Published in final edited form as:

Neuropharmacology. 2019 December 15; 161: 107446. doi:10.1016/j.neuropharm.2018.11.034.

Pharmacological classification of centrally acting drugs using EEG in freely moving rats: an old tool to identify new atypical dopamine uptake inhibitors

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Abstract

Atypical dopamine uptake inhibitors (DUIs) bind to the dopamine transporter and inhibit the reuptake of dopamine but have lower abuse potential than psychostimulants. Several atypical DUIs can block abuse-related effects of cocaine and methamphetamine, thus making them potential medication candidates for psychostimulant use disorders. The aim of the current study is to establish an in-vivo assay using EEG for the rapid identification of atypical DUIs with potential for medication development. The typical DUIs cocaine and methylphenidate dose-dependently decreased the power of the alpha, beta, and gamma bands. The atypical DUI modafinil and its F-analog, JBG1-049, decreased the power of beta, but in contrast to cocaine, none of the other frequency bands, while JHW007 did not significantly alter the EEG spectrum. The mu-opioid receptor agonists heroin and morphine dose-dependently decreased the power of gamma and increased power of the other bands. The effect of morphine on EEG power bands was antagonized by naltrexone. The NMDA receptor antagonist ketamine increased the power of all frequency bands. Therefore, typical and atypical DUIs and drugs of other classes differentially affected EEG spectra, showing distinctive features in the magnitude and direction of their effects on EEG. Comparative analysis of the effects of test drugs on EEG indicates a potential atypical profile of JBG1-049 with similar potency and effectiveness to its parent compound modafinil. These data suggest that EEG can be used to rapidly screen compounds for potential activity at specific pharmacological targets and provide valuable information for guiding the early stages of drug development.

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Keywords

EEG; DAT inhibitors; Cocaine; JHW007; Opioids; in vivo; Modafinil; Heroin; Morphine; Ketamine

1. Introduction

Cocaine and methylphenidate bind with high affinity to the dopamine transporter (DAT) and inhibit the reuptake of dopamine, which increases levels of dopamine in the extracellular cleft (Carroll et al., 2002). The resulting indirect agonist action at dopamine receptors in the central nervous system is considered a crucial determinant of their psychostimulant as well as abuse-related effects (Di Chiara and Imperato, 1988; Hiranita and Collins, 2015; Ritz et al., 1987). Nevertheless, despite their high (low nanomolar) to moderate (low micromolar) affinity and selectivity for the DAT, other compounds bearing structural similarity to cocaine have been shown to vary in their effectiveness as psychostimulants and have been called atypical DUIs (Reith et al., 2015; Tanda et al., 2009).

Among these atypical DUIs, the N-substituted benztropine analog JHW007 is mostly devoid of the behavioral effects commonly observed in preclinical assays after cocaine administration (Agoston et al., 1997; Tanda et al., 2009). In particular, JHW007 does not stimulate locomotor activity, shares only limited discriminative-stimulus effects with cocaine and under a wide-range of dosing conditions is not self-administered (Desai et al., 2014, 2005; Hiranita et al., 2009; Kohut et al., 2014; Li et al., 2013). Another benzhydryl-containing DUI, modafinil (Provigil®) shares some of the behavioral effects of cocaine, but still with fewer indications of risk for abuse (Mereu et al., 2017, 2013; Zolkowska et al., 2009).

Modafinil has wake-promoting effects and produced drug-lever responding in animals trained to discriminate cocaine or amphetamine from vehicle, but it is self-administered at rates comparable with those of vehicle or a weak reinforcer (e.g. l-ephedrine) (Deroche-Gamonet et al., 2002; Gold and Balster, 1996; Heal et al., 2013; Hermant et al., 1991; Loland et al., 2012; Mereu et al., 2017; Paterson et al., 2010; Quisenberry et al., 2013). In humans, modafinil is used to treat sleep disorders and while it produced positive subjective effects (i.e. rating of “like”), it is self-administered within a laboratory setting only when drug effects could facilitate specific compensated activities (Billiard et al., 1994; Jasinski, 2000; Stoops et al., 2005; Vosburg et al., 2010). These findings and early data from post-marketing surveillance of modafinil suggest low if any abuse liability as compared with other DUIs (Jasinski and Kovacevic-Ristanovic, 2000; Myrick et al., 2004; Reith et al., 2015).

The potential modulation of the abuse related effects of typical DUIs by administration of atypical DUIs has been evaluated in preclinical and clinical studies (Reith et al., 2015; Tanda et al., 2009). In rodents, pretreatment with JHW007 shifts the cocaine or methamphetamine self-administration dose-effect curve downward at doses that have minimal effects on responding reinforced by food or other drugs (Hiranita et al., 2014, 2009; Zanettini et al., 2018). Similarly, chronic modafinil treatment decreases in a reinforcer-selective fashion

responding maintained by cocaine in rhesus monkeys, as well as self-administration of cocaine and its physiological effects under laboratory settings in humans (Hart et al., 2008; Newman et al., 2010). Despite these initial promising results, successive randomized clinical trials have not consistently shown effectiveness of modafinil for cocaine or methamphetamine use disorders (Anderson et al., 2012, 2009; Dackis et al., 2012; Schmitz et al., 2014). Nevertheless, an increase in measures of cocaine abstinence have been observed with modafinil treatment in patients that had limited alcohol use, supporting the use of modafinil in at least a sub-population of cocaine dependent patients (Dackis et al., 2012; Kampman et al., 2015). Therefore, preclinical and clinical findings indicate potential therapeutic utility of atypical compounds targeting DAT as medications to attenuate the effects and/or replace abused psychostimulants (Grabowski et al., 2004; Howell and Negus, 2014; Reith et al., 2015).

The development and optimization of atypical DUIs as candidate pharmacotherapies for psychostimulant use disorders could be greatly advanced by prediction and selection of compounds with atypical profiles early in the in-vivo preclinical stages of drug development. The current study evaluates the effects of DUIs and of JBG1-049, a new modafinil analog with improved solubility, on the electroencephalographic activity (EEG) of freely moving rats with the aim to establish an early rapid in-vivo assay for the identification of DUIs with a potential atypical profile. EEG records the variation of electric potential from pyramidal neurons with high temporal and spatial resolution and is extensively used at different stages of the drug development pipeline to profile new chemical entities (Fink, 1980; Krijzer and van der Molen, 1987; Dimpfel et al., 2003; Leiser et al., 2011; Ahnaou et al., 2014; Maher et al., 2016). While some of the effects of psychostimulants on the EEG of animals and humans are known, a quantitative analysis and comparison of neurosignatures of different typical and atypical DUIs has not yet been reported. The pharmacological selectivity of the obtained EEG drug profiles was also assessed by characterizing compounds with other mechanisms of action and behavioral effects. These studies further indicate the utility of this technique for determining unique signatures of different centrally active classes of compounds. It is anticipated that EEG might be useful in a broad spectrum of drug development programs. Herein, we demonstrate its utility in identifying novel atypical DUIs for development as therapeutics to treat psychostimulant use disorders.

2. Methods

2.1 Subjects

Adult male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) were individually housed in a temperature- and humidity-controlled room with food and water ad libitum under a 12:12-h light/dark cycle. Daily food rations were adjusted to maintain body weight of animals at approximately 350g. The animal facilities are fully accredited by AAALAC International and all procedures were conducted in accordance with the guidelines of the Institutional Care and Use Committee of the NIDA Intramural Research Program.

2.2 Drugs

Typical dopamine uptake inhibitors, cocaine HCl (Mallinckrodt, St. Louis, MO) and methylphenidate HCl (Sigma-Aldrich, St. Louis, MO), the atypical dopamine uptake inhibitor JHW007 (synthesized in the Medicinal Chemistry Section, NIDA-IRP, according to the methods described in Agoston et al. 1997), the mu-opioid agonists heroin (RTI International, Research Triangle Park, NC), morphine sulfate (Sigma-Aldrich), and the NMDA-receptor antagonist, ketamine HCl (Hospira, Lake Forest, IL) were dissolved in saline (0.9% sodium chloride, USP; Hospira). The atypical DUI (±)-modafinil and its analog *R*-(−)-JBG1-049 (synthesized in the Medicinal Chemistry Section, NIDA-IRP according to methods described in Cao et al., 2010 and Keighron et al 2018 EJN submitted) were dissolved in a vehicle of 10% DMSO, 15% TWEEN 80 and saline. The structures of all the DUIs described can be seen in Fig. 1.

2.3 Intravenous catheter and EEG implant surgery

Rats were anesthetized with intraperitoneal injections of ketamine (60 mg/kg) and xylazine (20 mg/kg). Intravenous jugular catheters (RJV-1, SAI Infusion Technology, Lake Villa, IL) and relative back mounts (313-000BM-10-5UP, PlasticsOne Inc., Roanoke, VA) were implanted as previously described in Zanettini et al. (2018). Catheters were flushed with infusion of 0.2 ml of a gentamicin-heparin solution (0.4 mg/ml - 30 U/ml, respectively) and back mounts were kept closed with dust-cups (C313CAC, PlasticsOne Inc.).

Stainless steel screws (2AE96, Grainger, Lake Forest, IL) soldered to striped electric wire (UAA3601, MicronMeters, Saint George, UT) served as electrodes and were implanted bilaterally (coordinates in mm from bregma) on the frontal (AP: 3, ML: ±2), parietal (AP: −2, ML: ±4) and occipital (AP: −6, ML: ±4) regions of the skull; two additional electrodes worked as reference and ground (AP: −11, ML: ±2.5). Electrodes were connected through a custom-made electrode-interface board to a connector (A71314-801, OMNETICS, Minneapolis, MN) that was chronically implanted on animal's skull and served as receptacle for the acquisition of the EEG signals. The antibiotic Baytril ® (enrofloxacin,) was administered subcutaneously at a dose of 10 mg/kg for at least 3 days post-surgery.

2.4 Experimental procedure and data collection.

During experimental sessions, animals were placed in a microdialysis bowl cage (MD-1514, Basi, West Lafayette, IN) containing clean bedding. The bowl cage was located on a Stand-Alone Raturn (Basi) inside a ventilated and illuminated holding cubicle that was equipped with metal mesh to provide electromagnetic isolation. The connector on the animal was coupled to an headstage amplifier board (RHD2132 #C3314, Intan, Los Angeles, CA) in which signal was band passed between 0.1 to 125 Hz, digitized at 2 kHz, and sent to an USB-interface board (RHD2000 #3100, Intan) through a SPI cable (RHD2000 #33206, Intan). The interface was controlled by a Windows based computer running a recording-system software (v1.5, Intan).

During sessions, a 2.5-mL syringe (Hamilton, Reno, NV) containing the test drug or vehicle was placed in the syringe driver (CMA/100, Carnagie Medicine, Stockholm, Sweden), which operates at a rate of 4.125 μL/min. A polyethylene tubing (BPTE-50), which was

protected by a metal spring (C313CS, PlasticsOne), connected the syringe to the back mount of the animal. In-session dose-effect curves were determined for each subject administering intravenously doses of the test compound at fixed-intervals of time. For each compound, pharmacokinetic data and/or pilot time-course studies were used to guide the selection of the length of the session and of the fixed-intervals of injection such that the maximal effect of each dose of drug and of the dose-effect curve was captured. Cumulative doses of cocaine (0.1–3.2 mg/kg) or methylphenidate (0.1–5.6 mg/kg) were administered at 10 min intervals whereas cumulative doses of modafinil (1–32 mg/kg), JHW007 (1–10 mg/kg), JBG1-049 (1–32 mg/kg) or morphine (0.32–5.6 and 10–17.8 mg/kg) every 30 min. Because of their short half-life, full doses (i.e. not cumulative) of ketamine or heroin were administered every 30 min. In selected sessions, a single dose of naltrexone (0.032 mg/kg) was administered subcutaneously 5 min before the determination of the morphine dose-effect curve. Animals were tested no more than once every 7 days and drugs were administered in an unsystematic order. A white noise generator located in the experimental room was kept on during the session recording.

2.5 Data analysis

Initial analysis was performed with python (Python Software Foundation, https://www.python.org/). Data were imported and power was estimated for epochs of 10 sec at 0.5 Hz interval steps using the *scipy* function *scipy.signal.spectrogram* with windows of 10 sec and a step of 2 s (Jones et al., 2001). R (The R core team, http://www.R-project.org) and the relative *reticulate* and *tidyverse* packages were used to calculate for each animal the average power of delta (0–4 Hz], theta (4– 8Hz], alpha (8–13], beta (13–30], gamma (30–50 Hz] bands using 1 min bins for heroin and ketamine and 5 min bins for all the other drugs. For each animal and electrode, the power of the frequency band was then normalized to the pre-infusion interval (baseline) and expressed as % of baseline values ± Standard Error of the Mean (S.E.M) (Allaire et al., 2018; Wickham, 2017). Group data were obtained by averaging the power of bands recorded in the same region and then across subjects. Cumulative dose-effect curves plotted the % of baseline value of the last bin of each injection interval against the corresponding bin after dose administration (i.e. 5 min after injection of cocaine and methylphenidate and 25 min after injection of the other test compounds). Because full doses of heroin and ketamine were administered (i.e. not cumulative), the 3^{th} and 4^{th} bin of each injection intervals (i.e. 3 and 4 min after injection) were used in dose-effect curves, respectively. Dose-effect curves of each compound were analyzed by one-way repeated measure ANOVA with dose as independent factor. Low (0.1–5.6 mg/kg) and high doses of morphine (10–17.8 mg/kg) were tested in different sessions (to limit the duration of the session) and analyzed in separate ANOVAs. Power at each dose was then compared with the one obtained during the baseline period by Dunnet's post-hoc test. The *nlme* and *multcomp* packages were used to perform statistical analysis (Hothorn et al., 2008; Pinheiro et al., 2018). Radar plots were modified from graphs created in R using the package *fmsb* (Nakazawa, 2018).

3 Results

Administration of the typical DUIs, cocaine and methylphenidate, altered baseline EEG signal (Fig. 2). Spectral analysis revealed that the typical DUIs decreased power of high but not low frequencies bands with similar potency and minima. In particular, cocaine dose-dependently decreased the power of alpha ($F_{4,16}$=3.723, p<0.05), beta ($F_{4,16}$=8.533, p<0.01) and gamma bands ($F_{4,16}$=15.217, p<0.01). Methylphenidate dose-dependently decreased power of the beta band ($F_{5,25}$=9.556, p<0.05) and post-hoc analysis revealed that the doses of 0.32 and 3.2 mg/kg decreased the power of the gamma-band power (Fig. 3, Fig. 5a).

The atypical DUIs, modafinil and its analog JBG1-049, dose-dependently reduced power of the beta-band power ($F_{4,14}$=3.121, p<0.01; $F_{4,19}$=5.792, p<0.01, respectively) but in contrast with cocaine, they did not significantly alter the power of either alpha or gamma bands. No significant change from baseline power was obtained after administration of the benztropine analog, JHW007 (1–10 mg/kg) (Fig. 2, Fig. 3, Fig. 5b).

The mu-opioid agonists heroin and morphine produced a synchronization and increase in the amplitude of the signal (Fig. 2). The power of delta, theta, alpha and beta bands were increased while the power of gamma was decreased by administration of the mu-opioid agonists morphine ($F_{2,8}$=17.34; $F_{2,8}$=8.406; $F_{2,8}$=24.875; $F_{2,8}$=14.589; $F_{2,8}$=10.418, p <0.01) or heroin ($F_{3,15}$=9.656; $F_{3,15}$=12.167; $F_{3,15}$=17.232; $F_{3,15}$=3.489; $F_{3,15}$=31.505, p<0.01). Low doses of morphine produced a modest decrease in theta ($F_{4,\ 20}$=2.823, p = 0.05) and the dose of 5.6 mg/kg of the beta power (t=−3.034, p<0.01). The two opioids showed comparable maximal effects on EEG spectra with heroin approximately 10-fold more potent than morphine (Fig. 3, Fig. 5c). The NMDA receptor antagonist ketamine increased slow wave signal and the power of delta ($F_{3,12}$ = 8.928, p<0.01), theta ($F_{3,12}$=3.287, p=0.05), alpha ($F_{3,12}$=17.567, p<0.01) and beta ($F_{3,12}$=39.586, p<0.01) bands to similar maxima observed after mu-opioid agonists administration. However, in contrast with opioids, ketamine increased power of the gamma band ($F_{3,12}$=14.067, p<0.01; Fig. 2, Fig. 3, Fig. 5c).

The effects of morphine on the EEG signal and power were prevented by administration of 0.032 mg/kg naltrexone. While no significant effect of morphine on theta or alpha bands was observed, a small yet significant reduction in the power of delta ($F_{3,12}$=5.732, p=0.01), beta ($F_{3,12}$=7.063, p<0.01) and gamma (F3,12=5.181, p<0.05) was observed in animals pretreated with naltrexone (Fig. 4, Fig. 5d).

4 Discussion

Atypical dopamine uptake inhibitors (DUIs) have preferential selectivity for DAT with affinity in the low nanomolar to low micromolar range. Nevertheless, atypical DUIs have distinct behavioral effects from cocaine and predicted low abuse potential. Preclinical and clinical evidence suggest that this class of compounds might have therapeutic utility for treating psychostimulant use disorders. The current study explored the effects of several typical and atypical DUIs as well as other classes of centrally active drugs, on EEG of freely

moving rats to identify a potential neurosignature of atypical DUIs that could be used to guide drug development and optimization of pharmacotherapies.

The typical DUIs cocaine and methylphenidate produced a desynchronization of the EEG signal with a specific decrease in the power of the high frequencies alpha, beta and gamma.

These results are consistent with other reports of effects of those DUIs and amphetamines on the brain electrical activity of rats under resting conditions and are indicative of increases in levels of arousal (Devilbiss and Berridge, 2008; Ferger et al., 1994; Glatt et al., 1983; Luoh et al., 1994). In particular, the decrease in the power of those high bands produced by cocaine correlates with both an increase in dopamine dialyzed from the prefrontal cortex of rats and behavioral measures of motor stimulation and these effects can be prevented by antagonism of D1-D2 dopamine receptors (Ferger et al., 1994; Luoh et al., 1994). Similarly, in early clinical studies employing frequency and amplitude analysis amphetamines and DUIs were categorized as a class of drugs producing EEG desynchronization (Fink, 1969). While more recent clinical studies have reported increased EEG activity after administration of cocaine (Lukas et al., 1989), this effect was characterized by an increase of the frontal power of low/high frequencies, in contrast with animal studies (Herning et al., 1994; Reid et al., 2006). This discrepancy between clinical and preclinical studies might be the result of species-specific brain differences and/or the particular experimental conditions of testing. A possible important determinant of these effects is the drug history of the subjects that in clinical, but not preclinical, studies had exposure/dependence to psychostimulants and therefore expected persistent baseline changes in electric brain activity (Alper et al., 1998; Newton et al., 2003). Repeated treatment with stimulants has also been shown to produce effects on the power of EEG bands in rats that can markedly differ in its direction when compared with that of acute drug administration (Ferger et al., 1996; Stahl et al., 1997).

The atypical DUIs JHW007 and modafinil had an EEG profile distinct from that of the typical DUIs cocaine and methylphenidate. The absence of significant alteration of the EEG spectrum by the atypical DUI JHW007 parallels previous findings obtained in preclinical behavioral assays of locomotor activity, drug self-administration, and cocaine discrimination (Reith et al., 2015). Conversely, modafinil produced a desynchronization of the EEG signal characterized by a decrease in the power of beta frequencies also reported by another laboratory (Sebban et al., 1999). Therefore, modafinil shared some of the effects of cocaine and methylphenidate on EEG (i.e. decrease in beta power) but not others (decrease in alpha and gamma). These findings are consistent with reports that modafinil, but not JHW007, produces some of the stimulating effects (i.e. wake promotion) of abused DUIs in humans and animals, but still has low abuse potential.

The compound JBG1-049, a modafinil analog with improved solubility, but similar affinity for DAT (K_i=4830 nM vs. K_i=5480 nM for modafinil; (Keighron et al., 2018 EJN submitted), had EEG effects that overlapped with those of modafinil, suggesting a potential atypical profile. This hypothesis is supported by a recent comparison of the behavioral and neurochemical effects of JBG1-049 and R-modafinil (Keighron et., al 2018 Eur. J. Neurosci, in press). Moreover, the equivalent potency and effectiveness of JBG1-049 and its parent

compound exclude possible solubility factors as a determinant of the differential effects on EEG by modafinil and typical DUIs (Lazenka and Negus, 2017).

A series of other compounds with effects and mechanisms of action different than DUIs were assessed to evaluate the pharmacological selectivity of the current assay. Mu opioids and the NMDA receptor antagonist ketamine had effects on EEG that were qualitatively and quantitatively different than those of typical and atypical DUIs. Heroin and morphine produced a synchronization of the EEG signal with increases in slow and medium frequency bands, whereas ketamine administration lead to a generalized elevation of the power of all bands including gamma (Ferger and Kuschinsky, 1995; Jones et al., 2012; Lukas et al., 1982; Young et al., 1987; Zuo et al., 2007). Increases in frequency power and synchronization of the signal have been previously reported with opioids (Zuo et al., 2007) and are associated with a corresponding rise in measures of stupor, sedation and catalepsy (Lukas et al., 1980). Similarly, an elevation of gamma oscillations has been observed after administration of another NMDA receptor antagonist, MK801 (Hakami et al., 2009; Pinault, 2008), and the ketamine-induced change in gamma was normalized by administration of the antipsychotic haloperidol (Jones et al., 2012). Taken together, these data indicate that drugs from the same pharmacological class (i.e., opioids, typical and atypical DUIs and NMDA antagonists) have similar EEG profiles, which are distinct from those of other classes. In addition, the pharmacological nature of the effects observed in the current study was further supported by the blockade of the mu opioid antagonist naltrexone on the opioid EEG signature. This experiment also exemplifies the additional value of EEG for exploring drug-drug interactions and identifying compounds that attenuate the effects of drugs of abuse.

In summary, quantitative analysis of EEG spectra revealed different neurosignatures of typical and atypical DUIs and of other central nervous system active drugs. These data suggest that evaluation of the EEG signal can be used to identify new DUIs, such as JBG 1-049, with potential atypical profiles in the early preclinical phase of drug development and can accelerate the discovery of possible treatments for psychostimulant use disorders. Similar strategies have been used in the past in clinical and preclinical research to predict therapeutic effectiveness of candidate pharmacotherapies for anxiety and depression (Krijzer and van der Molen, 1987) and have been successful in the early recognition of the antidepressant potential of the tricyclics doxepin and mianserin (Itil et al., 1972; Simeon et al., 1969; for an historical account Fink, 2010). Moreover, the current study supports the use of EEG as a functional assay to study drug-drug interactions and to facilitate the discovery of new chemical entities that can attenuate the effects of drugs of abuse.

Acknowledgments

We thank Brenna Swider and Mark Coggiano for administrative assistance.

7 Funding and Disclosure

The current studies were supported by funding from the National Institute on Drug Abuse (NIDA) Intramural Research Program (IRP) ZIA DA000389 and ZIA DA000611. The authors are all employees of the NIH and have no disclosures. Care of the animals was in accordance with the guidelines of the National Institutes of Health and the National Institute on Drug Abuse Intramural Research Program Animal Care and Use Program, which is fully accredited by AAALAC International.

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Highlights

- Atypical dopamine uptake inhibitors are candidate pharmacotherapies for psychostimulant use disorders.
- Typical and atypical dopamine uptake inhibitors, as well as centrally active drugs from other classes, produce distinct EEG neurosignatures.
- EEG can be used for the early identification of dopamine uptake inhibitors with an atypical profile.

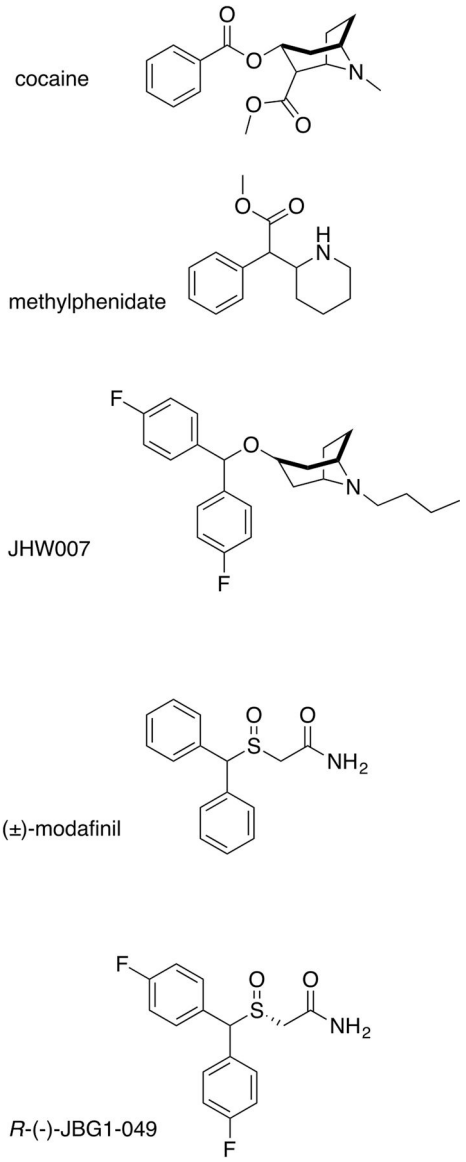

Fig. 1.
Chemical structures of typical and atypical DUIs.

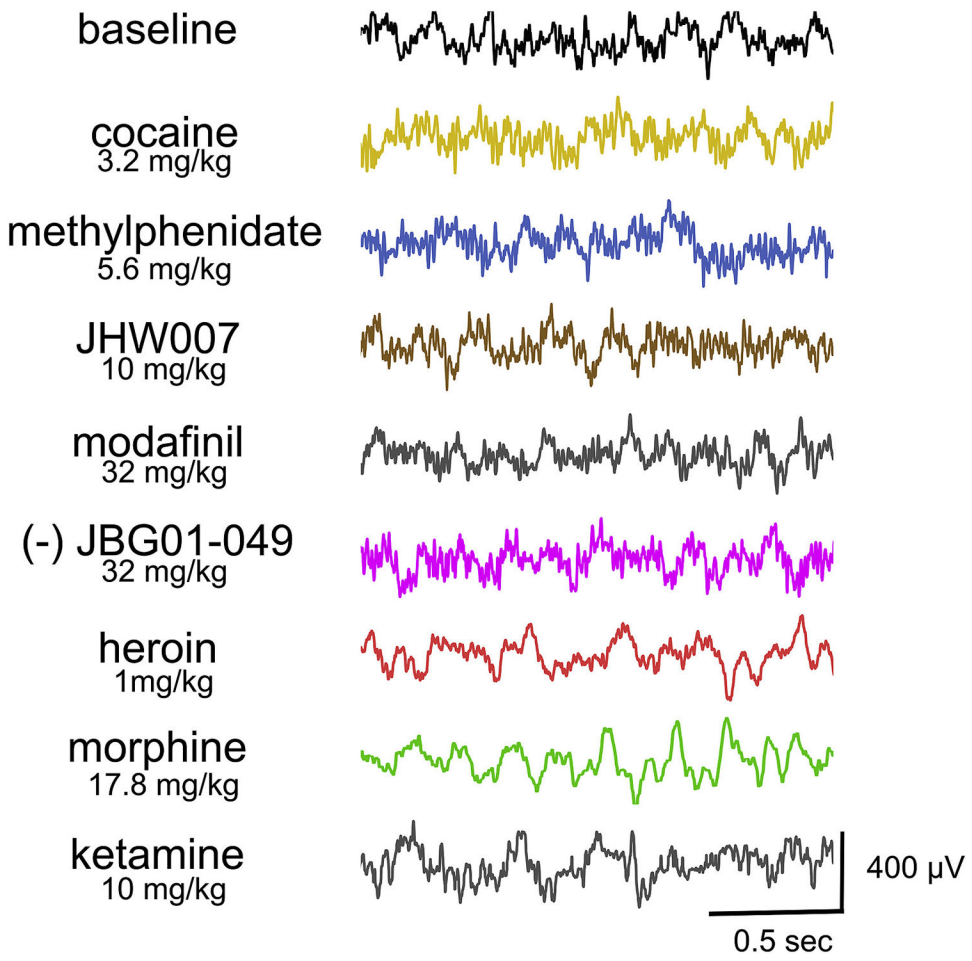

Fig. 2.

Representative EEG signals from frontal electrodes of rats during baseline and after administration of test compounds. Ordinates: µVolts. Abscissa: Time in seconds.

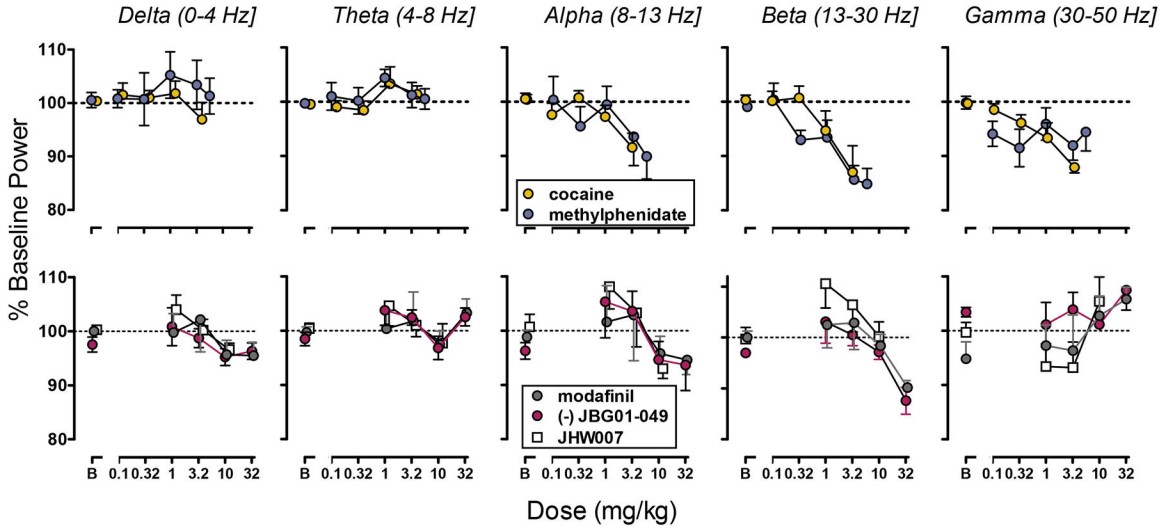

Fig. 3.

Top panels: Effects of the typical DUIs cocaine (N=6) and methylphenidate (N=6, top panels), on the power of frontal frequencies bands. Bottom panels: Effect of atypical DUIs modafinil (N=7) and JHW007 (N=5) and of JBG1-049 (N=6) on frontal frequencies bands. Ordinate: Percentage of Baseline Power (mean ± S.E.M). Abscissa: Dose expressed in mg/kg.

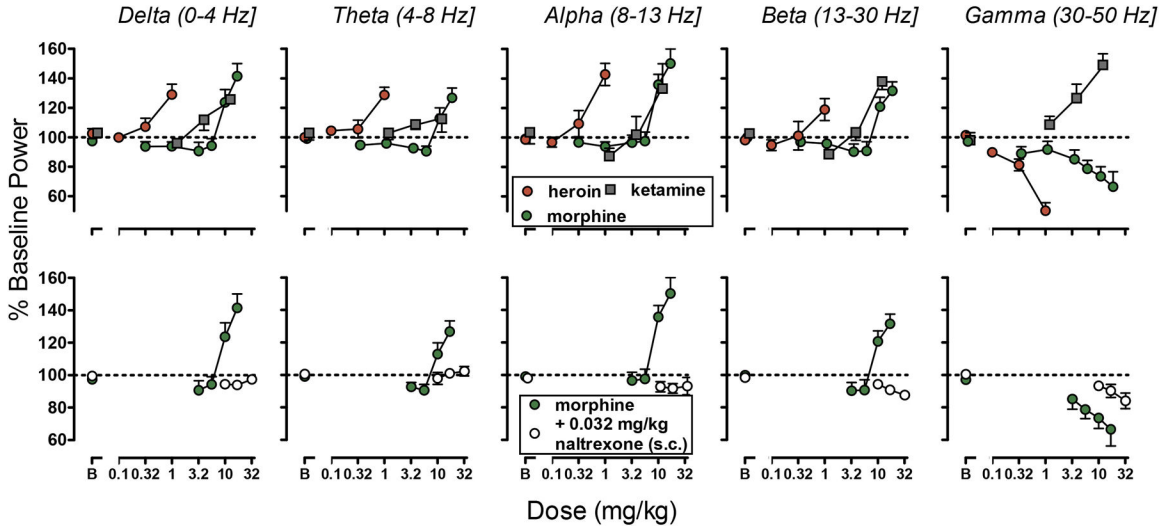

Fig. 4.

Top panels: Effects of the μ-opioid receptor agonists heroin (N=6) and morphine (N=6) and the NMDA receptor antagonist ketamine (N=5) on the power of frontal frequencies bands. Bottom panels: Effect of pretreatment with naltrexone (N=5) on morphine induced modulation of the power of frontal frequencies bands. Ordinate: Percentage of Baseline Power (mean ± S.E.M). Abscissa: Dose expressed in mg/kg.

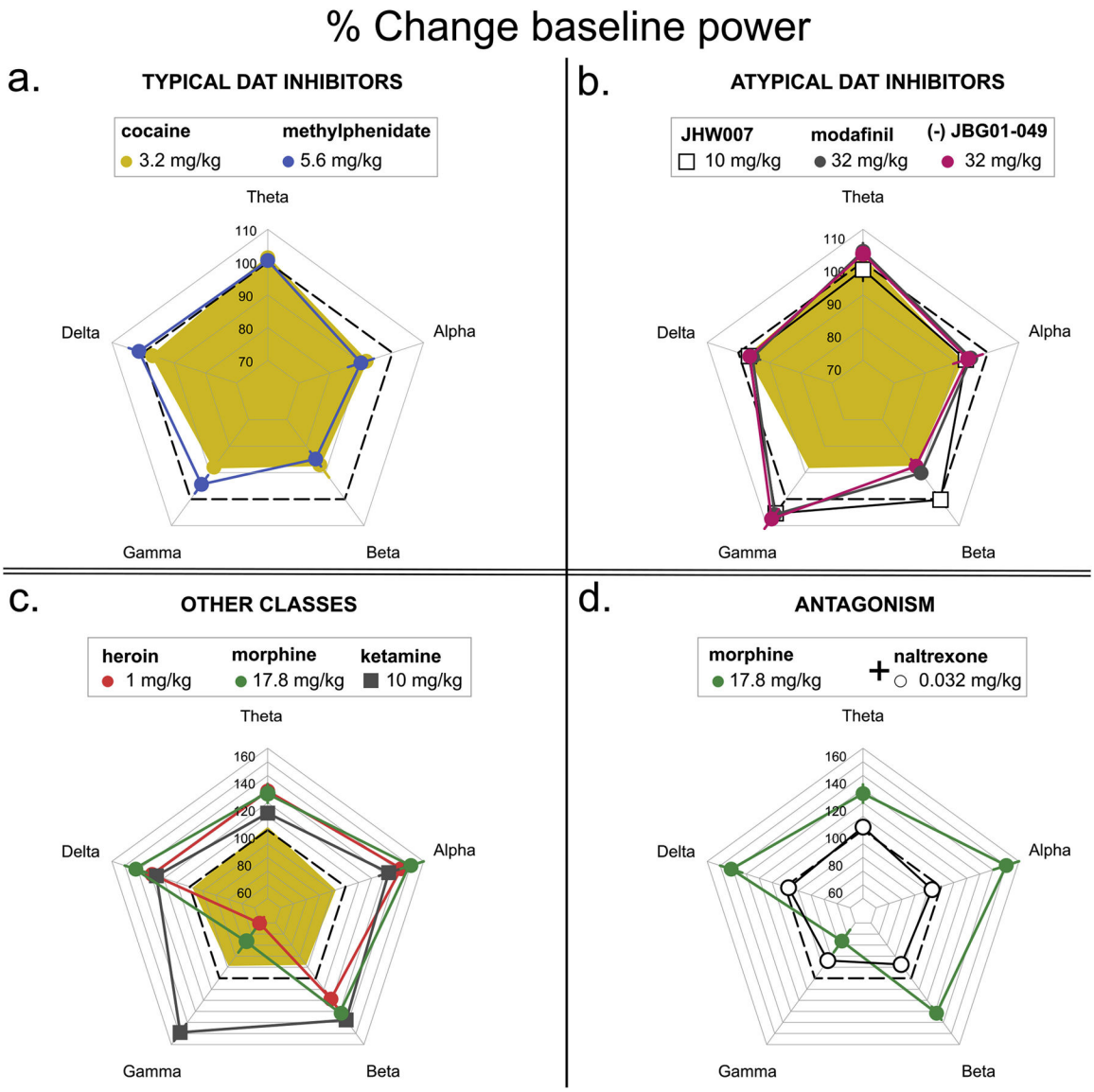

Fig. 5.

Maximal effects of typical (a.), atypical DUIs (b.), opioids and NMDA antagonist ketamine (c.), and morphine + naltrexone (d.) on frequency power. For comparison purposes, the effects of 3.2 mg/kg cocaine (yellow) are also reported in panel b and c. Ordinate: Percentage of Baseline Power (mean ± S.E.M).