of the average response latencies. Choices that were not taken within the time limit are very few (34 in the sulpiride and 37 in the placebo group out of 6080 choices). The likelihoods that a choice is missing, is not different in the sulpiride and placebo group (t-test, $p$ = 0.893, $n$ = 6080). Table S5 shows the average response latencies and statistical tests comparing the sulpiride and the placebo group.

Table S5. Response Latencies

| | Gain | | | | Loss | | |
|---|---|---|---|---|---|---|---|
| **Trials** | Placebo | Sulpiride | Sign. ($p$) | **Trials** | Placebo | Sulpiride | Sign. ($p$) |
| **1-40** | 648 | 675 | 0.212 | **1-40** | 822 | 849 | 0.503 |
| **1-8** | 840 | 828 | 0.713 | **1-11** | 930 | 925 | 0.968 |
| **9-24** | 635 | 666 | 0.257 | **12-30** | 791 | 835 | 0.255 |
| **25-40** | 566 | 611 | 0.044 | **31-40** | 767 | 792 | 0.621 |

*Notes.* Average response latencies in milliseconds in the gain and loss domains, with significance levels for the three phases and all 40 trials derived from Student t-tests. For the calculation of the t-tests we used the log-transformed response latencies to meet statistical distributional assumptions (Judd and McClelland, 1989). Significant difference in response latencies was observed only in the last phase of the gain domain, in line with the time-point of behavioral impairments observed in the task.

# References

Bai JS, Perron P (1998). Estimating and testing linear models with multiple structural changes. *Econometrica* **66**: 47-78.

Bond A, Lader M (1974). Use of analog scales in rating subjective feelings. *Br J Med Psychol* **47**: 211-218.

Chamberlain SR, Müller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ (2006). Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science* **311**: 861-863.

Eisenegger C, Knoch D, Ebstein RP, Gianotti LRR, Sandor PS, Fehr E (2010a). Dopamine receptor D4 polymorphism predicts the effect of L-DOPA on gambling behavior. *Biol Psychiatry* **67**: 702-706.

Eisenegger C, Naef M, Snozzi R, Heinrichs M, Fehr E (2010b). Prejudice and truth about the effect of testosterone on human bargaining behaviour. *Nature* **463**: 356-359.

Judd CM, McClelland GH (1989). *Data analysis, a model-comparison approach*: Orlando, FL.

Muller EE, Locatelli V, Cella S, Penalva A, Novelli A, Cocchi D (1983). Prolactin-Lowering and Prolactin-Releasing Drugs Mechanisms of Action and Therapeutic Applications. *Drugs* **25**: 399-432.

Rush CR, Stoops WW, Hays LR, Glaser PEA, Hays LS (2003). Risperidone attenuates the discriminative-stimulus effects of d-amphetamine in humans. *J Pharmacol Exp Ther* **306**: 195-204.