Supplementary Information for

Opioid modulation of value-based decision making in healthy humans

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This supplementary file includes:

Contents

Alcohol and drug screening

In a pre-testing telephone screening interview relevant items from AUDIT and DUDIT (Alcohol/Drug Use Disorders Identification Test (Berman *et al*, 2005; Saunders *et al*, 1993)) were used to assess alcohol and drug use. Participants reported consuming an average of 5.5 alcoholic units per week (range: 0.75-20 units). Regarding life-time use of illegal drugs, 23 volunteers reported use of cannabinoids, ten of whom had used cannabinoids in the last 12 months. Seven volunteers reported life-time use of amphetamines, nine volunteers reported use of cocaine/crack, and nine reported use of hallucinogens (ecstasy, LSD). One participant reported life-time use of an illegal opiate. Three volunteers reported previous use of prescription morphine and 23 participants reported previous use of codeine drugs for acute pain relief. Eleven of the volunteers used nicotine daily (cigarettes or snus), and six used nicotine occasionally. Of the 11 regular nicotine users, all but one used nicotine within three hours before each session started (minutes since last nicotine consumption, mean(SD) morphine: 72(42); placebo: 58(32); naltrexone: 80(56))". Of the occasional nicotine users, two had used nicotine on one of the test days, one 180 minutes before the morphine session, the other 250 minutes before the placebo session.

Drug bioavailability

The bioavailability of oral morphine is on average 30-40 %. Morphine has maximal effect (t-max) at 1-2 hours after oral administration, and a half-life of 2-4 hours (Lugo and Kern, 2002). Like morphine, the maximal plasma concentration of naltrexone is reached after one hour (Verebey *et al*, 1976).

Value-based decision making task properties

The three pairs of mouths (Figure S1) used as stimuli were chosen and piloted to ensure equivalent task difficulty (75%-85% overall accuracy) while avoiding learning effects in the three sessions. The diameter of the face was always 5.3 cm (degrees of visual angle: 3.794º), and the participant was seated with a neck rest, eyes 80 cm from the monitor. The first set of stimuli (Version A) consisted of faces with two horizontal lines (mouths) of different length: 11mm and 12mm (0.788 and 0.859 degrees of visual angle respectively). This stimulus pair mirrored a previously used version of this task (Pizzagalli *et al*, 2005). In the second stimulus-pair (Version B) the positioning of the mouth (11.5mm: 0.624 degrees of visual angle) varied along the horizontal axis; and appeared slightly to the left or right of the center. The difference between the two stimuli was 1mm (0.072 degrees of visual angle), with each mouth positioned 0.5mm from the center of the face. In the final pair of faces (Version C), the line (11.5mm) was given a slight angle (1 degree) either upwards to the right or to the left (see Figure S1 for illustration

of the three stimulus pairs. Face outline and eyes were identical across tasks. Responses were given with the dominant hand using the “1” and “2” keys on a standard keyboard numpad. Stimulus-response button associations were pseudo-randomized and counterbalanced across drug conditions.

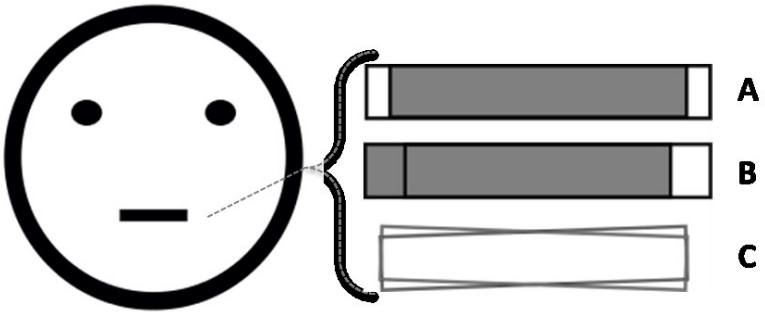

Fig. S1. Illustration of the three stimulus pairs. A separate stimulus pair was used in each of three versions of the value-based decision making task to avoid session learning effects. The mouths from each stimulus pair are superimposed on each other and inflated for illustration purposes. The perceptual properties of the stimuli are described in Supporting materials and methods. The shaded areas mark the overlaps between the two stimuli in pairs A and B. The angled stimulus pair (C) is shown with outlines.

Prior to the task, participants were given spoken and written instructions about the stimulus properties of the two faces and the corresponding response buttons. Ten practice trials (five trials of each stimulus type) preceded the test. During the practice trials participants received accuracy feedback instead of monetary rewards. Participants were instructed that only correct responses could lead to a reward. Further, participants were encouraged to try to make as much money as possible by answering quickly and accurately. After completion of 100 and 200 trials a message appeared on the screen encouraging the participant to take a short break before continuing the task. At the end of the three blocks, the amount of money won in that session was displayed on the screen.

Data exclusion

Missed trials (i.e. responses on invalid keyboard keys) were excluded from the analyses. Trials with reaction times < 250 and >2500 milliseconds and trials falling outside of 3 standard deviations of each participant’s mean were excluded from analyses. Data from three participants were excluded prior to DDM analysis due to missing data from more than one block or failure to follow task instructions.

Hierarchical Bayesian Regression Model for DDM parameters

The regression model directly provides estimates for the effects of interest, specifically the comparison of each drug condition with placebo. Because the regression model has as many predictors as conditions of interest, regression parameter estimates can also be used to calculate additional contrasts, like the comparison of naltrexone with morphine, and to provide estimates of DDM model parameters in each condition. Because we had no hypotheses concerning the *non-decision time* parameter of the DDM, *t*, this parameter was kept constant across conditions. We did not estimate the additional DDM parameters describing trial-by-trial variation in non-decision time, drift rate, and starting point because parameter recovery experiments showed that these are hard to estimate reliably, and because their estimation is computationally expensive.

The regression model for the key diffusion model variables of interest: drift rate (v), starting point (z), and decision boundary (a) used following predictor variables:

1. The contrast naltrexone - placebo
2. The contrast morphine - placebo
3. The contrast block 1 - block 2
4. The contrast block 3 - block 2
5. The interaction of predictor a and c (modeling the dependence of the naltrexone effect on block 1 vs 2).
6. The interaction of predictor a and d (modeling the dependence of the naltrexone effect on block 3 vs 2).
7. The interaction of predictor b and c (modeling the dependence of the morphine effect on block 1 vs 2).
8. The interaction of predictor b and d (modeling the dependence of the morphine effect on block 3 vs 2).
9. The intercept (effectively modeling a parameter in the second block of the placebo condition).

Statistics from the DDM analyses are presented in Table S1 and Table S2. For most parameters we report estimates of Cohen's *d* as a measure of effect size. The exception here is the starting point parameter. The starting point parameter (*z*) is bound between 0 and 1, which necessitates an estimation using a nonlinear logistic transformation, which prohibits the calculation of easily interpretable effect sizes for single contrasts of the starting point parameters.

Overall task performance: DDM results in the placebo condition

DDM parameter values for the placebo condition only were inspected separately to assess the overall effects of the task on behavior. Block-wise results from the placebo condition are displayed in Fig. S2.

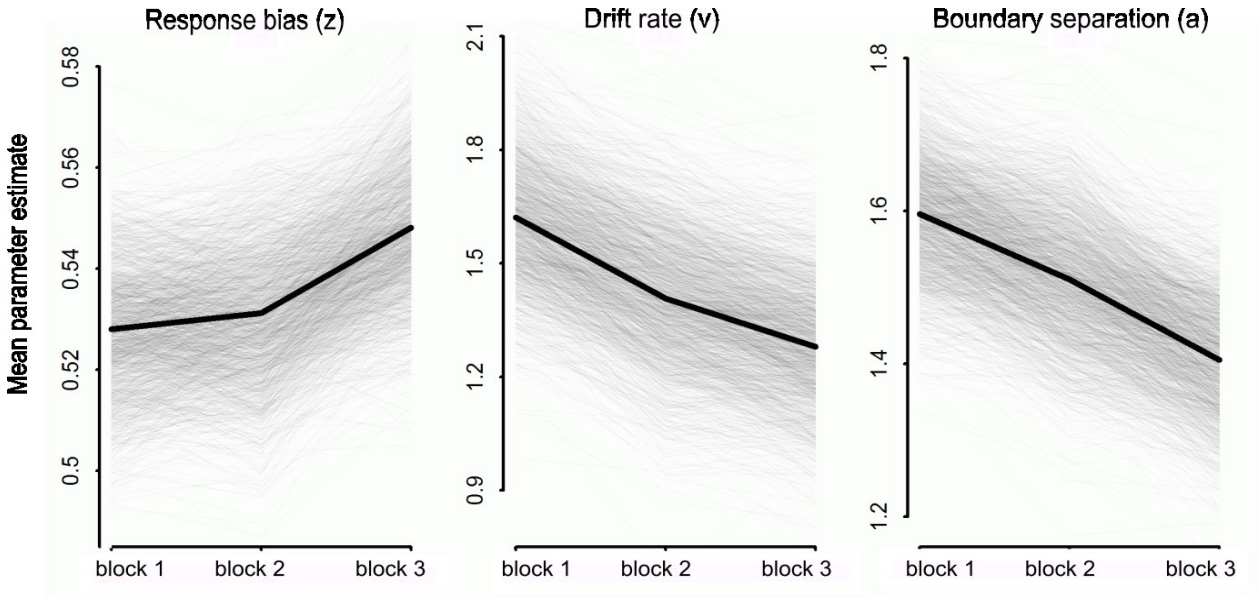

Fig. S2. Block-wise group level parameter estimates from the placebo condition. The thick black lines connect the mean parameter estimates for the three blocks. The thin lines represent variation due to differences between participants and due to uncertainty about parameter estimates. For each participant (N=27) 250 random parameter values were drawn from the posterior distribution of parameters for that participant and then plotted as a thin transparent line.

The posterior predictive check

A posterior predictive check (Gelman *et al*, 2014) was performed to visualize if and how well the model and estimated model parameters captured the data (Figure S3). To perform the posterior predictive check, we simulated experiments by using posterior distributions of model parameters as stand in for participants. The posterior predictive check for the DDM analysis followed this pseudo code:

```
for each drug condition
  for each block
    for 1000 simulated experiments
      for each participant
        randomly choose a set of DDM parameters
        simulate participant's responses and reaction times
      concatenate responses and response times of all participants
      calculate response time histogram for correct and incorrect responses
      plot semi-transparent histograms above each other
      overlay histogram for observed data
```

This algorithm provides a comparison of observed responses and response times for each of the nine conditions with predictions derived from the model and model parameters. The Figure is visually inspected to verify that there are no major differences between observed data and predictions (Figure S3).

Table S1. Statistics for drift diffusion parameters *v*, *z* and *a*. Table abbreviations: mu.mean = group mean; mu.sd = standard deviation of group mean; mu.perc > 0 = likelihood for group mean being above zero; HPDI/u = 90% highest posterior density lower/upper limit; sd.mean = mean standard deviation; d.mean = Cohen's *d*; M > P = contrast: morphine > placebo; M > N = morphine > naltrexone; P > N = placebo > naltrexone; b = block, blocks are numbered (1, 2, 3). Values for cells with NA are not available due to model restrictions.

Drift rate (v)	P>N	M>P	M>N	b2>1	b3>2	P>N b2>1	M>P b2>1	P>N b3>2	M>P b3>2
mu.mean	0.171	0.126	0.297	-0.107	-0.056	-0.073	0.005	-0.065	0.035
mu.sd	0.071	0.087	0.113	0.029	0.025	0.035	0.046	0.040	0.044
mu.perc>0	0.991	0.928	0.995	0.000	0.015	0.017	0.548	0.049	0.796
mu.HPDl	0.058	-0.015	0.110	-0.156	-0.096	-0.129	-0.070	-0.130	-0.037
mu.HPDu	0.290	0.268	0.484	-0.060	-0.013	-0.015	0.082	0.000	0.106
sd.mean	0.375	0.415	NA	0.114	0.081	0.151	0.210	0.171	0.192
sd.sd	0.057	0.066	NA	0.028	0.027	0.038	0.044	0.040	0.041
sd.perc>0	1	1	NA	1	1	1	1	1	1
sd.HPDl	0.282	0.309	NA	0.067	0.036	0.088	0.137	0.108	0.125
sd.HPDu	0.464	0.514	NA	0.158	0.122	0.211	0.279	0.237	0.258
d.mean	0.456	0.304	NA	-0.939	-0.691	-0.483	0.024	-0.380	0.182
d.sd	1.246	1.318	NA	1.036	0.926	0.921	1.045	1.000	1.073
d.perc>0	0.991	0.928	NA	0.000	0.015	0.017	0.548	0.049	0.796
d.HPDl	0.206	-0.049	NA	-2.328	-2.667	-1.466	-0.511	-1.204	-0.296
d.HPDu	0.625	0.521	NA	-0.380	-0.107	-0.071	0.294	0.000	0.411
Starting point (z)	P>N	M>P	M>N	b2>1	b3>2	P>N b2>1	M>P b2>1	P>N b3>2	M>P b3>2
mu.mean	0.032	0.041	0.073	0.029	0.038	0.021	0.019	0.003	-0.009
mu.sd	0.037	0.027	0.047	0.014	0.015	0.017	0.020	0.019	0.020
mu.perc>0	0.809	0.935	0.938	0.984	0.993	0.887	0.829	0.571	0.329
mu.HPDl	-0.030	-0.004	-0.008	0.007	0.013	-0.008	-0.014	-0.028	-0.043
mu.HPDu	0.092	0.084	0.147	0.051	0.062	0.049	0.051	0.033	0.024
sd.mean	0.245	0.185	NA	0.055	0.061	0.086	0.095	0.109	0.081
sd.sd	0.037	0.029	NA	0.014	0.015	0.022	0.021	0.023	0.021
sd.perc>0	1	1	NA	1	1	1	1	1	1
sd.HPDl	0.186	0.139	NA	0.033	0.037	0.051	0.060	0.071	0.047
sd.HPDu	0.303	0.230	NA	0.078	0.085	0.121	0.128	0.145	0.114
d.mean	0.131	0.222	NA	0.527	0.623	0.244	0.200	0.028	-0.111
d.sd	1.000	0.931	NA	1.000	1.000	0.773	0.952	0.826	0.952
d.perc>0	0.809	0.935	NA	0.984	0.993	0.887	0.829	0.571	0.329
d.HPDl	-0.161	-0.029	NA	0.212	0.351	-0.157	-0.233	-0.394	-0.915
d.HPDu	0.304	0.365	NA	0.654	0.729	0.405	0.398	0.228	0.211
Boundary Separation (a)	P>N	M>P	M>N	b2>1	b3>2	P>N b2>1	M>P b2>1	P>N b3>2	M>P b3>2
mu.mean	0.010	0.028	0.038	-0.062	-0.062	-0.004	0.026	-0.016	0.021
mu.sd	0.039	0.041	0.057	0.019	0.018	0.020	0.019	0.020	0.020
mu.perc>0	0.606	0.756	0.749	0.001	0.001	0.421	0.912	0.209	0.856
mu.HPDl	-0.054	-0.040	-0.057	-0.094	-0.091	-0.035	-0.006	-0.050	-0.013

mu.HPDu	0.075	0.095	0.132	-0.032	-0.033	0.029	0.058	0.017	0.054
sd.mean	0.106	0.082	NA	0.051	0.053	0.060	0.077	0.050	0.082
sd.sd	0.017	0.014	NA	0.010	0.010	0.012	0.015	0.012	0.016
sd.perc>0	1	1	NA	1	1	1	1	1	1
sd.HPDl	0.077	0.058	NA	0.034	0.038	0.039	0.054	0.030	0.057
sd.HPDu	0.132	0.102	NA	0.067	0.070	0.079	0.101	0.070	0.106
d.mean	0.094	0.341	NA	-1.216	-1.170	-0.067	0.338	-0.320	0.256
d.sd	2.294	2.929	NA	1.900	1.800	1.667	1.267	1.667	1.250
d.perc>0	0.606	0.756	NA	0.001	0.001	0.421	0.912	0.209	0.856
d.HPDl	-0.701	-0.690	NA	-2.765	-2.395	-0.897	-0.111	-1.667	-0.228
d.HPDu	0.568	0.931	NA	-0.478	-0.471	0.367	0.574	0.243	0.509

Table S2. Non-decision time (*t*) statistics. The *t* parameter was held constant across conditions in the drift diffusion model. Sd = standard deviation of the mean. HPDI/u = 90% highest posterior density lower/upper limit.

T (non-decision time)	mean	sd	HDPl	HDPu
t.mean	0.206	0.021	0.172	0.241
t.sd	0.108	0.020	0.077	0.148

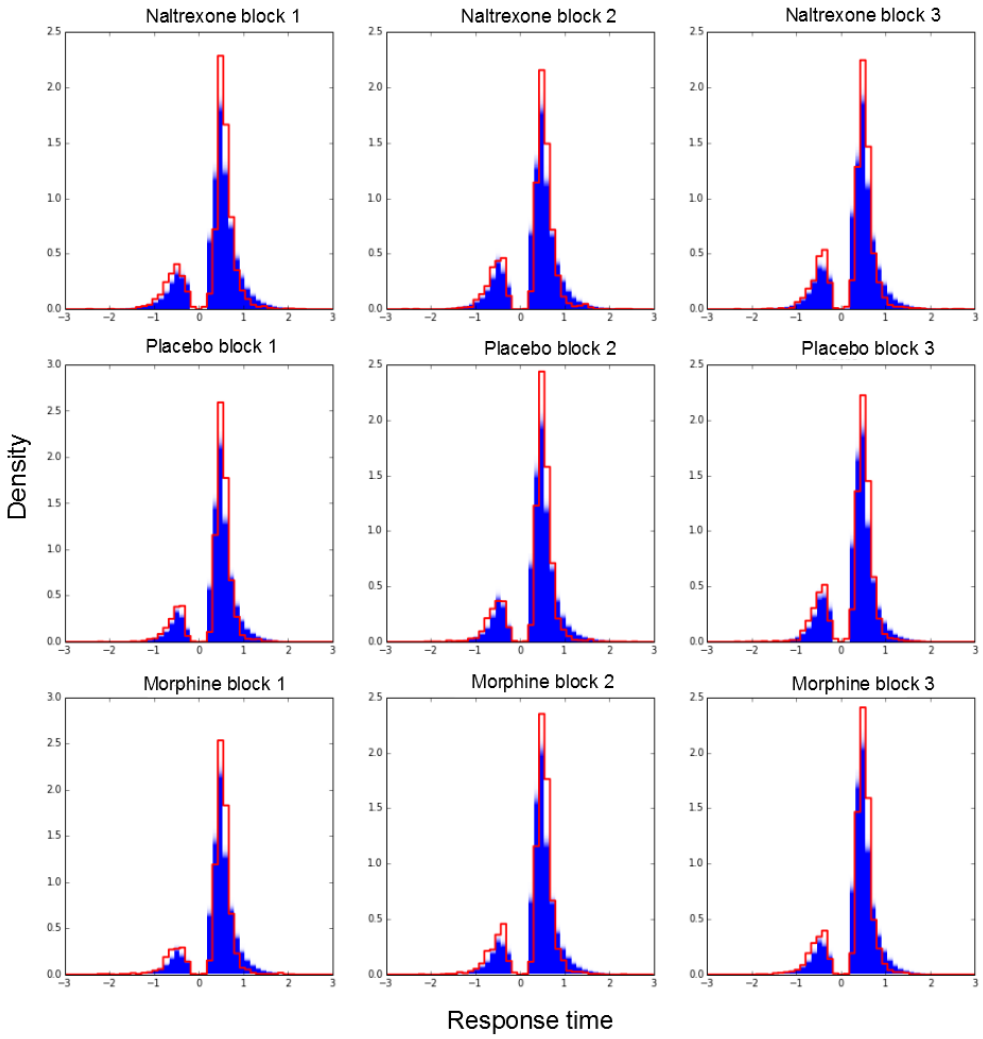

Figure S3. Plots of the posterior predictive check for each drug and block. The plots show predicted (blue) and observed (red) RTs for correct responses (positive RTs) and incorrect responses (negative RTs) for all nine conditions obtained by crossing three drugs with three time conditions. The plot shows that while predicted and observed RTs are generally in agreement, RTs tend to be slightly overestimated for incorrect responses and slightly underestimated for correct responses, likely due to the omission of parameter for trial to trial variability of DDM parameters. Importantly, the simulated data capture the main behavioral effects, in particular the increasing accuracy from the naltrexone over the placebo to the morphine condition, and the decreasing accuracy from block 1 to block 3.

Analysis of mood ratings

Potential drug effects on mood state were assessed at four time points during each session. (I) Immediately before drug ingestion(baseline); (II) 60 min after drug ingestion; (III) approximately 40 minutes into testing; and (IV) after completion of all tasks. The average rating for these mood items are presented in the main text (Figure 3). We used a Bayesian hierachical regression to estimate the effect of drugs on mood. With the R package “brms” (Bayesian Regression models using stan: Bürkner, in press) we specified the regression as delta ~ (drug * block | scale) + (scale|ID), where delta is the rating in the current block minus the rating before drug intake, “scale” refers to the different mood scales and “ID” refers to different participants. To account for the heavy tails of the delta variables we implemented a robust regression approach. In particular, the scales "good", "happy", "irritable", where modeled with student-t distributions (whereby each scale had its own degrees of freedom and standard deviation parameter) and the scale “anxious” was modeled with a double-exponential distribution. Finally, the scales “anxious” and “irritable” were flipped before calculating delta scores, so that for all scales a negative delta values corresponds to a worsening of the mood. The Bayesian regression model was fitted default settings of the rstan package (Stan Development Team, 2014). i.e. 4 chains with 2000 iterations each, of which the first 1000 warm-up samples were discarded before calculating statistics. As indicated by Rhat values below 1.1 for all parameters, the 4 chains converged successfully. All statistics were hence calculated based on 4000 samples (1000 from each chain.)

The results of this analysis show that participants report slightly less “good” over time, there were no clear trends for the other mood scales, nor were there an indication for systematic differences in how mood changed over time between the different drug conditions (i.e. the zero was in the 50% HDI for all parameters).

Table S3. Statistics from the mood rating analysis. PLAC = placebo, MOR = morphine, NTX = naltrexone. HDIL = lower boundary for the HDI, HDIU = upper boundary for the HDI.

Mood	parameter	mean	HDIL50	HDIU50	HDIL90	HDIU90	% > 0
good	PLAC	-0.18	-0.26	-0.02	-0.62	0.13	0.14
	MOR	-0.01	-0.03	0.03	-0.14	0.10	0.43
	NTX	0.01	-0.03	0.04	-0.11	0.15	0.56
	block	-0.03	-0.05	0.02	-0.16	0.05	0.26
	MOR:block	-0.01	-0.05	0.03	-0.17	0.14	0.43
	NTX:block	-0.05	-0.09	0.03	-0.30	0.10	0.26
happy	PLAC	-0.04	-0.15	0.06	-0.47	0.25	0.38
	MOR	0.00	-0.03	0.03	-0.12	0.10	0.49
	NTX	-0.01	-0.03	0.03	-0.14	0.10	0.41
	block	-0.02	-0.05	0.01	-0.15	0.05	0.29
	MOR:block	-0.02	-0.05	0.03	-0.21	0.11	0.35
	NTX:block	-0.02	-0.08	0.03	-0.21	0.14	0.38
anxious	PLAC	0.12	-0.02	0.19	-0.23	0.52	0.79
	MOR	0.01	-0.02	0.02	-0.06	0.08	0.60
	NTX	-0.01	-0.03	0.02	-0.10	0.05	0.35
	block	0.00	-0.01	0.02	-0.05	0.06	0.54
	MOR:block	0.03	-0.01	0.05	-0.04	0.14	0.76
	NTX:block	-0.01	-0.04	0.02	-0.10	0.09	0.44
irritable	PLAC	0.04	-0.11	0.12	-0.32	0.51	0.60
	MOR	-0.01	-0.04	0.02	-0.16	0.08	0.37
	NTX	-0.02	-0.05	0.02	-0.15	0.07	0.34
	block	-0.02	-0.04	0.02	-0.15	0.04	0.27
	MOR:block	0.00	-0.04	0.03	-0.13	0.14	0.50
	NTX:block	-0.11	-0.13	0.01	-0.30	0.03	0.12

Analyses of motor-coordination

To assess possible motor effects of the drugs participants completed a motor coordination task (Bradykinesia Akinesia Incoordination task, Giovannoni *et al*, 1999) 100 minutes after drug administration. Participants used their dominant index finger to alternate between two keyboard keys, 15 cm apart, as quickly and accurately as possible for 60 seconds. The main outcome measure, the Dysmetria score, provides a weighted score of number of incorrect presses corrected for speed. Drug effects on the Dysmetria score were assessed using a Bayesian hierarchical implementations of generalized linear models in Stan via RStan (Stan Development Team, 2014). We used a mixed effects model with individual level estimates of

motor performance in the placebo condition and fixed effects estimates of the effect of naltrexone and morphine. That is, we estimated mean and variance of a group level normal distribution for the placebo condition, which in turn was the source for individual level estimates in the placebo condition. Estimates of naltrexone and morphine conditions were obtained by adding the same (fixed) drug effect for all participants. Our key estimates of interest were the fixed effects estimates of the drug effects. The dysmetria scores were not normally distributed. Outliers were removed > 1.8s (leading to removal of 1 participant), and a gamma distribution was used. A gamma distribution and set priors for mean and variance were used, which were transformed to rate and scale parameters to obtain likelihoods from the gamma distributions. An exponential transform was used to constrain means (that result from multiplying the design matrix with parameters) to non-negative numbers. The analysis was conducted with 6000 iterations; the first 1000 were used for warm-up. Rhat (Gelman and Rubin, 1992) values (all < 1.1) confirmed successful convergence of all chains, and visual inspection of the chains showed no problematic autocorrelation.

The results show no credible differences in motor coordination across the drug conditions (Table S4).

Table S4. Statistics from the motor coordination (dysmetria) analysis. PLAC= placebo, NTX = naltrexone, MOR = morphine. The overlap of highest density intervals with zero and a mostly symmetrical distribution of drug effects around 0 indicated no evidence for an effect of drugs on motor performance.

Dysmetria	mean	sd	2.50%	25%	50%	75%	97.50%	prop>0
group mean PLAC	0.15	0.02	0.11	0.14	0.16	0.17	0.19	1.00
group sd PLAC	0.08	0.01	0.05	0.07	0.08	0.09	0.11	1.00
NTX	0.00	0.02	-0.03	-0.01	0.00	0.02	0.04	0.18
MOR	-0.01	0.02	-0.04	-0.02	-0.01	0.01	0.03	0.20

Measures of drugs and their metabolites in blood

Blood samples were collected at the end of each experiment session (approximately 150 minutes following drug ingestion) to determine levels of morphine and its two major metabolites (morphine-3-glucuronide and morphine-6-glucuronide) and naltrexone and its major metabolite (6-β-naltrexol). Sample analyses were performed at The Norwegian Institute of Public Health, Division of Forensic Medicine and Drug Abuse Research. Sample preparation using protein precipitation was performed in accordance with a previously published method (Karinen *et al*, 2009). The samples were analyzed with a modified opiate method (Gottas *et al*, 2012) using ultra performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS). The separation is performed on a Waters Aquity UPLC-system with an acidic mobile phase, and analyzed with a66666 Waters Quattro Premier XE tandem mass spectrometer. The results are displayed Table S5 and confirmed the successful uptake of the per-oral drugs. The levels are comparable to what we expected based on earlier studies.

Table S5. Descriptive statistics for morphine, naltrexone and metabolites in the blood. Blood levels of morphine, naltrexone and major metabolites ~150 min after per oral drug ingestion.

	Mean (ng/ML)	Std.dev
Morphine	3.0	0.9
morphine-3-glucronide	71	19.0
morphine-6-glucronide	15	0.4
Naltrexone	6.0	3.0
6-β-naltrexol	54	13.0

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