

Supplementary Information

Supplementary Material and Methods

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.¹ In line with this, blood plasma prolactin levels increased significantly by 33.4 mg/ml (+349%) after sulpiride administration (Wilcoxon signed-ranks test, $p = 0.000$, $n = 36$), and this increase was significantly higher (Mann Whitney test, $p = 0.000$, $n = 72$) than the changes in the placebo group -0.91 mg/ml (-11%). The laboratory was not able to extract reliable prolactin data for three volunteers due to blood contamination.

Side-Effects

Items in the visual analogue scales (VAS) 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tense/relaxed, attentive/dreamy, incompetent/proficient, happy/sad, antagonistic/amicable, interested/bored and withdrawn/gregarious.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,^{2, 3} 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. Supplementary Table 1 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 check⁴ shows that volunteers did not notice whether they got sulpiride or placebo. While 32% volunteers who received placebo believed to have received sulpiride, 35% of volunteers believed so in the sulpiride group (Mann-Whitney test, $p = 0.81$, $n = 74$).

Supplementary Tables

Supplementary Table 1: Side Effects of 800mg Sulpiride

side effects	time point	N	Plac.	Sulp.	Sign. (<i>p</i>)
Heart rate	base	75	68.6	67.8	0.966
	3 h	75	63.0	65.4	0.402
	δ	75	-5.6	-2.4	0.538
Blood pressure systolic [mm hg]	base	75	131.1	133.2	0.439
	3 h	75	126.9	127.8	0.614
	δ	75	-4.1	-5.4	0.600
Blood pressure diastolic [mm hg]	base	75	75.5	76.8	0.742
	3 h	75	71.5	70.8	0.762
	δ	75	-4.0	-6.1	0.216
VAS: alertness (mean)	base	75	21.4	23.7	0.840
	3 h	74	24.9	29.0	0.697
	δ	74	3.5	5.7	0.513
VAS: contentedness (mean)	base	75	22.7	19.8	0.596
	3 h	74	27.6	22.5	0.524
	δ	74	4.9	3.2	0.250
VAS: calmness (mean)	base	75	18.3	24.4	0.874
	3 h	74	20.4	23.3	0.888
	δ	74	2.1	-0.4	0.996
NVL: any effect	3h	74	23.0	-38.3	0.709
NVL: bad effects	3h	74	23.9	-43.0	0.430
NVL: good effects	3h	74	0.9	-40.5	0.669
NVL: high	3h	74	-31.0	-41.4	0.311
NVL: rush	3h	74	-42.4	-43.5	0.238
NVL: like drug	3h	74	-38.7	-13.8	0.369
NVL: stimulated	3h	74	-41.9	-36.6	0.131
NVL: performance impaired	3h	74	-41.5	-35.6	0.118
NVL: performance improved	3h	74	-16.4	-41.2	0.559
NVL: willing to take again	3h	74	-39.3	4.3	0.593
NVL: willing to pay for	3h	74	-39.4	-40.6	0.392
NVL: active-alert-energetic	3h	74	-39.3	-37.7	0.940
NVL: shaky/jittery	3h	74	10.5	-36.2	0.236
NVL: euphoric	3h	74	-39.5	-38.5	0.203
NVL: irregular or racing heart	3h	74	-33.7	-44.6	0.335
NVL: talkative-friendly	3h	74	-43.6	-31.5	0.044
NVL: nauseated, queasy or sick to stomach	3h	74	-42.1	-46.5	0.343
NVL: nervous or anxious	3h	74	-44.0	-45.0	0.692
NVL: restless	3h	74	-39.4	-30.4	0.107
NVL: sluggish-lazy-fatigued	3h	74	-46.8	-23.5	0.509

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

Supplementary Table 2: Supplementary Table 3 Analysis of Variance of the number of errors and the strategy used in SWM

	<i>df</i> (n)	<i>df</i> (d)	<i>F</i>	<i>P</i>	η^2
<i>Between errors</i>					
Sulpiride	1	70	2.15	0.147	0.03
Genotype	1	70	2.79	0.099*	0.04
Sulpiride x Genotype	1	70	0.13	0.720	0.00
Task difficulty level	4	1020	202.26	0.000***	0.44
Sulpiride x Task difficulty level	4	1020	2.66	0.031**	0.01
Genotype x Task difficulty level	4	1020	2.55	0.038**	0.01
Sulpiride x Genotype x Task difficulty level	4	1020	0.49	0.746	0.00
<i>Rel. use of inefficient strategy</i>					
Sulpiride	1	70	0.63	0.431	0.01
Genotype	1	70	0.39	0.535	0.01
Sulpiride x Genotype	1	70	0.60	0.441	0.01
Task difficulty level	4	280	50.30	0.000***	0.42
Sulpiride x Task difficulty level	4	280	0.40	0.807	0.01
Genotype x Task difficulty level	4	280	0.65	0.630	0.01
Sulpiride x Genotype x Task difficulty level	4	280	2.48	0.044**	0.03

Notes. Repeated and Mixed-Measure ANOVA with between-search errors, and the relative strategy score as dependent variables. The number of observation is 1110 consisting of 74 volunteers taking each 15 decisions in the first estimation. The estimation with the relative strategy score as dependent variable consists of 370 observations as the strategy score is calculated for each of the 5 difficulty levels. Significance levels: <0.01 '***', <0.05 '**', <0.10 '*'

Supplementary Table 3: Analysis of Variance of the accuracy and response latency in decisions in OTSOC.

	<i>df</i> (n)	<i>df</i> (d)	<i>F</i>	<i>P</i>	η^2
<i>Accuracy: No. of moves above minimum</i>					
Sulpiride	1	71	5.09	0.027**	0.07
Genotype	1	71	0.01	0.941	0.00
Sulpiride x Genotype	1	71	0.85	0.361	0.01
Task difficulty level	5	1705	45.60	0.000***	0.12
Sulpiride x Task difficulty level	5	1705	1.71	0.129	0.00
Genotype x Task difficulty level	5	1705	1.84	0.103	0.01
Sulpiride x Genotype x Task difficulty level	5	1705	0.61	0.691	0.00
<i>Log latency until first response</i>					
Sulpiride	1	71	0.67	0.416	0.01
Genotype	1	71	0.82	0.367	0.01
Sulpiride x Genotype	1	71	0.11	0.746	0.00
Task difficulty level	5	1705	402.61	0.000**	0.54
Sulpiride x Task difficulty level	5	1705	3.43	0.004**	0.01
Genotype x Task difficulty level	5	1705	0.30	0.912	0.00
Sulpiride x Genotype x Task difficulty level	5	1705	0.59	0.709	0.00

Notes. Repeated and Mixed-Measure ANOVA with the number of moves above the minimum number of moves or the log latency until first response as dependent variable. The number of observation is 1800 consisting of 75 volunteers taking each 24 decisions. Significance levels: <0.01 '***', <0.05 '**', <0.10 '*'

Supplementary Table 4: OLS regression of the Speed accuracy trade off in decisions in OTSOC.

Dep. Variable Accuracy	Hard problem (level 6)	Medium problem (level 5)	Easy problems (level 1 – 4)
Log latency until first response	0.167* (0.0982)	0.266* (0.154)	-0.104** (0.0508)
Sulpiride	-2.035*** (0.515)	0.184 (0.742)	-0.0851 (0.230)
Sulpiride * log latency	0.554*** (0.142)	-0.104 (0.214)	0.0232 (0.110)
Constant	4.967*** (0.352)	4.835*** (0.537)	6.140*** (0.103)
Observations	74	75	74
R ²	0.458	0.080	0.080

Notes. Ordinary least square (OLS) regression with accuracy as dependent variables. Accuracy is defined as the average number of moves above the minimum number of moves in the various difficulty levels. The table reports the regression coefficients with robust standard errors in parenthesis. Significance levels: <0.01 '***', <0.05 '**', <0.10 '*'.

Supplementary References

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2. Chamberlain SR, Müller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ. Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science* 2006; **311**(5762): 861-863.
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