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Effects of haloperidol and aripiprazole on the human mesolimbic motivational system: a pharmacological fMRI study

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Abstract

The atypical antipsychotic drug aripiprazole is a partial dopamine (DA) D2 receptor agonist, which differentiates it from most other antipsychotics. This study compares the brain activation characteristic produced by aripiprazole with that of haloperidol, a typical D2 receptor antagonist. Healthy participants received an acute oral dose of haloperidol, aripiprazole or placebo, and then performed an active aversive conditioning task with aversive and neutral events presented as sounds, while blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) was carried out. The fMRI task, targeting the mesolimbic motivational system that is thought to be disturbed in psychosis, was based on the conditioned avoidance response (CAR) animal model – a widely used test of therapeutic potential of antipsychotic drugs. In line with the CAR animal model, the present results show that subjects given haloperidol were not able to avoid more aversive than neutral task trials, even though the response times were shorter during aversive events. In the aripiprazole and placebo groups more aversive than neutral events were avoided. Accordingly, the task-related BOLD-fMRI response in the mesolimbic motivational system was diminished in the haloperidol group compared to the placebo group, particularly in the ventral striatum, whereas the aripiprazole group showed task-related activations intermediate of the placebo and haloperidol groups. The current results show differential effects on brain function by aripiprazole and haloperidol, probably related to altered DA transmission. This supports the use of pharmacological fMRI to study antipsychotic properties in humans.

Introduction

Antipsychotic drugs are commonly referred to as typical or atypical, based on their properties and potential adverse effects. Typical antipsychotic drugs are dopamine (DA) antagonists, specifically blocking DA D2 receptors, and the “model drug” is haloperidol. Atypical antipsychotics have a less specific pharmacological profile, and generally give less extrapyramidal side effects. In addition to the influence on the DA system, they also affect serotonin receptor subtypes such as serotonin 2A (5-HT_{2A}) (Meltzer, 2013). Aripiprazole is an atypical antipsychotic, and in addition to being a partial agonist at the 5-HT_{1A} receptor subtype (Jordan et al., 2002), it is a partial DA D2 receptor agonist with a lower affinity to the 5-HT_{2A} than for the D2 receptor (Mamo et al., 2007).

Dopaminergic signaling has been suggested to mediate the incentive motivational salience of environmental stimuli and their associations (Berridge and Robinson, 1998). It has been found that DA signaling often precedes a hedonic experience which suggests that DA has a role in motivational prediction (Schultz, 2002). Recently it was hypothesized that increased chaotic activity of the dopaminergic mesolimbic motivational system in patients with schizophrenia results in an aberrant assignment of salience to internally and externally generated representations (Heinz and Schlagenhauf, 2010; Kapur, 2003; Winton-Brown et al., 2014), i.e. the motivational predictions are altered in patients. The mesolimbic motivational system is involved in detecting incentives in the environment, promoting learning about those and their association, and in driving goal-directed behavior. A central region in this system is the ventral striatum (VS) that has a high density of D2 receptors (Joyce et al., 1986) that subsequently are blocked by antipsychotic drugs. In addition, the anterior insula and the anterior cingulate cortex (ACC) have repeatedly been implicated in salience processing (Menon and Uddin, 2010; Seeley et al., 2007) and anticipation related processes (Liu et al.,

2011), and are thought to communicate critical information between the amygdala, the VS and the motor areas. The amygdala has been found to respond to motivationally relevant stimuli (Sander et al., 2003), independent of emotional content (Ousdal et al., 2012) and thus plays a central role in early stages of motivational salience. Hence, the VS, the anterior insula, the ACC and the amygdala make up a network underlying processing of incentive motivational salience.

Preclinical studies have shown that antipsychotic drugs block dopaminergic neural transmission (Carlsson and Lindqvist, 1963; Creese et al., 1976). One of the most common animal models to evaluate pharmacological and behavioral effects of antipsychotic drugs is the conditioned avoidance response (CAR) experiment. Animals challenged with antipsychotic drugs show a selective suppression of avoidance (Wadenberg, 2010) that can be reversed by drugs increasing dopaminergic activity, suggesting an association between the blocking properties of DA and the ability to suppress CAR (Davies et al., 1973). CAR is a reliable screening tool with predictive ability of antipsychotic effect (Wadenberg, 2010). In humans, paradigms translated from the animal CAR experiment to blood-oxygen-level dependent (BOLD) functional magnetic resonance imaging (fMRI) have been made (Bolstad et al., 2013; Jensen et al., 2003).

There has been several attempts to investigate the effects of antipsychotics in humans using BOLD-fMRI where a few of them have targeted the mesolimbic motivational system (Juckel et al., 2006; Kirsch et al., 2007; Menon et al., 2007; Schlagenhauf et al., 2008a). The results are somewhat contradictory but suggest that a change in medication affects the BOLD-fMRI-response in the VS (Juckel et al., 2006; Kirsch et al., 2007; Schlagenhauf et al., 2008b) and also that an acute dose administered to healthy subjects reduces the BOLD-fMRI-response in comparison with placebo (Menon et al., 2007). However, it should be noted that the

contradictory results can be due to differences in sample (patients/controls), drugs and dose used, and differences in paradigm (reward/punishment).

The main aim of the current study was to elucidate how neural activity in the mesolimbic motivational system is influenced by a typical antipsychotic drug with dopaminergic antagonist profile (haloperidol) compared to an atypical antipsychotic drug with a partial agonist profile (aripiprazole). Using arterial spin labelling it has been shown that both acute doses of haloperidol and aripiprazole increases the regional cerebral blood flow in the striatum in a sample of healthy controls, but the effect was larger in the haloperidol challenge (Handley et al., 2013). In addition, there was a decrease in the frontal cortex metabolism using both drugs, but the decrease was more widespread in the aripiprazole challenge. Similarly, one study found that an acute dose of aripiprazole in healthy controls was associated with decreased frontal metabolism in addition to longer response times in a working memory task (Kim et al., 2013).

The current study used an fMRI task based on CAR that has previously shown to robustly target brain regions employed in the mesolimbic motivational system (Bolstad et al., 2013). We hypothesized that these antipsychotic drugs would have a dampening effect on activity in the motivational system, specifically in the VS. We expected to observe diminished task-related activity after haloperidol challenge in comparison with placebo, while aripiprazole challenge was expected to induce a similar but weaker effect. In addition, we anticipated that the response times would be longer for the drug groups than the placebo group.

Experimental procedures

Participants and medication

This study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics and The Norwegian Medicines Agency. All subjects signed a written informed consent, and only healthy subjects were included. They underwent a somatic status examination by a medical doctor, a structured psychiatric health examination (Mini International Neuropsychiatric Interview (Lecrubier et al., 1997)), and were asked about their health history. Subjects with abnormalities in their electrocardiograms (ECG) or structural brain MRI scans, and subjects that had used psychotropic medication the previous two years or recreational drugs or other medication the last two weeks were excluded, as were subjects with contraindications for aripiprazole or haloperidol as determined by hematology and clinical chemistry. They were screened for drug usage and females were tested for pregnancy. Subjects were of age 18 – 50 (25, standard deviation (s.d.) 6) yrs. and weighed 56 – 94 (72, s.d. 11) kg. Two subjects were excluded because of brain abnormalities and three based on abnormal ECGs. Fifty-four subjects were included and randomized to one of the three treatment groups. They were recruited by posted advertisement, and were financially compensated after completing their participation.

The subjects received one single oral dose of drug or placebo at one time, administered in the morning 4.5 hours prior to MRI scanning. Subjects were given either 2 or 3 mg of haloperidol (1 mg tablets), 10 or 15 mg of aripiprazole (5 mg tablets), or two or three placebo pills depending on weight (≤ 75 kg or > 75 kg). Because of side effects the dosage were lowered to 1 or 2 mg of haloperidol, or 5 or 10 mg of aripiprazole, respectively after four subjects in each group were scanned. Total average doses were 0.02 mg/kg of haloperidol and 0.12

mg/kg of aripiprazole. Two participants (one haloperidol, one aripiprazole) were not scanned because of adverse effects.

Three data sets (two placebo, one aripiprazole) were excluded from analysis due to excessive head movements (> 3 mm) in the scanner. One data set (aripiprazole) was lost due to technical issues. 48 datasets were subjected to analysis: 15 (age 26.4 (s.d.) 7.7), 8 males) in the aripiprazole group, 17 (age 24.8 s.d. 6.9, 8 males) in the haloperidol group and 16 (age 23.3 s.d. 3.2, 7 males) in the placebo group.

To get an impression of the participants subjective experience a subjective state questionnaire (SSQ) was used, where they were asked to rate how well a set of adjectives described their state on a range from “*not at all*” to “*very much*” on Likert scales. Each word belonged to one of four categories describing either pleasant stimulation (e.g. alert), pleasant sedation (e.g. calm), unpleasant stimulation (e.g. restless) or unpleasant sedation (e.g. sleepy). In addition, the subjects were asked to guess if they had been given placebo or a drug. These data were collected two hours after the scan.

All participants abstained from caffeine on the experiment day before entering the scanner.

fMRI task

We employed an event-related fMRI paradigm based on avoidance (Bolstad et al., 2013). During one trial of the task, a turquoise or an orange circle against black background appeared for two seconds. The circle preceded a target (yellow star) at which the subjects were to respond to avoid a subsequent sound. One colored circle predicted a loud aversive sound (individually titrated beforehand) and the other colored circle predicted a low-volume neutral tone. The subjects were told that if they responded sufficiently quickly they could avoid the sound (both in aversive and neutral trials). After the response, there was either 1.5 seconds of sound or silence depending on their response times. The task contained 40 aversive and 40

neutral trials and a sound was presented in approximately 20% of the trials within each condition (the paradigm adapted to individual response times). The subjects were informed beforehand which color predicted which sound. The trial sequence was randomized across subjects, and the inter-trial-interval was jittered between 3 – 7 s with an average duration of 5 s.

fMRI data acquisition

E-Prime software (Psychology software tools Inc., Pittsburgh, Pennsylvania, USA) was used to program the task and to control the experiment. The task presentation and MRI uptake was synchronized using SyncBox hardware (Nordic Imaging Lab, Bergen, Norway). In the scanner the stimuli were presented through VisualSystem goggles, responses collected by ResponseGrips and sounds were delivered through AudioSystem, all MRI-compatible hardware (Nordic Imaging Lab, Bergen, Norway).

The examinations were performed on a 3T General Electric Signa HDxt scanner (GE Healthcare, Milwaukee, WI, USA). The BOLD-fMRI protocol consisted of a T2*-weighted sequence in the transverse plane with the following parameters: repetition time (TR) = 2000 ms; echo time (TE) = 25 ms and flip angle = 78 degrees; matrix = 64; field-of-view (FOV) = 256 mm; slice thickness = 3.5 mm; slice gap = 0.5 mm; slices = 36. One run consisted of 456 (± 6) volumes. Three dummy acquisitions were acquired initially during each scan and discarded. A sagittal T1-weighted image series used the following parameters: TR = 7.7 s; TE = 3.0 s; flip angle = 12 degrees; slices = 172; slice thickness = 1.2 mm; FOV = 256 mm; matrix = 256. The structural scan was obtained on a day prior to the experiment day and used in the co-registration and spatial normalization of the fMRI time series and for radiological screening to identify subjects with anatomical abnormalities.

Behavior analysis

The behavioral data were analyzed using Statistical Package for the Social Sciences (SPSS, Version 21, SPSS Inc., Chicago, Illinois, USA). A mixed ANOVA and paired sample t-tests were used to analyze the response times. As the avoidance success rates, subjective experience ratings and doses were not normally distributed non-parametric tests were employed. Kruskal-Wallis and Mann-Whitney U tests were used to explore between-group effects, and Wilcoxon signed rank test was used to test condition effects. Spearman coefficients were used to describe associations between behavioral data and doses.

Image analysis

DICOM image files were converted to NIfTI-1 format using the NordicICE software (Nordic Imaging Lab, Bergen, Norway). Raw data were visually inspected to secure image quality. Data pre-processing and analyses was performed using the Statistical Parametric Mapping software 8 (SPM8; <http://www.fil.ion.ucl.ac.uk/spm/>) implemented in Matlab 7.5 (Mathworks, Natick, Massachusetts, US). Individual structural MR images were normalized to the Montreal Neurological Institute (MNI) reference brain. Functional image volumes were aligned to the first volume and spatially normalized to MNI using the parameters from the structural image normalization before being resampled at a voxel size of 3 x 3 x 3 mm, and smoothed using an 8 mm full-width at half maximum Gaussian isotropic kernel. Possible slow signal drift was removed with a high-pass filter with a 128 s cut-off.

A general linear model (GLM) was constructed by convolving stick functions with a canonical hemodynamic response function. Only onsets for cues (colored circles) were included in the model. The regressors of interest were time onsets for *cue for aversive stimulus (aversive)* without sound outcome and time onsets for *cue for neutral stimulus (neutral)* without sound outcome. Aversive and neutral trials where sounds were delivered

(approximately 20% of the trials) were included in the model, but *not* used in any contrasts because of risk of BOLD signal contamination by sudden head movements. In addition there were six movement parameters – all together ten regressors. Individual t-images from the contrast *aversive > neutral* was moved to second-level analysis, and one-sample t-tests were carried out within each group. To test for task-related effects in the mesolimbic motivational system, voxel-wise small volume corrections based on predefined regions of interest (ROIs) were performed, followed by tests of whole-brain effects, all corrected for multiple comparison at peak level threshold of $p_{FWE} < .05$. To explore possible interaction and main effects a 2 (aversive, neutral) x 3 (aripiprazole, haloperidol, placebo) flexible factorial model was set up, and corrected values at threshold $p_{FWE} < .005$ were used. Possible group effects were explored performing two sample t-tests within the aforementioned ROIs, corrected at peak level threshold $p_{FWE} < .05$.

The *a priori* ROIs were the VS, the amygdala, the ACC and the anterior insula. Bilateral masks were created using the aal atlas in the SPM Wake Forest University (WFU) PickAtlas toolbox (<http://fmri.wfubmc.edu/software/PickAtlas>, version 2.5; (Maldjian et al., 2003)). Since an appropriate mask for the VS was not available in the PickAtlas, a mask from the BrainMap database was used (Fox and Lancaster, 1994).

Results

Behavioral findings

All subjects understood the task, and were able to avoid the sounds during both aversive and neutral conditions in at least 73% and 58% of the trials, respectively. The avoidance success rates and the response times are given in Table 1. A mixed between-within subject analysis of variance yielded a strong main effect of condition with shorter response times during aversive than neutral conditions ($F = 47.31, p < .001$), a trend interaction effect ($F = 2.85, p = .068$) but

no effect of group. The difference between conditions was significant within each separate group. Analyses of avoidance success rate showed that in the placebo and aripiprazole groups, but not the haloperidol group, the subjects were more successful in aversive than neutral trials (Table 1).

The doses (mg/kg) of aripiprazole and haloperidol were correlated with avoidance success rate and response times to see whether these directly influenced the performance. In the haloperidol group there was a significant positive correlation between dose and response times that was evident only during aversive conditions ($\rho = .51, p = .036$). There was no correlation between haloperidol dose and avoidance success rate. Aripiprazole dose had no influence on performance.

Analyses of the subjective state scores yielded differences across the three groups within the *pleasant sedation* ($\chi^2 = 13.3, p = .001$), *unpleasant sedation* ($\chi^2 = 9.1, p = .011$) and *pleasant stimulation* ($\chi^2 = 7.3, p = .025$) word categories. This is illustrated in Figure 1. There was a negative correlation between aripiprazole dose and *pleasant stimulation* ($\rho = .70, p = .007$).

When asked to guess whether they had received one of the two drugs or the placebo, 80% of the subjects in the aripiprazole group correctly guessed that they had received a drug, whereas in the haloperidol group only 58% thought they had been given pills with an active ingredient. In the placebo group 57% of the subjects erroneously guessed that they had received one of the two drugs.

fMRI findings

Replicating a previous study in healthy subjects that employed the same paradigm (Bolstad et al., 2013), ROI analyses were performed within the VS, the amygdala, the anterior insula and the ACC. In the placebo group there were activations in the bilateral VS (Figure 2A and B), the bilateral amygdala and the bilateral anterior insula, but none in the ACC (Table 2).

Analysis within the aripiprazole group showed bilateral activations in the VS (Figure 2C and D) and in the left amygdala, bilateral anterior insula and left ACC. In the haloperidol group there were activations in the right VS (Figure 2E and F), left anterior insula and bilateral ACC. When Bonferroni correcting for multiple comparisons (four bilateral regions), all ROI activations were still significant in the placebo group, the VS and the left amygdala remained significant in the aripiprazole group, while no activations were found in the haloperidol group. Whole-brain analysis for the contrast *aversive* > *neutral* yielded one cluster in the placebo group, located in the VS ($Z = 4.79$, $p_{\text{FWE}} = .026$, $k = 3$), but none in either of the medication groups.

An analysis employing a 2 x 3 flexible factorial model showed a strong effect of condition yielding activations in several brain areas (Table 3), but no interaction effect. Between-groups analysis employing the same ROIs as in the within-groups analysis showed stronger activations in the right VS ($Z = 3.24$, $p_{\text{FWE}} = .018$.) in the placebo group than the haloperidol group (Figure 3).

For each group VS activations were correlated with behavioral data. Beta values for each individual were extracted from the right VS peak voxel found for each group. The difference in beta values between aversive and neutral conditions was correlated with the corresponding difference in response times. There was a positive correlation in the haloperidol group ($r = .57$, $p = .016$), but not within the two other groups. A similar analysis for avoidance success rate yielded no significant correlations.

The VS activations were also correlated with the scores on subjective experience, and in the aripiprazole group there was a correlation between the beta values and *unpleasant sedation* scores ($\rho = .68$, $p = .011$).

Side effects

Out of the four first subjects that were given aripiprazole, three reported nausea, and out of the first four subjects that were given haloperidol, one reported claustrophobia. Given this high incidence of adverse effects, the rest of the participants were given the lower dose regimen as described in the Methods section. Out of these, two subjects in the aripiprazole group reported nausea and dizziness, respectively. None of the participants reported side effects neither at one day nor one week after participation in the study.

Discussion

The main finding of the present study was that our fMRI paradigm based on the CAR screening test robustly target brain regions employed in the mesolimbic motivational system, and detect effects of antipsychotic drug action. Haloperidol challenge showed a dampening effect on the activity in the motivational system, specifically in the VS, while the effect of aripiprazole challenge was similar to placebo. This supports the role of DA in mediating the motivational salience of environmental stimuli, and support the use of this pharmacological fMRI paradigm as a tool to study antipsychotic drug induced effects in the mesolimbic motivational system.

The response times were shorter during aversive than neutral conditions in all groups, suggesting that the conditions were experienced differently as the subjects were more eager to avoid the aversive sound. The percentage of tasks with successful avoidance of sound was higher during aversive than neutral conditions in the aripiprazole and the placebo groups, but not in the haloperidol group, indicating a more indifferent attitude to the aversive noise after haloperidol administration. These subjects were not able to avoid more tasks in the aversive than the neutral condition, but still they had shorter response times in aversive than neutral tasks. There was also a positive association between dose and response times during aversive

conditions in the haloperidol group. One might speculate that this is in line with the findings from the rodent CAR model, i.e. the rats are able to escape the shock, but they do not avoid it (Herz, 1960), but the sample size is too small to make these assumptions.

The BOLD-fMRI results showed that the paradigm is robust and activates similar regions as reported in Bolstad et al. (2013) when administering placebo to the subjects. The haloperidol group seems to recruit less regions during aversive relative to neutral tasks compared to placebo, which is in line with previous research (Menon et al., 2007). As hypothesized the aripiprazole group displayed activation intermediate of the other two groups, both when comparing number of activated regions and the statistical values. However, the only significant between-group difference was that the haloperidol group activated the right VS less than the placebo group. This is also in line with work by Menon and colleagues (Menon et al., 2007), showing a decreased activation in the haloperidol group as compared to placebo although they used a passive task. Since both drugs are antipsychotic, it could be argued that in a CAR-like task, we should expect similar effects between the groups. However, even though animal studies with aripiprazole demonstrate inhibition of CAR (Natesan et al., 2011), the cause of our differential fMRI-BOLD activations may be that a partial agonist impacts this measure differently as compared to an antagonist.

Initially, human neuroimaging studies showed that the mesolimbic system is mainly involved in positive rewards. It has been found that the VS activate especially during anticipation of a reward and the magnitude of the reward correlates with the activation (Knutson and Greer, 2008). It has also been shown that DA release and activations in the VS are correlated during performance of a monetary incentive delay paradigm (Schott et al., 2008). Importantly, using fMRI, several studies have found that similar regions are also activated in connection with aversive stimuli (Becerra et al., 2001; Boschen et al., 2011; Delgado et al., 2008; Jensen et al., 2003; Jensen et al., 2007; Pohlack et al., 2012), and the task-related activations in the current

study are in line with these findings. The VS, with a high density of D2 receptors (Joyce et al., 1986) that are blocked by most antipsychotic drugs, plays a central role in the mesolimbic motivational system and has been suggested to serve as interface between motivation to action (Mogenson et al., 1993). It has a dual role in representing motivation since it is recruited both during affect and motivational incentive processes. However, depleting the dopaminergic signaling in this region changes the motivational incentive process without changing the affect (Berridge and Robinson, 1998). Thus, when it comes to prediction of motivational salience, the VS has been of central importance. It is hypothesized that increased activity of the dopaminergic mesolimbic motivational system results in an aberrant assignment of salience in patients with schizophrenia (Heinz and Schlagenhauf, 2010; Kapur, 2003), and antipsychotic drugs are thought to relieve positive symptoms by dampening this aberrant salience through diminishing the dopaminergic hyperactivity. In the current study, we show that in healthy subjects haloperidol reduce mesolimbic activity and possibly induce indifference to salient stimuli. This might be paralleling what is observed during antipsychotic treatment in patients, and shows resemblance to what happens in the CAR animal model.

Some have suggested that the CAR model is showing a disrupted ability to *initiate* the voluntary motor response to the conditioned stimuli (but the animal still display escape behavior because of reflex motor responses), rather than a disruption of the motivational system (Aguilar et al., 2000). However, it has been shown that CAR disruption is not likely explained by motor impairment effects, as animals given an antipsychotic drug during the acquisition phase of CAR, still shows CAR inhibition when the drug is no longer present (Li et al., 2004), suggesting that CAR inhibition reflects altered incentive motivation.

In general, subjects that were given aripiprazole reported higher level of discomfort. They reported less pleasant sedation and stimulation and more unpleasant sedation. Thus, the aripiprazole group experienced less subjective well-being and aripiprazole was also found to

cause nausea and dizziness more frequently. Aripiprazole has been reported to give more nausea compared to several other atypical antipsychotics, but this was found in long-term treatment of patients (Khanna et al., 2013). Our finding may suggest that this effect is also apparent upon acute administration.

Previous studies using resting state fMRI have reported decreased connectivity between the midbrain and the default mode network as a result of haloperidol administration (Cole et al., 2013a; Cole et al., 2013b). These studies are valuable in characterizing system level functional effects of DA neuromodulation, and promising as a tool to describe medication effects. However, this approach lacks the possibility to target a specifically interesting area by controlling the cognitive processes that the subjects engage in when in the scanner. The strengths of the current study are the robust activations obtained in the placebo group, and that this paradigm describes the effects on the mesolimbic BOLD-fMRI-response by antipsychotic drugs.

Since only healthy subjects were included, this study does not suffer from possible effects of illness. However, there are some issues that should be considered. The current haloperidol dose is lower than the clinically equivalent dose of aripiprazole (Andreasen et al., 2010; Woods, 2003). However, this strengthens the finding that haloperidol yields stronger inhibition of mesolimbic activity than aripiprazole. The current results should be considered with caution in relation to patient studies as acute effects may differ from effects of long term antipsychotic treatment. In addition, the sample sizes are relatively small, which also increase the risk of type II errors.

In summary, the current fMRI task based on the CAR model concept robustly targeted the mesolimbic motivational system, where activations were more attenuated in the haloperidol

group than the aripiprazole group. To conclude, this supports the use of pharmacological fMRI to study antipsychotic properties in humans.

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Contributors

JJ, SK and OAA conceived and designed the study. IB and JJ were responsible for execution of the study, data acquisition and statistical analysis, and wrote the first draft of the manuscript. IG, AS and IS participated in data acquisition and quality control. All authors contributed to revising the manuscript and have approved the final version.

Conflict of interest

The authors declare no conflict of interest.

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Table 1. Overview of behavioral data. Avoidance success rates are reported in percent as median and interquartile range, and response times are reported in milliseconds as mean and standard deviation. Significant differences are denoted by asterisks (** = $p \leq .005$; * = $p \leq .05$).

	Group	Aversive	Neutral		Difference
Response times	Aripiprazole	212 (33)	244 (47)	33 (7)	t = 4.51**
	Haloperidol	202 (31)	215 (37)	13 (5)	t = 2.84*
	Placebo	203 (22)	226 (30)	24 (5)	t = 4.20**
Avoidance success rate	Aripiprazole	83 (78–85)	78 (73–80)	7 (2–10)	Z = 2.88**
	Haloperidol	83 (80–85)	83 (79–84)	0 (-1– 3)	Z = 1.26
	Placebo	85 (83–85)	83 (78–84)	2 (0–5)	Z = 2.57**

Table 2. Effect of condition (aversive > neutral) within groups. Peak voxels of significant small-volume-corrected ($p_{FWE} < .05$) activations within the four predefined bilateral ROIs are listed. Coordinates are given in Montreal Neurological Institute and Hospital (MNI) coordinate system.

PLACEBO						
Region	Hemisphere	p_{FWE}	Z	x	y	z
Ventral striatum	Right	<0.001	4.79	18	11	-11
	Left	0.005	3.71	-9	8	-2
Amygdala	Right	0.005	3.59	21	2	-14
	Left	0.007	3.51	-24	2	-17
Anterior insula	Right	0.003	4.11	33	23	-11
	Left	0.007	3.8	-36	20	1
Anterior cingulate cortex	Right	ns				
	Left	ns				
ARIPIPRAZOLE						
Region	Hemisphere	p_{FWE}	Z	x	y	z
Ventral striatum	Right	0.007	3.71	18	8	1
	Left	0.002	4.12	-15	-1	-2
Amygdala	Right	ns				
	Left	0.012	3.39	-18	-1	-11
Anterior insula	Right	0.025	3.47	48	17	-2
	Left	0.019	3.56	-30	11	13
Anterior cingulate cortex	Right	ns				
	Left	0.029	3.55	-6	20	22
HALOPERIDOL						
Region	Hemisphere	p_{FWE}	Z	x	y	z
Ventral striatum	Right	0.03	3.15	15	-1	-5
	Left	ns				
Amygdala	Right	ns				
	Left	ns				
Anterior insula	Right	ns				
	Left	0.027	3.41	-30	29	4
Anterior cingulate cortex	Right	0.032	3.48	12	20	28
	Left	0.017	3.69	-9	26	25

Table 3. Main effect of condition (aversive > neutral) across groups. Peak voxels of significant clusters are listed ($p_{FWE} < .005$, $k > 10$). Coordinates are given in Montreal Neurological Institute and Hospital (MNI) coordinate system.

Region	Hemisphere	Cluster size	Z	x	y	z
Cerebellum		309	6.77	0	-64	-41
Medial frontal gyrus (SMA)	Left	415	6.44	-3	-1	64
Thalamus	Left	349	5.94	-12	-19	4
Cerebellar posterior lobe	Right	52	5.68	42	-55	-38
Anterior insula	Right	78	5.63	51	20	-2
Ventral striatum	Right	45	5.52	12	5	1
Calcarine sulcus	Right	11	5.45	24	-94	1
Anterior insula	Left	44	5.32	-30	23	1
Middle frontal gyrus	Left	22	5.32	-48	-4	55
Inferior frontal gyrus	Right	15	5.21	30	26	10

Figure 1. Subjective state ratings. Average scores illustrated for each group within each of the four categories in the subjective state questionnaire. Significant group differences are indicated by one or two asterisks ($p < .05$ and $p < .01$, respectively). There are two datasets missing in the aripiprazole group.

Figure 2. BOLD-fMRI activation within the ventral striatum. Statistical parametric maps demonstrating significant activations during the contrast *aversive > neutral* are shown for the placebo (A), aripiprazole (C) and haloperidol (E) groups. Colors indicate t-values of activated voxels, and are coded in the respective bars on the right. Small volume corrections were applied within bilateral ROIs at threshold $p_{FWE} < .05$. Graphs show peak voxel beta values within the right side ventral striatum for the two conditions for the placebo (B), aripiprazole (D) and haloperidol (F) groups (means, standard error).

Figure 3. BOLD-fMRI activation difference between Placebo and Haloperidol groups. Statistical parametric map showing ventral striatal voxels that activate stronger ($p_{FWE} = .018$) in the placebo than the haloperidol group during the contrast *aversive > neutral* (A). The graph shows beta values for each group for the contrast *aversive > neutral* (B; means, standard error).

Figure 1.

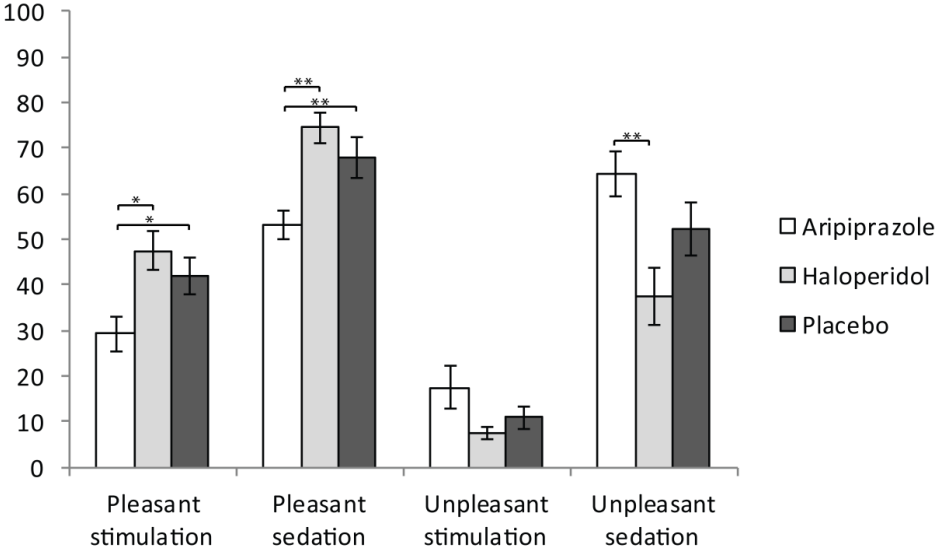


Figure 2.

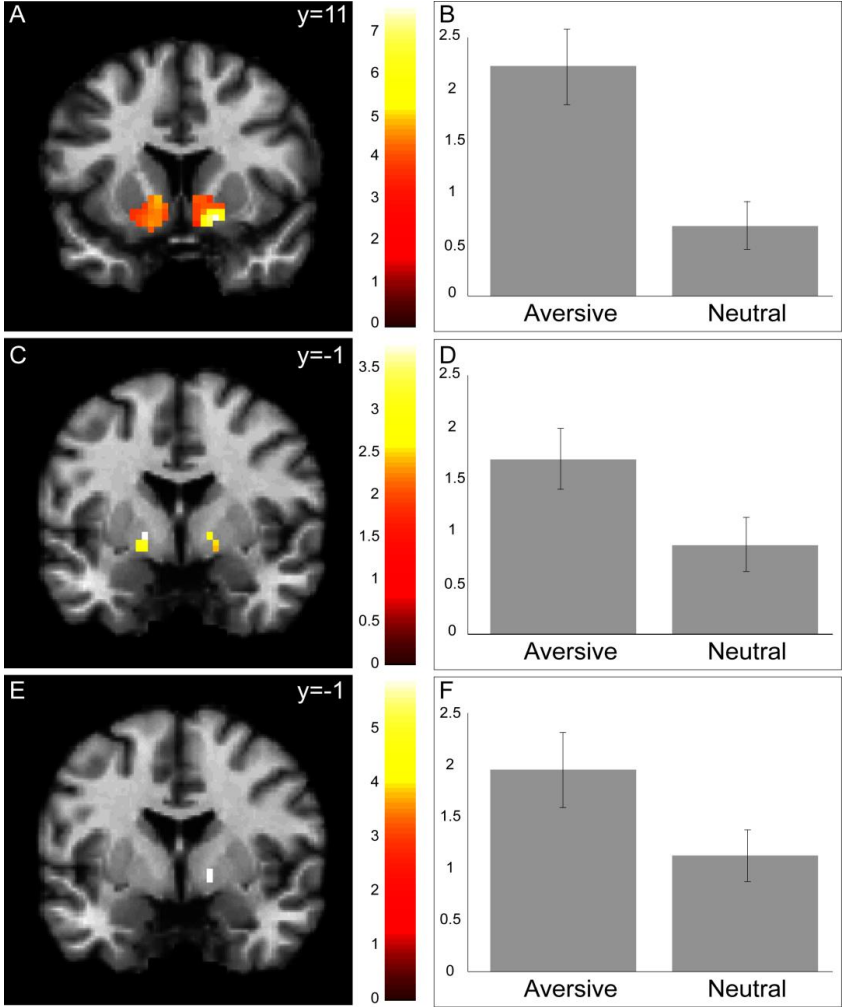


Figure 3.

