Effects of Hallucinogens on Neuronal Activity

L. Lladó-Pelfort, P. Celada, M.S. Riga, E. Troyano-Rodríguez, N. Santana and F. Artigas

Abstract Hallucinogens evoke sensory, perceptual, affective, and cognitive effects that may be useful to understand the neurobiological basis of mood and psychotic disorders. The present chapter reviews preclinical research carried out in recent years in order to better understand the action of psychotomimetic agents such as the noncompetitive NMDA receptor (NMDA-R) antagonists and serotonergic hallucinogens. Our studies have focused on the mechanisms through which these agents alter cortical activity. Noncompetitive NMDA-R antagonists, such as phencyclidine (PCP) and MK-801 (dizocilpine), as well as the serotonergic hallucinogens DOI and 5-MeO-DMT, produce similar effects on cellular and population activity in prefrontal cortex (PFC); these effects include alterations of pyramidal neuron discharge (with an overall increase in firing), as well as a marked attenuation of the low frequency oscillations (0.2–4 Hz) to which neuronal discharge is coupled in anesthetized rodents. PCP increases *c-fos* expression in excitatory neurons from various cortical and subcortical areas, particularly the thalamus. This effect of PCP involves the preferential blockade of NMDA-R on GABAergic neurons of the reticular nucleus of the thalamus, which provides feedforward inhibition to the rest of thalamic nuclei. It is still unknown whether serotonergic hallucinogens also affect thalamocortical networks. However, when examined, similar alterations in other cortical areas, such as the primary visual cortex (V1), have been observed, suggesting that these agents affect cortical activity in sensory and associative areas. Interestingly, the disruption of PFC activity induced by PCP, DOI and 5-MeO-DMT is reversed by classical and atypical antipsychotic drugs. This effect suggests a possible link between the mechanisms underlying the disruption of

L. Lladó-Pelfort · P. Celada · M.S. Riga · E. Troyano-Rodríguez · N. Santana · F. Artigas
Department of Neurochemistry and Neuropharmacology, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Institut d'Investigacions Biomèdiques de Barcelona (IIBB-CSIC-IDIBAPS), Barcelona, Spain

F. Artigas (✉)
Department of Neurochemistry and Neuropharmacology, IIBB-CSIC (IDIBAPS), Rosselló, 161, 6th Floor, 08036 Barcelona, Spain
e-mail: fapnqi@iibb.csic.es

Curr Topics Behav Neurosci (2017) 36: 75–105
DOI 10.1007/7854_2017_473
Published Online: 26 February 2017

perception by multiple classes of hallucinogenic agents and the therapeutic efficacy of antipsychotic agents.

Keywords 5-HT_{2A} receptors · Antipsychotic drugs · NMDA receptors · Prefrontal cortex · Thalamus

Contents

1 Hallucinogens as Pharmacological Models in Schizophrenia Research

Schizophrenia is one of the most severe psychiatric conditions, affecting approximately 1% of the population. It has an early onset (typically late adolescence or early adulthood) and shows a chronic and deteriorating course. Many affected individuals suffer from a lifelong disability, with a poor quality of life, and nearly 10% commit suicide. Schizophrenia is characterized by a variety of symptoms, including positive (hallucinations, delusions, disorganized thought and speech, aberrant behavior, etc.) and negative symptoms (emotional blunting, social withdrawal, depression, anxiety, etc.) together with cognitive deficits. Anatomical, cellular and neurochemical alterations have been reported in various brain areas of schizophrenic patients and notably in the prefrontal cortex (PFC) (Harrison 1999a; Selemon and Goldman-Rakic 1999; Lewis and Lieberman 2000; Harrison and Weinberger 2005; Lewis and Gonzalez-Burgos 2006) (see below for additional information).

Historically, schizophrenia has been associated with derangements of multiple neurotransmitter systems, due to the ability of pharmacological agents acting on those systems to mimic symptoms of the illness in healthy individuals and to aggravate symptoms in patients. Hence, more classical views on the pathophysiology of schizophrenia indicated a hyperactivity of midbrain dopaminergic systems,

suggested by the ability of dopamine-releasing agents to evoke psychotic symptoms (Carlsson 1977). This early view was later supported by positron emission tomography (PET) scan studies showing a larger striatal dopamine release in schizophrenic patients compared to healthy controls after receiving an amphetamine challenge (Laruelle et al. 1996) as well as a higher basal occupancy of dopamine D_2 receptors (Abi-Dargham et al. 2000). Subsequently, the dopamine hypothesis of schizophrenia was refined, suggesting the function of the ascending mesocortical dopamine system was reduced, which might account for the negative symptoms—and possibly, cognitive deficits—of the illness (Weinberger 1987). This view received support from PET studies showing alterations of postsynaptic dopamine D_1 receptor availability consistent with a low dopaminergic tone (Abi-Dargham et al. 2002).

In addition to dopamine, alterations of other neurotransmitter systems in schizophrenia have been proposed, including serotonin (5-hydroxytryptamine, 5-HT), glutamate, and GABA. In particular, alterations of 5-HT and glutamate receptors have been reported (Rasmussen et al. 2010, 2016; Harrison 1999b). For example, noncompetitive antagonists of NMDA receptors (NMDA-R) are extensively used as pharmacological models of schizophrenia due to the ability of these compounds to mimic the symptoms of the illness (Krystal et al. 2003). Additionally, atypical (second and third generation) antipsychotic drugs mainly target 5-HT receptors (Meltzer and Massey 2011).

In the present chapter, we review some electrophysiological and histological observations suggesting a common pattern of action of serotonergic and glutamatergic agents in the prefrontal cortex (PFC) of experimental animals that may account for the psychotomimetic properties of these agents. We also provide evidence that the alterations of PFC activity evoked by serotonergic hallucinogens and noncompetitive NMDA-R antagonists can be countered by classical (haloperidol) and atypical (clozapine) antipsychotic drugs.

1.1 Serotonergic Hallucinogens

Most 5-HT_{2A} receptor agonists, including *N,N*-dimethyltryptamine (DMT), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), lysergic acid diethylamide (LSD), 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), mescaline and psilocybin, produce hallucinogenic effects, altering perception, thought, emotion and mood in a manner that is similar to endogenous psychosis (Glennon 1991, 1994; Nichols 2004; Vollenweider and Kometer 2010). Chemically, these agents belong to two main families: indoleamines (such as DMT, 5-MeO-DMT, psilocybin, and LSD), which have some structural similarity to the 5-HT molecule, and phenethylamines [such as mescaline, DOI, 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB), and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM)] (Nichols 2004). One important reason for investigating psychedelic agents lies in their capacity to model certain aspects of psychosis in experimental research

(Geyer and Vollenweider 2008), as well as their ability to facilitate the identification of brain areas/circuits altered in psychiatric disorders (Vollenweider et al. 1997a, b). Moreover, some of these agents, such as LSD and psilocybin, have shown therapeutic efficacy in the treatment of psychiatric disorders [reviewed in Vollenweider and Kometer (2010)]. LSD was marketed by Sandoz in the 1950s to facilitate psychotherapeutic treatment of psychiatric disorders, due to its ability to increase introspection and recall of emotional memories. The widespread recreational use of LSD and its marked effects on perception, mood and personality had a profound influence on young people in the Western world, leading to the development of so-called psychedelic art in the 1960s and 1970s. The hallucinogenic properties of LSD and the role it played in countercultural activities led to its classification as a controlled substance in the USA and most other Western countries.

DOI is another synthetic compound with strong psychedelic effects that has been extensively used in pharmacological research. It evokes long-lasting alterations of consciousness and perception (Nichols 2004). DOI acts by stimulating 5-HT_{2A} receptors, since most of its behavioral, neurochemical and electrophysiological effects can be blocked by the selective 5-HT_{2A} receptor antagonist M100907 (Schreiber et al. 1994; Martin-Ruiz et al. 2001; Puig et al. 2003).

DMT and 5-MeO-DMT are natural components of *ayahuasca*, a hallucinogenic beverage used in religious ceremonies and for healing purposes in the upper Amazon (McKenna 2004; McKenna et al. 1984; Schultes et al. 1991) and recently investigated for potential clinical uses (McKenna 2004). The psychedelic effects induced by *ayahuasca* include visual and auditory hallucinations, synesthesia, and deep psychological introspection. In addition to the tryptamines, *ayahuasca* contains β-carbolines such as harmine, which act as reversible inhibitors of monoamine oxidase-A (MAO-A). The β-carbolines prevent the catabolism of the tryptamines in the gut, thus allowing the tryptamines to be active orally and prolonging their psychedelic effects (McKenna et al. 1984; Agurell et al. 1968). DMT and 5-MeO-DMT are also synthesized and distributed for recreational purposes (Yu 2008) and intoxications have been reported (Sklerov et al. 2005; Brush et al. 2004). Early reports identified 5-MeO-DMT as a possible endogenous psychotoxin and several groups theorized about its potential involvement in schizophrenia (Benington et al. 1965; Gillin and Wyatt 1976; Angrist et al. 1976).

Interestingly, not all 5-HT_{2A} receptor agonists produce hallucinogenic effects, raising questions about the neural mechanisms responsible for their effects, such as differences in signaling pathways (Kurrasch-Orbaugh et al. 2003; Gonzalez-Maeso et al. 2007, see also Chap. 2). Regardless of the cellular mechanisms that are responsible for the effects of hallucinogens, it is important to note that their main target—the 5-HT_{2A} receptor—is expressed at very high levels in the neocortex, including sensory and associative areas (Pazos et al. 1985, 1987; Jakab and Goldman-Rakic 1998; Hall et al. 2000; Lopez-Gimenez et al. 2001; Santana et al. 2004). The 5-HT_{2A} receptor is densely expressed in intermediate and deep layers of the frontal, temporal, parietal and occipital lobes (Pazos et al. 1987; Santana et al. 2004; de Almeida and Mengod 2007), suggesting that their activation may have a strong influence on the processing of information in cortical areas as well as

between cortical and subcortical brain regions. 5-HT_{2A} receptors are expressed in midbrain-projecting PFC pyramidal neurons (Vazquez-Borsetti et al. 2009) and 5-HT_{2A} receptor activation by DOI and other hallucinogens has marked effects on the activity of downstream serotonergic and dopaminergic neurons (Martin-Ruiz et al. 2001; Bortolozzi et al. 2003, 2005).

Activation of 5-HT_{2A} receptors by 5-HT and other agonists elicits several electrophysiological effects in cortical neurons recorded in vitro, including enhancement of the response to excitatory synaptic input (Aghajanian and Marek 1997, 1999), induction of membrane depolarization, and reduction of the afterhyperpolarization that follows a burst of spikes (Araneda and Andrade 1991; Villalobos et al. 2005). In vivo, 5-HT_{2A} receptor activation by endogenous 5-HT moderately increases the firing rate of pyramidal cells (Amargos-Bosch et al. 2004; Puig et al. 2005), whereas systemic administration of DOI evokes a dramatic increase in the firing rate of a subpopulation of PFC pyramidal neurons (Puig et al. 2003). However, despite the increasing knowledge of the cellular actions of hallucinogens, there is a conspicuous lack of information concerning their actions at the network level.

1.2 NMDA Receptors. Noncompetitive Antagonists

Rapid ionic effects of glutamate are mediated by three receptor subtypes, namely AMPA, kainate, and NMDA receptors. These receptors are ion channels, and their activation by glutamate allows extracellular Na^+ and Ca^{2+} ions to enter (and K^+ ions to leave) the cytoplasm, thus evoking rapid and marked changes of the membrane potential (depolarization in most instances), which subsequently results in the generation of action potentials. Glutamate can also act on a family of 8 G-protein coupled metabotropic receptors, analogous to monoamine receptors, which are suitable targets for drug development (Swanson et al. 2005; Niswender and Conn 2010).

NMDA-R are involved in a large number of key physiological functions, such as long-term potentiation and other forms of synaptic plasticity, and play a role in several neurological and psychiatric disorders (Lau and Zukin 2007; Paoletti and Neyton 2007). NMDA-R are tetrameric ion channels composed of two GluN1 and two GluN2 subunits (formerly called NR1 and NR2). A third type of NMDA-R subunits (GluN3) has been identified that changes the ionic sensitivity of the NMDA-R channel (Cavara and Hollmann 2008). The NMDA-R ion channel is voltage-sensitive, and the channel is blocked by Mg^{2+} ions at resting membrane potential. After the depolarization of the cell membrane, Mg^{2+} ions are released from the NMDA-R, allowing the passage of other ions (Na^+, Ca^{2+}, K^+) through the channel. Thus, in general, AMPA-induced depolarization precedes the functional activity of NMDA-R.

The NMDA-R contains several binding sites, including the orthosteric site that binds glutamate and competitive antagonists such as AP5 (also known as APV).

Likewise, the NMDA-R contains several regulatory sites, including a glycine binding site, located outside the channel, as well as binding sites for Mg^{2+} and noncompetitive antagonists such as phencyclidine (PCP), which are located inside the channel. The dissociative anesthetics ketamine and PCP are noncompetitive NMDA-R antagonists. These agents have been used as pharmacological models of schizophrenia due to their ability to mimic the positive (psychotic) and negative symptoms of schizophrenia in healthy individuals and to aggravate illness symptoms in schizophrenic patients (Krystal et al. 2003; Javitt and Zukin 1991). Moreover, PCP, ketamine, and dizocilpine (MK-801; not available for human use) evoke a series of behavioral alterations in experimental animals, including induction of hyperlocomotion and stereotypies, and disruption of sensorimotor gating. These alterations are partially or totally antagonized by antipsychotic drugs (Carlsson and Carlsson 1989; Geyer et al. 2001). However, the cellular elements and brain networks involved in these actions are still not completely understood, although work by different research groups in recent years has started to clarify the actions of NMDA-R antagonists on brain function, including activity and processing in the prefrontal cortex (PFC).

2 The Prefrontal Cortex

The PFC is the highest association cortex and plays an important role in the pathophysiology and treatment of psychiatric disorders, including schizophrenia. Not surprisingly, most research on the cellular actions of psychotomimetic agents has been carried in this cortical area. The PFC has poorly defined anatomical boundaries but it can be identified by its reciprocal connectivity with the mediodorsal (MD) nucleus of the thalamus. The PFC is involved in many higher brain functions, such as perception, attention, memory, and cognition. The dorsolateral PFC is primarily involved in cognitive processes, such as working memory and executive function, as well as action planning and decision making (Fuster 2001, 2008; Miller and Cohen 2001). In addition to cognitive functions, the PFC participates in the control of mood and affect. Hence, the anterior cingulate cortex, including its ventral subdivision, is heavily involved in emotional processing (Devinsky et al. 1995; Davidson and Irwin 1999; Cardinal et al. 2002; Phillips et al. 2003) and certain psychotic symptoms such as hallucinations are associated with hyperactivity in this PFC subdivision (Shergill et al. 2000). Likewise, alterations of energy metabolism in the ventromedial PFC have been reported in depressed patients (Drevets 2001; Seminowicz et al. 2004) and high frequency stimulation of this region evokes immediate antidepressant effects in patients refractory to standard treatments (Mayberg et al. 2005; Puigdemont et al. 2012).

As is the case with other cortical regions, the PFC is composed of $\sim$75–80% of pyramidal projection neurons, which use glutamate as a transmitter, and $\sim$20–25% of local circuit inhibitory interneurons, which use GABA as a transmitter. Pyramidal neurons integrate excitatory glutamatergic afferent input from various

thalamic nuclei, including the mediodorsal, centromedial and several midline nuclei, as well as the hippocampus, the amygdala, and other cortical areas (Fuster 2008; Groenewegen and Uylings 2000). Local inhibitory inputs arise from GABAergic interneurons. These interneurons have been classified according to their anatomical and neurochemical characteristics and their synaptic relationships with pyramidal neurons (DeFelipe et al. 2013). Firing patterns also differ markedly between subpopulations of interneurons. Fast-spiking, parvalbumin-containing GABAergic interneurons have been suggested to play a role in schizophrenia, in particular in deficits of cognitive control (Lewis et al. 2005, 2012).

PFC neurons are densely innervated by projections from brainstem monoaminergic nuclei such as the dorsal and median raphe nuclei, locus coeruleus and ventral tegmental area, which employ 5-HT, norepinephrine and dopamine, respectively, as neurotransmitters. These nuclei exert an important modulatory role of the excitatory and inhibitory inputs onto PFC neurons (Puig et al. 2005; Steinbusch 1981; Van Eden et al. 1987; Seamans and Yang 2004; Aston-Jones and Cohen 2005; Celada et al. 2013). A large population of pyramidal and GABAergic neurons in PFC express receptors for monoamine neurotransmitters (Santana et al. 2004, 2009, 2013; de Almeida and Mengod 2007, 2008). Atypical antipsychotic drugs such as clozapine show high affinity for monoamine receptors, suggesting that the PFC may be a key brain structure in their therapeutic action, in addition to the well-known blockade of dopamine D_2 receptors in ventral striatum (Artigas 2010).

3 Effects of Psychotomimetic Agents on Neuronal Activity in PFC

3.1 Serotonergic Hallucinogens

In one study (Puig et al. 2003), we examined the effect of DOI on the firing activity of pyramidal neurons in the rat medial PFC (mPFC). These neurons were identified by antidromic activation from the dorsal raphe or the ventral tegmental area, two areas targeted by projections from pyramidal neurons in deep PFC layers (Gabbott et al. 2005). More recent studies indicated that a large proportion of mPFC pyramidal neurons simultaneously project to both monoaminergic nuclei (Vazquez-Borsetti et al. 2011).

The i.v. administration of DOI (0.05–0.3 mg/kg) evoked three types of responses in mPFC pyramidal neurons. DOI enhanced the firing rate in 38% of the neurons examined (21/56), increasing the mean firing rate from 1.34 ± 0.36 to 6.45 ± 0.97 spikes/s (a 481% increase; $n = 21$). Another 32% of the projection neurons examined (18/56) were unaffected by administration of DOI at doses up to 0.3–0.8 mg/kg (i.v.), whereas the remaining cells (17/56, 30%) showed reductions of their firing rate (to 11 ± 3% of baseline). The baseline firing rate of the neurons that were excited or inhibited by DOI did not differ significantly (1.34 ± 0.36

spikes/s for excitations vs. 1.20 ± 0.33 spikes/s for inhibitions). Summing over all of the neurons examined, DOI significantly increased the output of mPFC projection neurons to 238% of baseline, from 1.23 ± 0.18 to 2.93 ± 0.53 spikes/s ($n = 56$; $p < 0.002$, paired t-test).

The DOI-induced excitations were reversed by M100907 (0.1–0.5 mg/kg i.v.) in 6 out of 9 cases examined. Because DOI is also an agonist at 5-HT_{2C} receptors, effects on some pyramidal neurons may also be mediated by this receptor subtype. Alternatively, M100907 may not be able to reverse the pyramidal excitation once the neurons become extensively depolarized, likely by activation of ionotropic glutamate receptors. The inhibition of firing elicited by DOI was also antagonized by M100907 (0.1–0.5 mg/kg i.v.; $n = 6$). In addition, the inhibitory effect of DOI was also reversed by the $GABA_A$ antagonist picrotoxinin (1–3 mg/kg i.v.), indicating that the pyramidal neuron inhibition is mediated by activation of 5-HT_{2A}-R located on GABAergic interneurons (Santana et al. 2004) (Fig. 1).

In another study (Wood et al. 2012), the effects of DOI on neuronal activity were examined in slightly different PFC subdivisions (orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC)) in freely moving rats. At a lower dose (1 mg/kg i.p.), DOI mainly increased population activity in ACC (as was observed in mPFC), whereas a larger proportion of the neurons were inhibited by a higher dose (5 mg/kg i.p.). In contrast, in the OFC, DOI evoked an excitation/inhibition ratio of ca. 1 at 1 mg/kg i.p., and produced a dose-dependent inhibition of neuronal activity at higher doses (Wood et al. 2012). The differences in the relative proportion of excited versus inhibited neurons in the two studies may be a consequence of the distinct PFC subdivisions examined as well as the use of choral hydrate anesthesia in the first study.

The effect of 5-MeO-DMT administration on pyramidal discharge was examined in chloral hydrate anesthetized rats pretreated with the MAO-A inhibitor clorgyline to mimic the effects of *ayahuasca*. The i.v. administration of 5-MeO-DMT (0.1 mg/kg) evoked a response in pyramidal neurons similar to that of DOI, increasing the firing rate of 51% of the neurons (to 406% of baseline), reducing the firing of 35% of the neurons (to 31% of baseline), and leaving the rest of the neurons (14%) unaffected (Fig. 2). Overall, 5-MeO-DMT increased pyramidal firing rate to 215% of baseline ($p < 0.001$, Student's t test; $n = 37$).

3.2 *Noncompetitive NMDA Receptor Antagonists*

Neuroimaging studies indicate that noncompetitive NMDA-R antagonists increase metabolic activity in the PFC (Breier et al. 1997). We therefore examined the actions of the noncompetitive NMDA-R antagonist PCP on the firing activity of pyramidal neurons in the mPFC of choral hydrate anesthetized rats. As with the studies of serotonergic hallucinogens, pyramidal neurons were identified by antidromic activation from midbrain nuclei, so the results are representative of the same neuronal population that was examined in the studies with DOI and 5-MeO-DMT.

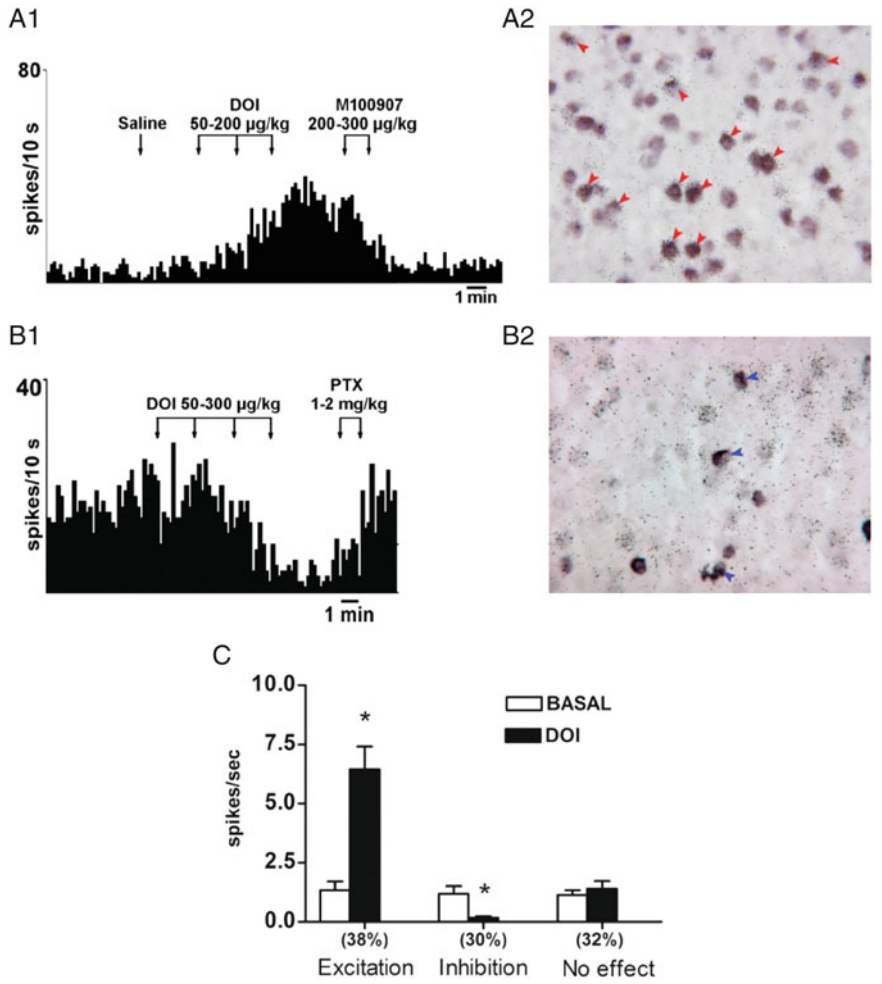


Fig. 1 Effect of 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) on the firing rate of pyramidal neurons in rat medial prefrontal cortex. **A1** Neuron that responded to DOI with an increase in firing rate. The excitatory effects of DOI were reversed by the 5-HT_{2A}-R antagonist M100907. **A2** Photomicrograph showing the presence of 5-HT_{2A}-R mRNA (^{33}P-labeled oligonucleotides) in pyramidal cells (*red arrows*) identified by the presence of vesicular glutamate transporter 1 (vGluT1) mRNA (dig-labeled oligonucleotides). **B1** Neuron that responded to DOI with a reduction in firing rate. The inhibitory effects of DOI were reversed by M100907 (data not shown) as well as by the $GABA_A$-R antagonist picrotoxinin (PTX). **B2** Photomicrograph showing the presence of 5-HT_{2A}-R mRNA (^{33}P-labeled oligonucleotides) in GABAergic cells (*blue arrows*) identified by the presence of glutamate decarboxylase (GAD) mRNA. **C** *Bar graph* showing the average effect of DOI according to the type of response. *$p < 0.05$ versus the basal firing rate. Adapted from Puig et al. (2003)

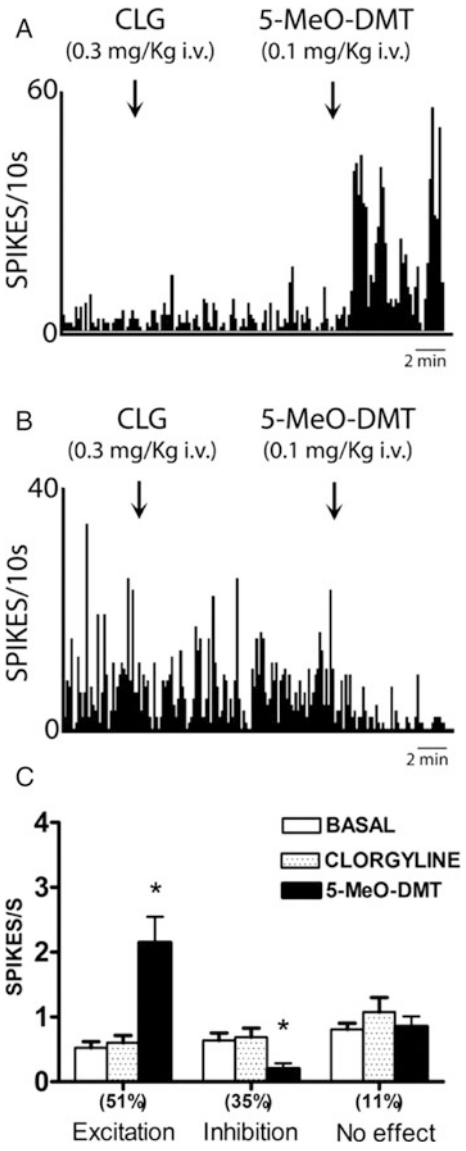


Fig. 2 Effect of 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) on the firing rate of pyramidal neurons in rat medial prefrontal cortex. Rats treated with 5-MeO-DMT were pretreated with the MAO-A inhibitor clorgyline (CLG) in order to mimic the effects of *ayahuasca*, which contains both β-carbolines (MAO-A inhibitors) and tryptamines. **A** Neuron that responded to CLG and 5-MeO-DMT with an increase in firing rate. **B** Neuron that responded to CLG and 5-MeO-DMT with a reduction in firing rate. **C** *Bar graph* showing the average effect of CLG and 5-MeO-DMT according to the type of response. $*p < 0.05$ versus the basal firing rate. Adapted from Celada et al. (2008)

The i.v. administration of PCP evoked complex effects on the discharge rate of mPFC pyramidal neurons (Kargieman et al. 2007). PCP (0.25 mg/kg i.v.) increased the discharge rate of 45% of the recorded neurons (to 286% of baseline) and reduced the discharge rate of 35% of the neurons (to 43% of baseline), with the remainder of the neurons (22%) unaffected (Fig. 3).

In a similar study, Katayama et al. (2007) also reported that PCP increased pyramidal neuron activity in rats anesthetized with pentobarbital followed by

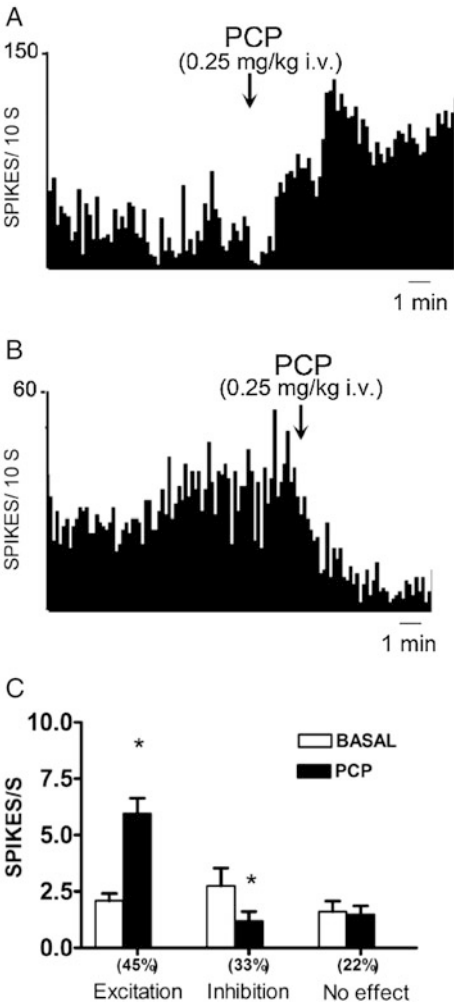


Fig. 3 Effect of phencyclidine (PCP) on the firing rate of pyramidal neurons in rat mPFC. **A** Neuron that responded to PCP with an increase in firing rate. **B** Neuron that responded to PCP with a reduction in firing rate. **C** *Bar graph* showing the average effect of PCP according to the type of response. $*p < 0.05$ versus the basal firing rate. Adapted from Kargieman et al. (2007). Note that the effects of PCP on pyramidal neuron firing are very similar to those produced by DOI (see panel **C** in Fig. 1) and 5-MeO-DMT (see panel **C** in Fig. 2)

urethane; this effect was antagonized by the local application of the AMPA/kainate receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX).

4 Role of Thalamocortical Inputs

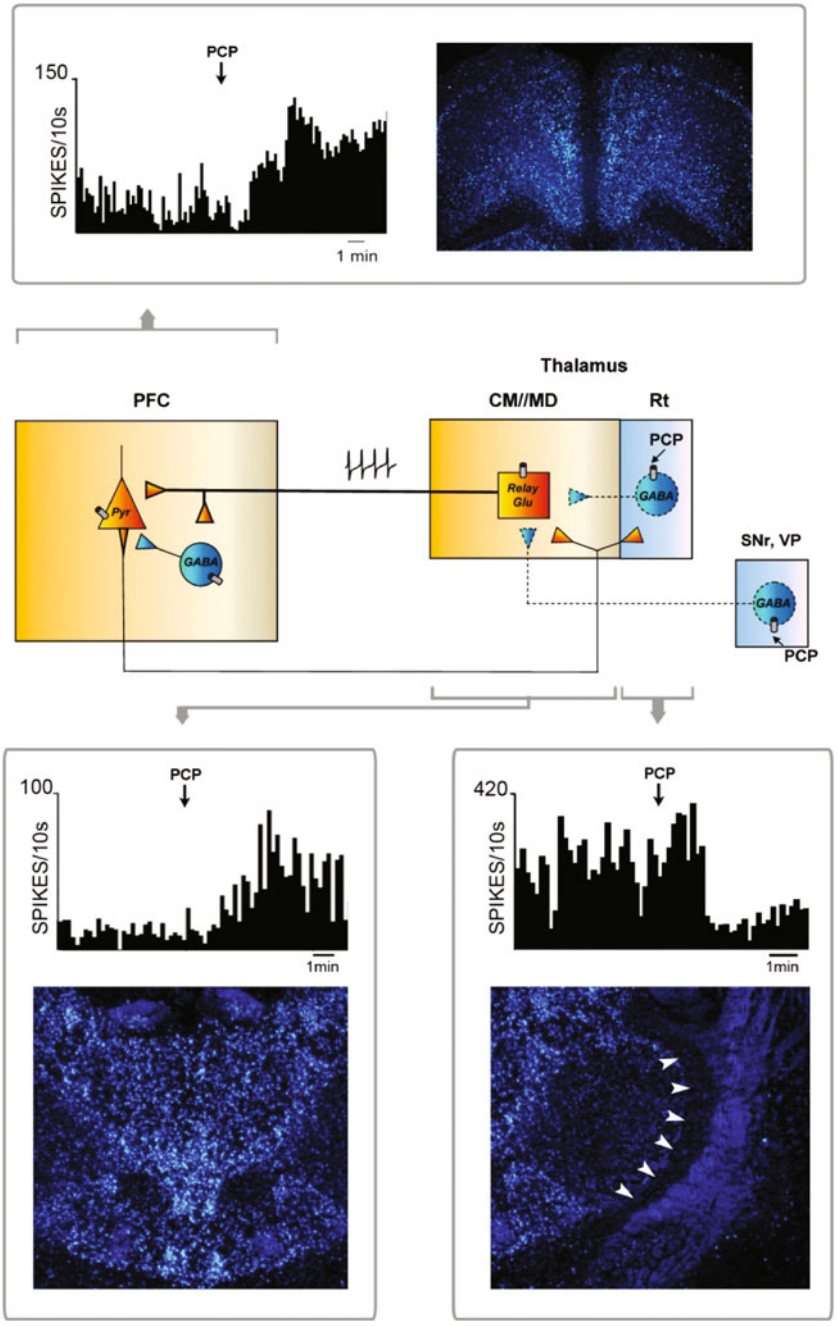
Despite the marked alteration of PFC activity produced by PCP, it is still not clear whether this action is essentially driven by intrinsic mechanisms (e.g., blockade of NMDA-R in the PFC) or whether other cortical and subcortical areas connected with the PFC—in particular the hippocampal formation and the thalamus—are also involved. The fact that systemic MK-801 administration has countervailing effects on

the activity of putative pyramidal and GABAergic neurons (increased and decreased discharge, respectively) led to the proposal that the main mechanism of action of this agent involves preferential blockade of NMDA-Rs on cortical GABAergic interneurons (Homayoun and Moghaddam 2007). However, the local application of PCP or MK-801 in the mPFC reduced the discharge rate of putative pyramidal neurons (Jodo et al. 2005; Suzuki et al. 2002) and, in the latter study, it was reported that the local application of PCP in the hippocampal formation facilitated pyramidal neuron activity in mPFC. Moreover, systemic—but not local—administration of noncompetitive NMDA-R antagonists increased neurotransmitter release in PFC (Amargos-Bosch et al. 2006; Lopez-Gil et al. 2007), suggesting that NMDA-R blockade in other brain areas may also contribute to the increase in PFC activity. In particular, interhemispheric projections may play a role since the bilateral (but not unilateral) application of MK-801 and ketamine in mPFC evoked neurochemical and behavioral changes similar to those produced by the systemic MK-801 administration (Lopez-Gil et al. 2012).

Double in situ hybridization experiments revealed that PCP (10 mg/kg i.p.) markedly increased *c-fos* expression in glutamatergic (vGluT1-positive) neurons from several cortical regions (prefrontal, somatosensory, retrosplenial, and entorhinal cortex) (Kargieman et al. 2007; Santana et al. 2011). PCP also induced a very marked increase of *c-fos* expression in various thalamic nuclei, in particular the centromedial and mediodorsal nuclei, which are reciprocally connected with the PFC (Gabbott et al. 2005; Berendse and Groenewegen 1991; Kuroda et al. 1998). PCP also increased *c-fos* expression in the amygdala, but only had a small effect in the hippocampal formation. The results of these *c-fos* studies led us to directly examine the effect of PCP on the discharge rate of neurons in the centromedial and mediodorsal thalamic nuclei. The administration of PCP (0.25 mg/kg i.v.) altered the discharge of thalamic neurons, increasing (to 424% of baseline) and decreasing (to 41% of baseline) the activity of 57 and 20% of the recorded neurons, respectively (23% of the neurons were unaffected) (Santana et al. 2011) (Fig. 4).

The activation of thalamocortical network activity by PCP appears to result from the preferential blockade of NMDA-R in the reticular nucleus of the thalamus (RtN). The RtN consists of a thin layer of GABAergic neurons that provide feedforward inhibition to excitatory thalamic nuclei. Hence, in parallel with the *c-fos* increase, systemic PCP administration evoked a dramatic and generalized decrease of neuronal activity in the RtN (Troyano-Rodriguez et al. 2014) at the same doses that increased excitatory neuronal discharge in the PFC and centromedial/mediodorsal nuclei (Kargieman et al. 2007; Santana et al. 2011) (Fig. 4).

Recent evidence from other groups also supports the involvement of thalamic nuclei in the action of NMDA-R antagonists. For example, ketamine administration increased the discharge rate of cells in the nucleus reuniens of the thalamus, and subsequently in the CA1 hippocampal subfield, a region to which the nucleus reuniens projects (Zhang et al. 2012). The same workers also reported that blockade of NMDA-R with the competitive antagonist APV in the reticular thalamic nucleus evoked bursts of delta oscillations (Zhang et al. 2009). Moreover, the effect of systemic MK-801 administration on slow oscillations (see below) in the PFC was mimicked by the local application of lidocaine in the mediodorsal nucleus of the


PCP
150
SPIKES/10s
1 min
Thalamus
PFC
CM//MD
Rt
PCP
Pyr
GABA
Relay
Glu
GABA
SNr, VP
GABA
PCP
PCP
100
SPIKES/10s
1min
PCP
420
SPIKES/10s
1min

◂**Fig. 4** Schematic representation of the action of phencyclidine (PCP) on thalamocortical circuits. PCP appears to exert a preferential blockade of NMDA receptors (NMDA-R) in the reticular nucleus (Rt) of the thalamus, which results in disinhibition of the excitatory thalamic nuclei that project to the neocortex (*bottom right panel*). The *upper* trace is an integrated firing rate histogram showing the effect of i.v. administration of PCP (0.25 mg/kg) on the discharge rate of a GABAergic neuron in the Rt. Note the lack of *c-fos* expression in the Rt (indicated by *arrowheads* in the lower image) (*bottom left panel*). In parallel with the reduction of GABAergic neuronal activity in the Rt, a large percentage of excitatory neurons in the mediodorsal (MD) and centromedial (CM) nuclei, reciprocally connected with the prefrontal cortex (PFC), are excited by PCP (0.25 mg/kg i.v.). These nuclei show also a dramatic increase in *c-fos* expression after i.p. administration of PCP (10 mg/kg), as shown in the *lower* histological image (*top panel*). Similar to the effect on the excitatory thalamic nuclei, PCP also increased the firing rate of a large percentage of the pyramidal neurons in the mPFC and increased *c-fos* expression in vGluT1-positive cells (pyramidal neurons). Overall, this combination of electrophysiological and histological evidence supports the view that PCP activates thalamocortical networks through a *bottom-up* process, although additional effects mediated by blockade of NMDA-R in other subpopulations of GABAergic neurons (e.g., fast-spiking cortical interneurons, substantia nigra reticulata (SNr) neurons, etc.) cannot be excluded

thalamus (Kiss et al. 2011a). Furthermore, the motor hyperactivity and the behavioral stereotypies induced by MK-801 in rats were prevented by bilateral application of the $GABA_A$ agonist muscimol directly into the anterior nucleus of the thalamus, indicating that MK-801 reduces $GABA_A$-mediated neurotransmission in the thalamus (Lopez Hill and Scorza 2012). Overall, these observations clearly support the involvement of thalamic nuclei in the behavioral, perceptual, and cognitive alterations induced by noncompetitive NMDA-R antagonists.

Thalamocortical inputs have also been claimed to play a role in the effects of serotonergic hallucinogens. For example, 5-HT and DOI were reported to evoke excitatory postsynaptic potentials in layer V pyramidal neurons in PFC slices, potentially by acting on presynaptic 5-HT_{2A} receptors located on thalamocortical afferents (Marek and Aghajanian 1998; Marek et al. 2001). However, this view has been challenged by several lines of experimental evidence, including the failure of histological studies to identify 5-HT_{2A} receptors located on presynaptic glutamatergic axons (Miner et al. 2003), the fact that DOI has identical effects on pyramidal neuron discharge in normal rats and in rats with extensive thalamic lesions (Puig et al. 2003), and the dependence of 5-HT-mediated facilitation of activity on 5-HT_{2A} receptors intrinsic to the PFC (Beique et al. 2007). However, presynaptic 5-HT_{2A} receptors have been recently identified in thalamocortical networks as modulators of associative learning (Barre et al. 2016).

5 Brain Oscillations: Relevance to Schizophrenia

Higher cognitive functions and executive functions emerge from the coordinated activity of different neuronal networks and brain areas. This coordinated activity is reflected in oscillatory activity, a characteristic feature of cortical dynamics. Brain oscillations can be assessed through electroencephalographic (EEG) recordings,

which detect the integrated activity of neuronal networks surrounding the electrodes (Barre et al. 2016). EEG oscillatory activity depends on the synchrony at which local and distal networks operate. Since the discovery of the EEG by Hans Berger (Nunez and Srinivasan 2006) and the first description of the most prominent rhythm (alpha, 8–12 Hz), multiple oscillatory activities have been described: slow (<1 Hz), delta (1–4 Hz), theta (4–7 Hz), beta (12–30 Hz) and gamma (30–80 Hz) rhythms. Brain oscillations are important because they serve to codify neural information and allow for coordinated activity between different neuronal networks in the temporal dimension: information is encoded not only by spiking activity, but also by the time at which the spikes are produced.

The generation of brain oscillations involves a balance between excitatory and inhibitory transmission within a network, which depends on the individual properties of the network components. For example, slow oscillations result from the interaction of cortical, thalamocortical and reticular nucleus oscillators (Berger 1929), whereas delta oscillations depend upon cortical and thalamocortical components (Crunelli and Hughes 2010; Petsche et al. 1984; Leresche et al. 1990; McCormick and Pape 1990; Llinas and Steriade 2006). Low frequency oscillations (slow and delta bands) are involved in several brain functions, including short- and long-term memory (Steriade et al. 1993; Bodizs et al. 2002; Marshall et al. 2006; Basar and Guntekin 2008). Additionally, they are essential for organizing higher frequency activities in sequences of complex oscillations (Binder et al. 2014). Gamma oscillations (30–80 Hz) deserve special attention due to their involvement in multiple cognitive processes (Steriade 2006): sensory and perceptual processing, short and long term memory, attention and executive functions, among others. Parvalbumin-positive GABAergic interneurons are heavily involved in the generation of gamma oscillations. These cells are fast-spiking interneurons, with special electrical properties, and are able to control large populations of pyramidal neurons via large dendritic networks connected by gap junctions (Engel and Singer 2001; Traub et al. 2000, 2001). These properties make them excellent candidates to spread fast oscillations through neuronal networks, although other cells and neurotransmitter systems may also be involved (Galarreta and Hestrin 2001; Belforte et al. 2010; Korotkova et al. 2010).

Because brain oscillations reflect neuronal and network dynamics, they may provide a valuable tool to study the etiology and pathophysiology of mental illnesses such as schizophrenia. Moreover, the study of brain oscillations can be a powerful translational tool, enabling comparisons between patients, healthy individuals and animal models. EEG recordings have been used to identify biomarkers, endophenotypes or prognostic indicators in schizophrenia. Indeed, schizophrenia symptoms may result from impaired connectivity, communication and coordination between brain regions (Carlen et al. 2012; Hoffman and McGlashan 1993; Skelly et al. 2008).

Recent studies show an increase of resting state gamma activity in schizophrenic patients compared to healthy controls (Camchong et al. 2011; Venables et al. 2009; Kikuchi et al. 2011). These findings are consistent with the alterations of GABAergic neurotransmission (especially in fast-spiking interneurons) (Lewis et al. 2005) and the deficits in NMDA-R glutamatergic neurotransmission

(Krystal et al. 2003; Spencer 2011; Konradi and Heckers 2003) that have been reported in schizophrenic patients. Likewise, abnormalities in corticosubcortical (e.g., thalamocortical) communication have been examined in schizophrenic patients via EEG sleep recordings. There are slow wave sleep deficits in schizophrenic patients, changes that are associated with negative symptoms. Specifically, schizophrenic patients show decreased delta wave counts, reductions in delta and theta power, and alterations in the laterality of these measures compared to healthy controls (Woo et al. 2008; Keshavan et al. 1998). Alterations in alpha activity during sleep have also been correlated with positive and negative symptom intensity (Sekimoto et al. 2007). Likewise, enhanced slow wave, delta, theta and beta activity, as well as decreased alpha activity in the resting state, have been associated with schizophrenia (Poulin et al. 2008; Rockstroh et al. 2007; Bates et al. 2009). Alterations of delta band frequency have been associated with negative symptoms of the illness (Begic et al. 2011). Moreover, EEG patterns can be used to distinguish schizophrenia patients from patients with other psychiatric disorders (Camchong et al. 2011; Poulin et al. 2008; Bates et al. 2009), different groups of schizophrenic patients (violent and nonviolent schizophrenic patients (Itoh et al. 2011)), and schizophrenia patients with "positive" versus "negative" symptoms (Schug et al. 2011; Begic et al. 2000).

Finally, different strategies have been used to model schizophrenia in healthy subjects. One such strategy is the administration of psychotomimetic drugs such as NMDA-R antagonists (Krystal et al. 2003). Using this approach, it has been shown that administration of subanesthetic doses of ketamine to healthy subjects augments high frequency oscillations (40–85 Hz) and reduces low frequency oscillations (1–5 Hz), mimicking some of the disturbances of oscillatory activity found in schizophrenia (Begic et al. 2009). Similar results have been reported using serotonergic hallucinogens (Hong et al. 2010; Oughourlian et al. 1971; Riba et al. 2002; Schenberg et al. 2015; Carhart-Harris et al. 2012; Kometer et al. 2015; Riba et al. 2004). After administration of psilocybin, decreases in broadband oscillatory power (Riba et al. 2004; Muthukumaraswamy et al. 2013), as well as reductions of blood flow (Schenberg et al. 2015), have been observed in areas of the default mode network (DMN).

6 Effects of Psychotomimetic Agents on Low Frequency Cortical Oscillations

The effects of hallucinogenic drugs on oscillatory activity have been examined in different animal models (Table 1). Our group has focused on the influence of psychotomimetic agents on low frequency oscillations. In rats and mice anesthetized with chloral hydrate, the aforementioned effects of PCP on pyramidal neuron activity were accompanied by simultaneous and marked reductions of low frequency cortical oscillations (LFCO; 0.3–4 Hz, with the most prominent intensity

Table 1 Effects of hallucinogen drugs in animal models: oscillatory activity in corticothalamic areas

	Area	Hallucinogen	Preparation	Effects	Ref.
NMDA receptor antagonists	mPFC	PCP	Anesthetized rats	↓ power of low frequency oscillations	Kargieman et al. (2007)
	mPFC	PCP	Anesthetized mice	↓ power of low frequency oscillations	Raichle et al. (2001)
	PFC	MK-801	Freely moving rats	↑ gamma power ↓ correlation between gamma power and discharge rate	Wood et al. (2012)
	mPFC	MK-801	Anesthetized rats, subiculum stimulation	Administration of MK-801 systemically or by microinjection into MD changed 2-Hz oscillations to a less regular delta rhythm ↓ paired pulse facilitation	Kiss et al. (2011a), Tseng et al. (2006)
	FC and V1	PCP	Awake macaques during WM task	↑ gamma power in FC and V1 ↓ alpha power in FC ↓ beta power in V1 Prolong P300 in FC	Kiss et al. (2011b)
	FC and sensorimotor cortex	PCP, MK-801	Conscious rats	↑ power of 1–3 Hz oscillations in FC ↑ or ↓ 9–30 Hz power depending on dose	Goonawardena et al. (2016)
	Neocortex	Ket, MK-801	Freely moving rats	↑ gamma power	Sebban et al. (2002)
	Visual cortex	Ket, PCP	Slices, rat	↑ phase coupling between gamma oscillations in layers III and V	Pinault (2008)
	FC-PC	Ket, PCP	Freely moving rats	↑ gamma power	Anver et al. (2011)
	MD and CM	PCP	Anesthetized rats	↓ power of low frequency oscillations	Santana et al. (2011)
	RtN and mPFC	PCP	Anesthetized rats	↓ power of low frequency oscillations ↓ coherence between PFC and RtN	Troyano-Rodriguez et al. (2014)

(continued)

Table 1 (continued)

	Area	Hallucinogen	Preparation	Effects	Ref.
5-HT_{2A} agonists	mPFC	DOI	Anesthetized rats	↓ power of low frequency oscillations	Kargieman et al. (2012)
	PFC	DOI	Freely moving rats	Dose-dependent ↓ of gamma power ↓ correlation between gamma power and discharge rate	Wood et al. (2012)
	mPFC and V1	5-MeO-DMT	Anesthetized rats	↓ power of low frequency oscillations	Celada et al. (2008)
	Various regions of cortex	2C-B	Freely moving rats	↓ beta and gamma power ↑ delta power Effects on coherence depending on the dose (↓ or ↑)	Upton et al. (2014)

↓ decrease; ↑ increase; **2C-B** 4-bromo-2,5-dimethoxyphenethylamine hydrochloride; **5-MeO-DMT** 5-methoxy-*N*,*N*-dimethyltryptamine; **CM** centromedial thalamic nucleus; **DOI** 2,5-dimethoxy-4-iodoamphetamine; **FC** frontal cortex; **Ket** ketamine; **MD** mediodorsal thalamic nucleus; **MK-801** dizocilpine ((5*S*,10*R*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine); **mPFC** medial prefrontal cortex; **PC** parietal cortex; **PCP** phencyclidine; PFC prefrontal cortex; **RtN** reticulotegmental nucleus; **V1** primary visual cortex; **WM** working memory

at ~1 Hz) in the mPFC (Kargieman et al. 2007; Santana et al. 2011; Raichle et al. 2001); PCP also reduced delta waves in the thalamus. Hence, PCP administration dramatically reduced the power of LFCO, recorded in parallel with neuronal discharge. The reduction of LFCO power occurred in all experiments, irrespective of whether the recorded pyramidal neuron was excited, inhibited or unaffected by PCP. Figure 5 shows the effect of PCP on LFCO in the mPFC of anesthetized rats. Interestingly, PCP also produced a very marked desynchronization of the neuronal discharge from the active ("up") phases of LFCO. Under normal conditions, spikes are typically fired during the active phases of LFCO, corresponding to "up" states

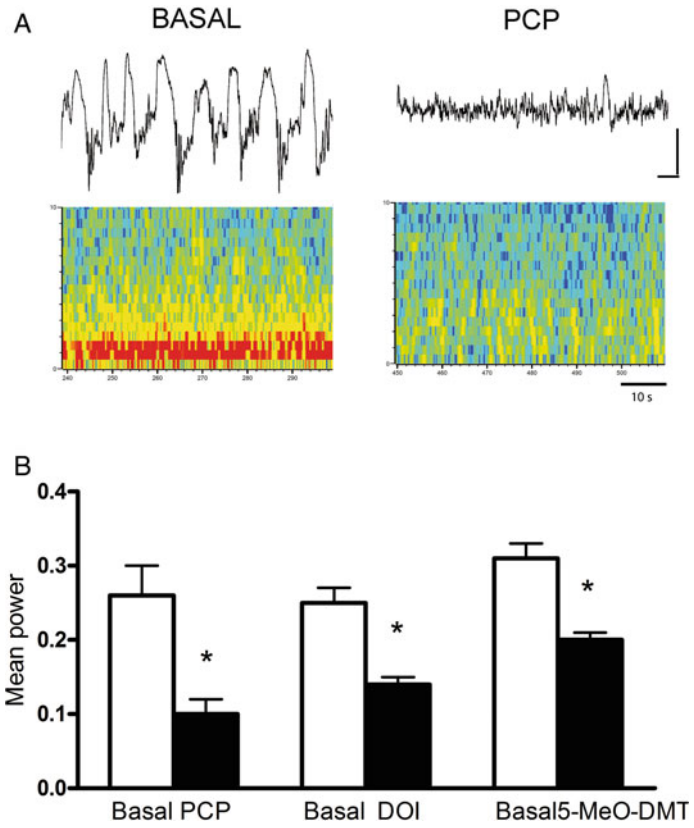


Fig. 5 **A** Representative examples of the local field potential recordings (*upper traces*) and the corresponding power spectrograms (*lower traces*) under basal conditions (*left side*) and after phencyclidine (PCP) administration (*right side*). Note that PCP produced a marked reduction of low frequency cortical oscillations (LFCO, ~1 Hz). The intensity of the power spectrum is color-coded (*red* high intensity; *blue* low intensity). **B** *Bar graph* showing the reduction in LFCO power produced by PCP (0.25 mg/kg i.v.), 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI; 0.25 mg/kg i.v.) and 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT; 0.1 mg/kg i.v.). *$p < 0.05$ versus the basal power level. Adapted from Kargieman et al. (2007, 2012), Celada et al. (2008)

(periods when neurons are depolarized). The percentage of spikes fired during the active phase of LFCO was 90 ± 3% at baseline conditions, whereas PCP reduced this value to 59 ± 11% (note that the maximum possible reduction was to 50% due to the random distribution of active and inactive phases of LFCO) (Kargieman et al. 2007).

The systemic administration of DOI (50–300 μg/kg i.v.) also caused a marked reduction of LFCO in PFC, to 56% of baseline (the effect of DOI on LFCO was slightly less marked than that of PCP). The effect of DOI was antagonized by the subsequent administration of M100907, indicating the exclusive involvement of 5-HT_{2A} receptors (Fig. 5) (Kargieman et al. 2012).

Likewise, the hallucinogen 5-MeO-DMT (0.1 mg/kg i.v.), a component of *ayahuasca*, also reduced the power of LFCO in PFC to 69% of baseline (Figs. 5 and 6) (Celada et al. 2008). Similar to DOI, the effect of 5-MeO-DMT on LFCO was also blocked by subsequent administration of M100907. Interestingly, 5-MeO-DMT also significantly altered neuronal firing and oscillatory activity in primary visual cortex (V1). Administration of 0.1 mg/kg i.v 5-MeO-DMT reduced LFCO power to a similar extent in V1 and PFC (Fig. 6). The reduction of LFCO power evoked by 5-MeO-DMT in PFC and V1 was accompanied by a significant reduction of BOLD signal in parallel fMRI studies (Celada et al. 2008). Interestingly, psilocybin also reduced the BOLD signal in the thalamus and various cortical areas of human volunteers (Schenberg et al. 2015), suggesting that this effect may be a common action of serotonergic hallucinogens. The decrease in BOLD signal may seem paradoxical in view of the fact that serotonergic hallucinogens primarily produce excitatory effects on neuronal activity in anesthetized rodents. However, because generation of LFCO is likely energetically demanding, reduction of oscillatory activity by serotonergic hallucinogens may counteract the energy requirements associated with the increase in neuronal firing, thus resulting in an overall decrease of cerebral blood flow. Additionally, differences in the overall excitatory/inhibitory effects of serotonergic hallucinogens due to the use of anesthesia may also be accountable.

7 Mechanisms Involved in the Reversal by Antipsychotic Drugs

Behavioral and neuronal alterations induced by noncompetitive NMDA-R antagonists and 5-HT_{2A} receptor agonists can be reversed by antipsychotic drugs, in particular by second generation or atypical antipsychotic drugs (Geyer et al. 2001). The similar disruptions of PFC activity produced by the two different models (NMDA-R antagonists and 5-HT_{2A} receptor agonists) indicates that these alterations may underlie their psychotomimetic activity (with the obvious limitation that these observations were carried out in anesthetized rodents). In spite of this limitation—common to most

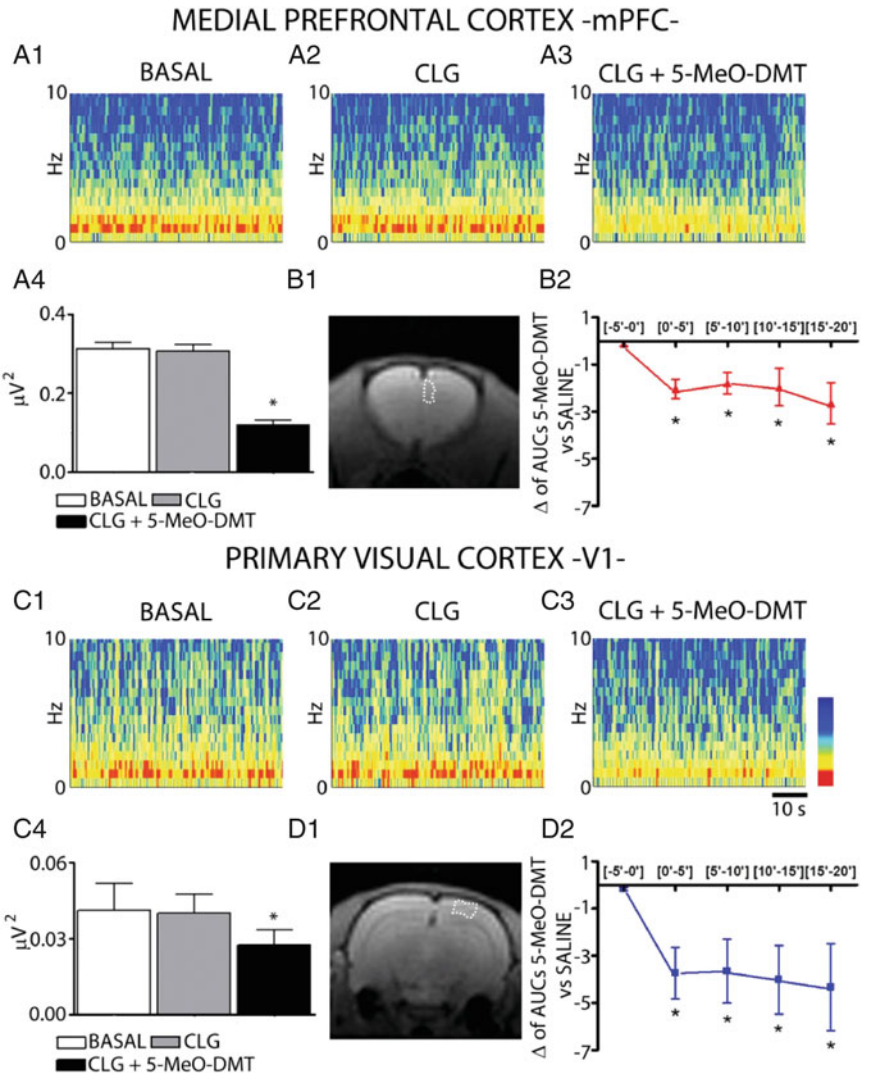


Fig. 6 Effect of the serotonergic hallucinogen 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) on low frequency cortical oscillations (LFCO) and blood oxygen level dependent (BOLD) response in anesthetized rats. **A1**–**A3** Spectrograms showing the effect of clorgyline (CLG) and 5-MeO-DMT on local field potentials in medial prefrontal cortex (mPFC). The intensity of the power spectrum is color-coded (*red* high intensity; *blue* low intensity). Note the lack of effect of CLG and the marked reduction of LFCO power induced by 5-MeO-DMT. **A4** Averaged effects of CLG and 5-MeO-DMT on power spectra in mPFC. **B1** Representative coronal section showing the regions of interest (ROI) used to assess effects on BOLD in mPFC. **B2** Kinetics of the effect of 5-MeO-DMT on BOLD signal in mPFC. The effect of 5-MeO-DMT on functional magnetic resonance imaging (fMRI) signal intensity was calculated by subtracting the effect of saline. **C1**–**C3** Effect of CLG and 5-MeO-DMT on local field potentials in primary visual cortex (V1). **C4** Averaged effects of CLG and 5-MeO-DMT on power spectra in V1. **D1** Representative coronal section showing the ROI used to assess effects on BOLD in V1. **D2** Kinetics of the effect of 5-MeO-DMT on BOLD signal in V1. *$p < 0.05$ versus the basal level. Adapted from Celada et al. (2008)

pharmacological studies employing in vivo electrophysiology—we attempted to reverse the effects of PCP on LFCO using antipsychotic drugs.

Interestingly, the alterations of PFC activity induced by PCP, DOI and 5-MeO-DMT were reversed by classical (haloperidol) and atypical (clozapine) antipsychotic drugs. The administration of clozapine completely reversed the increase in firing produced by PCP in PFC pyramidal neurons and in thalamic neurons (Kargieman et al. 2007; Santana et al. 2011). Likewise, clozapine pre-treatment prevented the PCP-induced increase in c-*fos* expression in all brain areas examined, including PFC and thalamic nuclei (Santana et al. 2011). Clozapine also reversed the reduction in LFO produced by PCP in PFC and thalamic nuclei (Kargieman et al. 2007; Santana et al. 2011), as well as the effects induced by the serotonergic hallucinogens DOI and 5-MeO-DMT in PFC (Kargieman et al. 2012; Celada et al. 2008) (Fig. 7). Likewise, the administration of haloperidol reversed

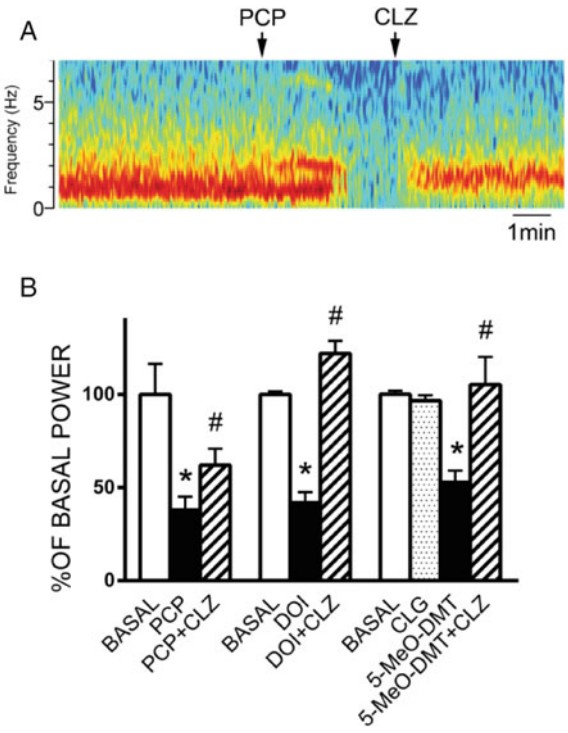


Fig. 7 **A** Representative spectrograms showing the reduction of low frequency cortical oscillations (LFCO) induced by phencyclidine (PCP; 0.25 mg/kg i.v.) in rat medial prefrontal cortex (mPFC) and the reversal induced by subsequent administration of clozapine (CLZ; 1 mg/kg i.v.). **B** *Bar graphs* showing the average effects of PCP, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI; 0.25 mg/kg i.v.), and 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT; 0.1 mg/kg i.v.) on the power of LFCO, as well as the ability of CLZ (1 mg/kg i.v.) to reverse those effects. $^{*}p < 0.05$ versus basal power; $^{\#}p < 0.05$ versus power in rats treated with PCP, DOI or 5-MeO-DMT alone. Data taken from Kargieman et al. (2007, 2012), Celada et al. (2008)

the effects of PCP, DOI and 5-MeO-DMT on LFCO, and when examined, on neuronal discharge (Kargieman et al. 2007, 2012; Celada et al. 2008).

The mechanisms involved in the reversal of PCP, DOI and 5-MeO-DMT effects have not been fully elucidated. At the cellular level, the reversal of PCP effects by clozapine may depend on increased GABA input to pyramidal neurons, given that the combination of PCP and clozapine had opposing effects on *c-fos* expression in GABAergic neurons (increased vs. PCP alone) and pyramidal neurons (reduced vs. PCP alone) (Kargieman et al. 2007). On the other hand, the reversal of the effects of DOI and 5-MeO-DMT by clozapine may simply involve the displacement of the 5-HT_{2A} receptor agonists from their binding sites by clozapine, which has high affinity and antagonist activity at such sites.

The reversal of PCP effects by clozapine appears to require the participation of 5-HT_{1A} receptors. Hence, PCP was equally effective in reducing LFCO in the PFC of wild-type (WT) mice and of mice lacking 5-HT_{1A} or 5-HT_{2A} receptors (1A-KO and 2A-KO mice, respectively) (Raichle et al. 2001). However, the subsequent administration of clozapine reversed the effects of PCP in WT mice and in 2A-KO mice, but failed to produce an effect in 1A-KO mice (Raichle et al. 2001), indicating the requirement of 5-HT_{1A} receptors. Recent pharmacological studies also support the involvement of 5-HT_{1A} receptors in the reversal of PCP effects on LFCO. Hence, the selective 5-HT_{1A} agonist BAY $\times$ 3702 completely reversed the reduction of LFCO power produced by PCP in rat PFC (Lladó-Pelfort et al. 2016; Riga et al. 2014). It does not appear that the reversal of PCP effects by clozapine can be explained by a direct interaction between the latter drug and 5-HT_{1A} receptors. Atypical antipsychotic drugs with low or no in vitro affinity for 5-HT_{1A} receptors—including clozapine—act as functional agonists at 5-HT_{1A} receptors in vivo, as shown by their ability to increase dopamine release in PFC (Meltzer and Massey 2011; Lladó-Pelfort et al. 2016; Rollema et al. 1997; Ichikawa et al. 2001; Diaz-Mataix et al. 2005). The mechanisms involved are unclear but may bear some relationship with the extensive co-expression of 5-HT_{1A} and 5-HT_{2A} receptors in PFC neurons (Amargos-Bosch et al. 2004).

Given the almost exclusive high affinity of haloperidol for dopamine D_2 receptors, the reversal of the effects of PCP and serotonergic hallucinogens by haloperidol cannot be explained by a direct competition with PCP, DOI or 5-MeO-DMT at 5-HT_{2A} receptor sites and likely involves network modulation. For example, ventral tegmental area stimulation excites PFC fast-spiking interneurons and concurrently inhibits PFC pyramidal neurons (Bortolozzi et al. 2010). Thus, haloperidol may attenuate PCP-induced excitation of pyramidal neurons via activation of dopamine D_1 receptors secondary to an autoreceptor-mediated increase of PFC dopamine release, which adds to the increase of dopamine release induced by PCP.

8 Concluding Remarks

Data obtained in recent years has revealed that psychotomimetic agents markedly disrupt neuronal activity in PFC and in its afferent thalamic areas, such as the centromedial and dorsomedial nuclei. In parallel, these agents reduce the power of low frequency oscillations in PFC and in the thalamus. Given the crucial role of these brain networks in adapting behavioral responses to external sensory input, it is likely that the observed abnormalities partly underlie the psychotomimetic action of these agents. The link between the effects on network activity and the production of schizophrenia-like symptoms is strengthened by the observation that antipsychotic agents reverse the disruption of thalamic and cortical network activity evoked by PCP, DOI and 5-MeO-DMT. Overall, the alterations of thalamocortical activity induced by psychotomimetic agents can be successfully used to gain further insight into the neurobiological basis of psychosis and to examine the potential antipsychotic efficacy of new drugs under development. Likewise, studies of altered PFC network activity may also provide new information on the mechanisms involved in the therapeutic activity of agents targeting NMDA-R and 5-HT_{2A} receptors.

Acknowledgements Supported by the Innovative Medicines Initiative Joint Undertaking (IMI) under Grant Agreement N° 115008 (NEWMEDS). IMI is a public–private partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations. Support from the following grants is also acknowledged: SAF 2015-68346-P (Ministry of Economy and Competitiveness and European Regional Development Fund), PI09/1245 and PI12/00156 (PN de I+D+I 2008–2011, ISCIII-Subdireccion General de Evaluación y Fomento de la Investigación cofinanced by the European Regional Development Fund. "Una manera de hacer Europa") and Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM (P82, 11INT3). Support from the Generalitat de Catalunya (SGR20093) is also acknowledged. MR is recipient of a IDIBAPS fellowship.

Statement of interest
None.

References

Abi-Dargham A et al (2000) Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. Proc Natl Acad Sci U S A 97(14):8104–8109

Abi-Dargham A et al (2002) Prefrontal dopamine D1 receptors and working memory in schizophrenia. J Neurosci 22(9):3708–3719

Aghajanian GK, Marek GJ (1997) Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. Neuropharmacology 36(4–5):589–599

Aghajanian GK, Marek GJ (1999) Serotonin, via 5-HT2A receptors, increases EPSCs in layer V pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release. Brain Res 825(1–2):161–171

Agurell S et al (1968) Identification of two new beta-carboline alkaloids in South American hallucinogenic plants. Biochem Pharmacol 17(12):2487–2488

Amargos-Bosch M et al (2004) Co-expression and in vivo interaction of serotonin1A and serotonin2A receptors in pyramidal neurons of prefrontal cortex. Cereb Cortex 14(3):281–299
Amargos-Bosch M et al (2006) Clozapine and olanzapine, but not haloperidol, suppress serotonin efflux in the medial prefrontal cortex elicited by phencyclidine and ketamine. Int J Neuropsychopharmacol 9(5):565–573
Angrist B et al (1976) Dimethyltryptamine levels in blood of schizophrenic patients and control subjects. Psychopharmacology 47(1):29–32
Anver H et al (2011) NMDA receptor hypofunction phase couples independent gamma-oscillations in the rat visual cortex. Neuropsychopharmacology 36(2):519–528
Araneda R, Andrade R (1991) 5-Hydroxytryptamine2 and 5-hydroxytryptamine1A receptors mediate opposing responses on membrane excitability in rat association cortex. Neuroscience 40(2):399–412
Artigas F (2010) The prefrontal cortex: a target for antipsychotic drugs. Acta Psychiatr Scand 121(1):11–21
Aston-Jones G, Cohen JD (2005) An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci 28:403–450
Barre A et al (2016) Presynaptic serotonin 2A receptors modulate thalamocortical plasticity and associative learning. Proc Natl Acad Sci U S A 113(10):E1382–E1391
Basar E, Guntekin B (2008) A review of brain oscillations in cognitive disorders and the role of neurotransmitters. Brain Res 1235:172–193
Bates AT et al (2009) Low-frequency EEG oscillations associated with information processing in schizophrenia. Schizophr Res 115(2–3):222–230
Begic D, Hotujac L, Jokic-Begic N (2000) Quantitative EEG in 'positive' and 'negative' schizophrenia. Acta Psychiatr Scand 101(4):307–311
Begic D, Mahnik-Milos M, Grubisin J (2009) EEG characteristics in depression, "negative" and "positive" schizophrena. Psychiatr Danub 21(4):579–584
Begic D et al (2011) Quantitative electroencephalography in schizophrenia and depression. Psychiatr Danub 23(4):355–362
Beique JC et al (2007) Mechanism of the 5-hydroxytryptamine 2A receptor-mediated facilitation of synaptic activity in prefrontal cortex. Proc Natl Acad Sci U S A 104(23):9870–9875
Belforte JE et al (2010) Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. Nat Neurosci 13(1):76–83
Benington F, Morin RD, Clark LC Jr (1965) 5-methoxy-N, N-dimethyltryptamine, a possible endogenous psychotoxin. Ala J Med Sci 2(4):397–403
Berendse HW, Groenewegen HJ (1991) Restricted cortical termination fields of the midline and intralaminar thalamic nuclei in the rat. Neuroscience 42(1):73–102
Berger H (1929) Electroencephalogram in humans. Archiv fur Psychiatrie und Nervenkrankheiten 87:527–570
Binder S et al (2014) Transcranial slow oscillation stimulation during NREM sleep enhances acquisition of the radial maze task and modulates cortical network activity in rats. Front Behav Neurosci 7:220
Bodizs R et al (2002) Sleep-dependent hippocampal slow activity correlates with waking memory performance in humans. Neurobiol Learn Mem 78(2):441–457
Bortolozzi A et al (2003) In vivo modulation of 5-hydroxytryptamine release in mouse prefrontal cortex by local 5-HT(2A) receptors: effect of antipsychotic drugs. Eur J Neurosci 18(5): 1235–1246
Bortolozzi A et al (2005) The activation of 5-HT receptors in prefrontal cortex enhances dopaminergic activity. J Neurochem 95(6):1597–1607
Bortolozzi A et al (2010) Dopamine release induced by atypical antipsychotics in prefrontal cortex requires 5-HT(1A) receptors but not 5-HT(2A) receptors. Int J Neuropsychopharmacol 13(10):1299–1314
Breier A et al (1997) Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in healthy volunteers. Am J Psychiatry 154(6):805–811

Brush DE, Bird SB, Boyer EW (2004) Monoamine oxidase inhibitor poisoning resulting from Internet misinformation on illicit substances. J Toxicol Clin Toxicol 42(2):191–195
Camchong J et al (2011) Altered functional and anatomical connectivity in schizophrenia. Schizophr Bull 37(3):640–650
Cardinal RN et al (2002) Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neurosci Biobehav Rev 26(3):321–352
Carhart-Harris RL et al (2012) Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. Proc Natl Acad Sci U S A 109(6):2138–2143
Carlen M et al (2012) A critical role for NMDA receptors in parvalbumin interneurons for gamma rhythm induction and behavior. Mol Psychiatry 17(5):537–548
Carlsson A (1977) Does dopamine play a role in schizophrenia? Psychol Med 7(4):583–597
Carlsson M, Carlsson A (1989) Dramatic synergism between MK-801 and clonidine with respect to locomotor stimulatory effect in monoamine-depleted mice. J Neural Transm 77(1):65–71
Cavara NA, Hollmann M (2008) Shuffling the deck anew: how NR3 tweaks NMDA receptor function. Mol Neurobiol 38(1):16–26
Celada P et al. (2008) The hallucinogen DOI reduces low-frequency oscillations in rat prefrontal cortex: reversal by antipsychotic drugs. Biol Psychiatry 64(5):392–400
Celada P, Puig MV, Artigas F (2013) Serotonin modulation of cortical neurons and networks. Front Integr Neurosci 7:25
Crunelli V, Hughes SW (2010) The slow (<1 Hz) rhythm of non-REM sleep: a dialogue between three cardinal oscillators. Nat Neurosci 13(1):9–17
Davidson RJ, Irwin W (1999) The functional neuroanatomy of emotion and affective style. Trends Cogn Sci 3(1):11–21
de Almeida J, Mengod G (2007) Quantitative analysis of glutamatergic and GABAergic neurons expressing 5-HT(2A) receptors in human and monkey prefrontal cortex. J Neurochem 103(2):475–486
de Almeida J, Mengod G (2008) Serotonin 1A receptors in human and monkey prefrontal cortex are mainly expressed in pyramidal neurons and in a GABAergic interneuron subpopulation: implications for schizophrenia and its treatment. J Neurochem 107(2):488–496
DeFelipe J et al (2013) New insights into the classification and nomenclature of cortical GABAergic interneurons. Nat Rev Neurosci 14(3):202–216
Devinsky O, Morrell MJ, Vogt BA (1995) Contributions of anterior cingulate cortex to behaviour. Brain 118(Pt 1):279–306
Diaz-Mataix L et al (2005) Involvement of 5-HT1A receptors in prefrontal cortex in the modulation of dopaminergic activity: role in atypical antipsychotic action. J Neurosci 25(47):10831–10843
Drevets WC (2001) Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol 11(2):240–249
Engel AK, Singer W (2001) Temporal binding and the neural correlates of sensory awareness. Trends Cogn Sci 5(1):16–25
Fuster JM (2001) The prefrontal cortex—an update: time is of the essence. Neuron 30(2):319–333
Fuster JM (2008) The prefrontal cortex, 4th edn. Academic Press, Los Angeles, California, USA
Gabbott PL et al (2005) Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. J Comp Neurol 492(2):145–177
Galarreta M, Hestrin S (2001) Electrical synapses between GABA-releasing interneurons. Nat Rev Neurosci 2(6):425–433
Geyer MA, Vollenweider FX (2008) Serotonin research: contributions to understanding psychoses. Trends Pharmacol Sci 29(9):445–453
Geyer MA et al (2001) Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. Psychopharmacology 156(2–3):117–154
Gillin JC, Wyatt RJ (1976) Evidence for and against the involvement of N, N-dimethyl-tryptamine (DMT) and 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) in schizophrenia. Psychopharmacol Bull 12(4):12–13

Glennon RA (1991) Discriminative stimulus properties of hallucinogens and related designer drugs. NIDA Res Monogr 116:25–44
Glennon RA (1994) Classical hallucinogens: an introductory overview. NIDA Res Monogr 146:4–32
Gonzalez-Maeso J et al (2007) Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. Neuron 53(3):439–452
Goonawardena AV et al (2016) Alterations in high-frequency neuronal oscillations in a cynomolgus macaque test of sustained attention following NMDA receptor antagonism. Neuropsychopharmacology 41(5):1319–1328
Groenewegen HJ, Uylings HB (2000) The prefrontal cortex and the integration of sensory, limbic and autonomic information. Prog Brain Res 126:3–28
Hall H et al (2000) Autoradiographic localization of 5-HT(2A) receptors in the human brain using [(3)H]M100907 and [(11)C]M100907. Synapse 38(4):421–431
Harrison PJ (1999a) The neuropathological effects of antipsychotic drugs. Schizophr Res 40 (2):87–99
Harrison PJ (1999b) The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 122(Pt 4):593–624
Harrison PJ, Weinberger DR (2005) Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry 10(1):40–68; image 5
Hoffman RE, McGlashan TH (1993) Neurodynamics and schizophrenia research: editors' introduction. Schizophr Bull 19(1):15–19
Homayoun H, Moghaddam B (2007) NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. J Neurosci 27(43):11496–11500
Hong LE et al (2010) Gamma and delta neural oscillations and association with clinical symptoms under subanesthetic ketamine. Neuropsychopharmacology 35(3):632–640
Ichikawa J et al (2001) 5-HT(2A) and D(2) receptor blockade increases cortical DA release via 5-HT(1A) receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. J Neurochem 76(5):1521–1531
Itoh T et al (2011) LORETA analysis of three-dimensional distribution of delta band activity in schizophrenia: relation to negative symptoms. Neurosci Res 70(4):442–448
Jakab RL, Goldman-Rakic PS (1998) 5-Hydroxytryptamine2A serotonin receptors in the primate cerebral cortex: possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. Proc Natl Acad Sci U S A 95(2):735–740
Javitt DC, Zukin SR (1991) Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 148(10):1301–1308
Jodo E et al (2005) Activation of medial prefrontal cortex by phencyclidine is mediated via a hippocampo-prefrontal pathway. Cereb Cortex 15(5):663–669
Kargieman L et al (2007) Antipsychotic drugs reverse the disruption in prefrontal cortex function produced by NMDA receptor blockade with phencyclidine. Proc Natl Acad Sci U S A 104 (37):14843–14848
Kargieman L et al (2012) Clozapine reverses phencyclidine-induced desynchronization of prefrontal cortex through a 5-HT(1A) receptor-dependent mechanism. Neuropsychopharmacology 37 (3):723–733
Katayama T et al (2007) Activation of medial prefrontal cortex neurons by phencyclidine is mediated via AMPA/kainate glutamate receptors in anesthetized rats. Neuroscience 150 (2):442–448
Keshavan MS et al (1998) Delta sleep deficits in schizophrenia: evidence from automated analyses of sleep data. Arch Gen Psychiatry 55(5):443–448
Kikuchi M et al (2011) Frontal areas contribute to reduced global coordination of resting-state gamma activities in drug-naive patients with schizophrenia. Schizophr Res 130(1–3):187–194
Kiss T, Hoffmann WE, Hajos M (2011a) Delta oscillation and short-term plasticity in the rat medial prefrontal cortex: modelling NMDA hypofunction of schizophrenia. Int J Neuropsychopharmacol 14(1):29–42

Kiss T et al (2011b) Role of thalamic projection in NMDA receptor-induced disruption of cortical slow oscillation and short-term plasticity. Front Psychiatry 2:14
Kometer M et al (2015) Psilocybin-induced spiritual experiences and insightfulness are associated with synchronization of neuronal oscillations. Psychopharmacology 232(19):3663–3676
Konradi C, Heckers S (2003) Molecular aspects of glutamate dysregulation: implications for schizophrenia and its treatment. Pharmacol Ther 97(2):153–179
Korotkova T et al (2010) NMDA receptor ablation on parvalbumin-positive interneurons impairs hippocampal synchrony, spatial representations, and working memory. Neuron 68(3):557–569
Krystal JH et al (2003) NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacology 169 (3–4):215–233
Kuroda M, Yokofujita J, Murakami K (1998) An ultrastructural study of the neural circuit between the prefrontal cortex and the mediodorsal nucleus of the thalamus. Prog Neurobiol 54(4): 417–458
Kurrasch-Orbaugh DM et al (2003) Serotonin 5-hydroxytryptamine 2A receptor-coupled phospholipase C and phospholipase A2 signaling pathways have different receptor reserves. J Pharmacol Exp Ther 304(1):229–237
Laruelle M et al (1996) Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci U S A 93(17):9235–9240
Lau CG, Zukin RS (2007) NMDA receptor trafficking in synaptic plasticity and neuropsychiatric disorders. Nat Rev Neurosci 8(6):413–426
Leresche N et al (1990) Pacemaker-like and other types of spontaneous membrane potential oscillations of thalamocortical cells. Neurosci Lett 113(1):72–77
Lewis DA, Gonzalez-Burgos G (2006) Pathophysiologically based treatment interventions in schizophrenia. Nat Med 12(9):1016–1022
Lewis DA, Lieberman JA (2000) Catching up on schizophrenia: natural history and neurobiology. Neuron 28(2):325–334
Lewis DA, Hashimoto T, Volk DW (2005) Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 6(4):312–324
Lewis DA et al (2012) Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci 35(1):57–67
Lladó-Pelfort L et al (2016) Phencyclidine-induced disruption of oscillatory activity in prefrontal cortex: effects of antipsychotic drugs and receptor ligands. Eur Neuropsychopharmacol 26(3):614–625
Llinas RR, Steriade M (2006) Bursting of thalamic neurons and states of vigilance. J Neurophysiol 95(6):3297–3308
Lopez Hill X, Scorza MC (2012) Role of the anterior thalamic nucleus in the motor hyperactivity induced by systemic MK-801 administration in rats. Neuropharmacology 62(7):2440–2446
Lopez-Gil X et al (2007) Clozapine and haloperidol differently suppress the MK-801-increased glutamatergic and serotonergic transmission in the medial prefrontal cortex of the rat. Neuropsychopharmacology 32(10):2087–2097
Lopez-Gil X et al (2012) Importance of inter-hemispheric prefrontal connection in the effects of non-competitive NMDA receptor antagonists. Int J Neuropsychopharmacol 15(7):945–956
Lopez-Gimenez JF et al (2001) Mapping of 5-HT2A receptors and their mRNA in monkey brain: [3H]MDL100,907 autoradiography and in situ hybridization studies. J Comp Neurol 429(4):571–589
Marek GJ, Aghajanian GK (1998) 5-Hydroxytryptamine-induced excitatory postsynaptic currents in neocortical layer V pyramidal cells: suppression by mu-opiate receptor activation. Neuroscience 86(2):485–497
Marek GJ et al (2001) A major role for thalamocortical afferents in serotonergic hallucinogen receptor function in the rat neocortex. Neuroscience 105(2):379–392
Marshall L et al (2006) Boosting slow oscillations during sleep potentiates memory. Nature 444(7119):610–613

Martin-Ruiz R et al (2001) Control of serotonergic function in medial prefrontal cortex by serotonin-2A receptors through a glutamate-dependent mechanism. J Neurosci 21(24):9856–9866
Mayberg HS et al (2005) Deep brain stimulation for treatment-resistant depression. Neuron 45 (5):651–660
McCormick DA, Pape HC (1990) Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. J Physiol 431:291–318
McKenna DJ (2004) Clinical investigations of the therapeutic potential of ayahuasca: rationale and regulatory challenges. Pharmacol Ther 102(2):111–129
McKenna DJ, Towers GH, Abbott F (1984) Monoamine oxidase inhibitors in South American hallucinogenic plants: tryptamine and beta-carboline constituents of ayahuasca. J Ethnopharmacol 10(2):195–223
Meltzer HY, Massey BW (2011) The role of serotonin receptors in the action of atypical antipsychotic drugs. Curr Opin Pharmacol 11(1):59–67
Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24:167–202
Miner LA et al (2003) Ultrastructural localization of serotonin2A receptors in the middle layers of the rat prelimbic prefrontal cortex. Neuroscience 116(1):107–117
Muthukumaraswamy SD et al (2013) Broadband cortical desynchronization underlies the human psychedelic state. J Neurosci 33(38):15171–15183
Nichols DE (2004) Hallucinogens. Pharmacol Ther 101(2):131–181
Niswender CM, Conn PJ (2010) Metabotropic glutamate receptors: physiology, pharmacology, and disease. Annu Rev Pharmacol Toxicol 50:295–322
Nunez PL, Srinivasan R (2006) A theoretical basis for standing and traveling brain waves measured with human EEG with implications for an integrated consciousness. Clin Neurophysiol 117(11):2424–2435
Oughourlian JM, Rougeul A, Verdeaux J (1971) Action of hallucinogens on electroencephalograms. Therapie 26(5):953–968
Palenicek T et al (2013) Behavioral, neurochemical and pharmaco-EEG profiles of the psychedelic drug 4-bromo-2,5-dimethoxyphenethylamine (2C-B) in rats. Psychopharmacology 225(1):75–93
Paoletti P, Neyton J (2007) NMDA receptor subunits: function and pharmacology. Curr Opin Pharmacol 7(1):39–47
Pazos A, Cortes R, Palacios JM (1985) Quantitative autoradiographic mapping of serotonin receptors in the rat brain. II. Serotonin-2 receptors. Brain Res 346(2):231–249
Pazos A, Probst A, Palacios JM (1987) Serotonin receptors in the human brain–IV. Autoradiographic mapping of serotonin-2 receptors. Neuroscience 21(1):123–139
Petsche H, Pockberger H, Rappelsberger P (1984) On the search for the sources of the electroencephalogram. Neuroscience 11(1):1–27
Phillips ML et al (2003) Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biol Psychiatry 54(5):504–514
Pinault D (2008) N-methyl d-aspartate receptor antagonists ketamine and MK-801 induce wake-related aberrant gamma oscillations in the rat neocortex. Biol Psychiatry 63(8):730–735
Poulin J, Stip E, Godbout R (2008) REM sleep EEG spectral analysis in patients with first-episode schizophrenia. J Psychiatr Res 42(13):1086–1093
Puig MV et al (2003) In vivo modulation of the activity of pyramidal neurons in the rat medial prefrontal cortex by 5-HT2A receptors: relationship to thalamocortical afferents. Cereb Cortex 13(8):870–882
Puig MV, Artigas F, Celada P (2005) Modulation of the activity of pyramidal neurons in rat prefrontal cortex by raphe stimulation in vivo: involvement of serotonin and GABA. Cereb Cortex 15(1):1–14
Puigdemont D et al (2012) Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression. Int J Neuropsychopharmacol 15(1):121–133
Raichle ME et al (2001) A default mode of brain function. Proc Natl Acad Sci U S A 98(2):676–682
Rasmussen H et al (2010) Decreased frontal serotonin2A receptor binding in antipsychotic-naive patients with first-episode schizophrenia. Arch Gen Psychiatry 67(1):9–16

Rasmussen H et al (2016) Low frontal serotonin 2A receptor binding is a state marker for schizophrenia? Eur Neuropsychopharmacol 26(7):1248–1250
Riba J et al (2002) Topographic pharmaco-EEG mapping of the effects of the South American psychoactive beverage ayahuasca in healthy volunteers. Br J Clin Pharmacol 53(6):613–628
Riba J et al (2004) Effects of the South American psychoactive beverage ayahuasca on regional brain electrical activity in humans: a functional neuroimaging study using low-resolution electromagnetic tomography. Neuropsychobiology 50(1):89–101
Riga MS et al (2014) The natural hallucinogen 5-MeO-DMT, component of ayahuasca, disrupts cortical function in rats: reversal by antipsychotic drugs. Int J Neuropsychopharmacol 17 (8):1269–1282
Rockstroh BS et al (2007) Abnormal oscillatory brain dynamics in schizophrenia: a sign of deviant communication in neural network? BMC Psychiatry 7:44
Rollema H et al (1997) Clozapine increases dopamine release in prefrontal cortex by 5-HT1A receptor activation. Eur J Pharmacol 338(2):R3–R5
Santana N et al (2004) Expression of serotonin1A and serotonin2A receptors in pyramidal and GABAergic neurons of the rat prefrontal cortex. Cereb Cortex 14(10):1100–1109
Santana N, Mengod G, Artigas F (2009) Quantitative analysis of the expression of dopamine D1 and D2 receptors in pyramidal and GABAergic neurons of the rat prefrontal cortex. Cereb Cortex 19(4):849–860
Santana N et al (2011) Activation of thalamocortical networks by the N-methyl-D-aspartate receptor antagonist phencyclidine: reversal by clozapine. Biol Psychiatry 69(10):918–927
Santana N, Mengod G, Artigas F (2013) Expression of alpha(1)-adrenergic receptors in rat prefrontal cortex: cellular co-localization with 5-HT(2A) receptors. Int J Neuropsychopharmacol 16(5): 1139–1151
Schenberg EE et al (2015) Acute biphasic effects of ayahuasca. PLoS ONE 10(9):e0137202
Schreiber R, Brocco M, Millan MJ (1994) Blockade of the discriminative stimulus effects of DOI by MDL 100,907 and the 'atypical' antipsychotics, clozapine and risperidone. Eur J Pharmacol 264(1):99–102
Schug RA et al (2011) Resting EEG deficits in accused murderers with schizophrenia. Psychiatry Res 194(1):85–94
Schultes RE, Hofmann A (1991) *The botany and chemistry of Hallucinogens*. Charles C Thomas Pub Ltd., Springfield, Illinois, USA
Seamans JK, Yang CR (2004) The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol 74(1):1–58
Sebban C et al (2002) Effects of phencyclidine (PCP) and MK 801 on the EEGq in the prefrontal cortex of conscious rats; antagonism by clozapine, and antagonists of AMPA-, alpha(1)- and 5-HT(2A)-receptors. Br J Pharmacol 135(1):65–78
Sekimoto M et al (2007) Reduced frontal asymmetry of delta waves during all-night sleep in schizophrenia. Schizophr Bull 33(6):1307–1311
Selemon LD, Goldman-Rakic PS (1999) The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biol Psychiatry 45(1):17–25
Seminowicz DA et al (2004) Limbic-frontal circuitry in major depression: a path modeling metanalysis. NeuroImage 22(1):409–418
Shergill SS et al (2000) Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. Arch Gen Psychiatry 57(11):1033–1038
Skelly LR et al (2008) Diffusion tensor imaging in schizophrenia: relationship to symptoms. Schizophr Res 98(1–3):157–162
Sklerov J et al (2005) A fatal intoxication following the ingestion of 5-methoxy-N, N-dimethyltryptamine in an ayahuasca preparation. J Anal Toxicol 29(8):838–841
Spencer KM (2011) Baseline gamma power during auditory steady-state stimulation in schizophrenia. Front Hum Neurosci 5:190
Steinbusch HWM (1981) Distribution of serotonin-immunoreactivity in the central nervous system of the rat-cell bodies and terminals. Neuroscience 6(4):557–618

Steriade M (2006) Grouping of brain rhythms in corticothalamic systems. Neuroscience 137(4): 1087–1106
Steriade M, Nunez A, Amzica F (1993) Intracellular analysis of relations between the slow (<1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. J Neurosci 13(8):3266–3283
Suzuki Y et al (2002) Acute administration of phencyclidine induces tonic activation of medial prefrontal cortex neurons in freely moving rats. Neuroscience 114(3):769–779
Swanson CJ et al (2005) Metabotropic glutamate receptors as novel targets for anxiety and stress disorders. Nat Rev Drug Discov 4(2):131–144
Traub RD et al (2000) A model of gamma-frequency network oscillations induced in the rat CA3 region by carbachol in vitro. Eur J Neurosci 12(11):4093–4106
Traub RD et al (2001) Gap junctions between interneuron dendrites can enhance synchrony of gamma oscillations in distributed networks. J Neurosci 21(23):9478–9486
Troyano-Rodriguez E et al (2014) Phencyclidine inhibits the activity of thalamic reticular gamma-aminobutyric acidergic neurons in rat brain. Biol Psychiatry 76(12):937–945
Tseng KY et al (2006) Excitatory response of prefrontal cortical fast-spiking interneurons to ventral tegmental area stimulation in vivo. Synapse 59(7):412–417
Upton N et al. (2014) NMDA receptor antagonist-induced changes in rat EEG power spectra as a model of schizophrenia. Program No. 230.04, in neuroscience 2014 abstracts 2014. Society for Neuroscience, Washington, USA
Van Eden CG et al (1987) Immunocytochemical localization of dopamine in the prefrontal cortex of the rat at the light and electron microscopical level. Neuroscience 22(3):849–862
Vazquez-Borsetti P, Cortes R, Artigas F (2009) Pyramidal neurons in rat prefrontal cortex projecting to ventral tegmental area and dorsal raphe nucleus express 5-HT2A receptors. Cereb Cortex 19(7):1678–1686
Vazquez-Borsetti P et al (2011) Simultaneous projections from prefrontal cortex to dopaminergic and serotonergic nuclei. Int J Neuropsychopharmacol 14(3):289–302
Venables NC, Bernat EM, Sponheim SR (2009) Genetic and disorder-specific aspects of resting state EEG abnormalities in schizophrenia. Schizophr Bull 35(4):826–839
Villalobos C et al (2005) Serotonergic regulation of calcium-activated potassium currents in rodent prefrontal cortex. Eur J Neurosci 22(5):1120–1126
Vollenweider FX, Kometer M (2010) The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. Nat Rev Neurosci 11(9):642–651
Vollenweider FX et al (1997a) Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. Neuropsychopharmacology 16(5):357–372
Vollenweider FX et al (1997b) Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [18F]fluorodeoxyglucose (FDG). Eur Neuropsychopharmacol 7(1):9–24
Weinberger DR (1987) Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 44(7):660–669
Woo TU, Kim AM, Viscidi E (2008) Disease-specific alterations in glutamatergic neurotransmission on inhibitory interneurons in the prefrontal cortex in schizophrenia. Brain Res 1218:267–277
Wood J, Kim Y, Moghaddam B (2012) Disruption of prefrontal cortex large scale neuronal activity by different classes of psychotomimetic drugs. J Neurosci 32(9):3022–3031
Yu AM (2008) Indolealkylamines: biotransformations and potential drug-drug interactions. AAPS J 10(2):242–253
Zhang Y, Llinas RR, Lisman JE (2009) Inhibition of NMDARs in the Nucleus Reticularis of the Thalamus Produces Delta Frequency Bursting. Front Neural Circuits 3:20
Zhang Y et al (2012) NMDAR antagonist action in thalamus imposes delta oscillations on the hippocampus. J Neurophysiol 107(11):3181–3189