Disruption of thalamocortical activity in schizophrenia models: relevance to antipsychotic drug action

Pau Celada1,2,3, Laia Lladó-Pelfort1,2,3, N. Santana1,2,3, L. Kargieman1,2,3, Eva Troyano-Rodriguez1,2,3, M. S. Riga1,2,3 and Francesc Artigas1,2,3

1 Department of Neurochemistry and Neuropharmacology, Institut d’Investigacions Biomèdiques de Barcelona, (IIBB-CSIC), Barcelona, Spain.
2 Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain
3 Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

Abstract

Non-competitive NMDA receptor antagonists are widely used as pharmacological models of schizophrenia due to their ability to evoke the symptoms of the illness. Likewise, serotonergic hallucinogens, acting on 5-HT2A receptors, induce perceptual and behavioural alterations possibly related to psychotic symptoms. The neurobiological basis of these alterations is not fully elucidated. Data obtained in recent years revealed that the NMDA receptor antagonist phencyclidine (PCP) and the serotonergic hallucinogen 1-(2,5-dimethoxy-4-iodophenyl-2-aminopropane; DOI) produce a series of common actions in rodent prefrontal cortex (PFC) that may underlie psychotomimetic effects. Hence, both agents markedly disrupt PFC function by altering pyramidal neuron discharge (with an overall increase) and reducing the power of low frequency cortical oscillations (LFCO; <4 Hz). In parallel, PCP increased c-fos expression in excitatory neurons of various cortical areas, the thalamus and other subcortical structures, such as the amygdala. Electrophysiological studies revealed that PCP altered similarly the function of the centromedial and mediodorsal nuclei of the thalamus, reciprocally connected with PFC, suggesting that its psychotomimetic properties are mediated by an alteration of thalamocortical activity (the effect of DOI was not examined in the thalamus). Interestingly, the observed effects were prevented or reversed by the antipsychotic drugs clozapine and haloperidol, supporting that the disruption of PFC activity is intimately related to the psychotomimetic activity of these agents. Overall, the present experimental model can be successfully used to elucidate the neurobiological basis of schizophrenia symptoms and to examine the potential antipsychotic activity of new drugs in development.

Received 14 March 2013; Reviewed 3 April 2013; Revised 10 May 2013; Accepted 10 May 2013; First published online 1 July 2013

Key words: 5-HT receptors, antipsychotic drugs, NMDA receptors, prefrontal cortex, thalamus.

Introduction

Schizophrenia is a severe psychiatric disease affecting about 1% of the world population. It has an early onset (typically late adolescence or early adulthood) and shows a chronic and deteriorating course. Affected individuals have a lifelong disability and nearly 10% commit suicide. Schizophrenia is characterized by a variety of symptoms, including positive (hallucinations, delusions, disorganized speech, aberrant behaviour etc.) and negative symptoms (depression, anxiety, emotional blunting, social withdrawal etc.) as well as cognitive dysfunction. Anatomical, cellular and neurochemical alterations have been reported in various brain areas of schizophrenic patients and notably in the prefrontal cortex (PFC; Harrison, 1999; Selemon and Goldman-Rakic, 1999; Lewis and Lieberman, 2000; Harrison and Weinberger, 2005; Lewis and Gonzalez-Burgos, 2006; see later for extended information). Likewise, anatomical and functional abnormalities of the thalamus have also been reported in schizophrenia (Jones, 1997; Clinton and Meador-Woodruff, 2004; Alelu-Paz and...
Gimenez-Amaya, 2008; Watis et al., 2008; Vukadinovic, 2011; Vukadinovic and Rosenzweig, 2012) and alterations in thalamic circuits have been suggested to be involved in the emergence of psychotic symptoms (Lisman et al., 2010). Here we review data produced by our group and others supporting the involvement of the PFC and related thalamic nuclei (centromedial and mediodorsal) in (a) the mechanism of action of psychotomimetic drugs, in particular N-Methyl-D-aspartate (NMDA) receptor antagonists and serotonin [5-hydroxytryptamine (5-HT)]2A receptor agonists and (b) the therapeutic action of antipsychotic drugs.

Prefrontal cortex and schizophrenia: an overview

The PFC plays an important role in the pathophysiology and treatment of schizophrenia. The PFC has poorly defined anatomical boundaries although it is defined by its reciprocal connectivity with the mediodorsal nucleus of the thalamus. The PFC is involved in many higher brain functions such as perception, attention, memory, language, intelligence, consciousness, affect etc. The dorsolateral PFC plays a key role in cognitive processes such as working (short-term) memory and executive functions as well as in action planning and decision making (Fuster, 2001, 2008; Miller and Cohen, 2001). In addition to cognitive functions, the PFC is involved in the control of mood and affect. Hence, the ventromedial PFC, or ventral cingulate cortex, is deeply involved in emotional processing (Devinsky et al., 1995; Davidson and Irwin, 1999; Cardinal et al., 2002; Phillips et al., 2003) and psychotic symptoms such as hallucinations are associated with hyperactivity of this PFC subdivision (Shergill et al., 2000).

Similarly to other cortical areas, the PFC is composed of ∼75–80% of pyramidal projection neurons, which use glutamate as a transmitter and ∼20–25% of local circuit inhibitory interneurons that use GABA as a transmitter. Pyramidal neurons integrate excitatory glutamatergic afferent inputs from various thalamic nuclei, including the mediodorsal, centromedial and several midline nuclei, the hippocampus, the amygdala and the rest of cortical areas to which it is connected (Groenewegen and Uylings, 2000; Fuster, 2008). Local inhibitory inputs arise from GABAergic interneurons. These have been classified according to anatomical and neurochemical characteristics and to their synaptic relationships with pyramidal neurons (Defelipe et al., 2013). Among them, large perysomatic, parvalbumin-containing neurons such as the chandelier and basket cells, play a major role in controlling excitatory pyramidal output by targeting GABA receptors located in the cell bodies and initial segments of pyramidal axons (Défélípe et al., 1989). This peculiar connectivity allows for a direct inhibitory control of the generation of nerve impulses by pyramidal neurons. Cortical parvalbumin-containing GABA interneurons have been suggested to play a role in schizophrenia symptoms; in particular, in cognitive control (Lewis et al., 2005, 2012).

Likewise, PFC neurons receive a dense innervation from the brainstem monoaminergic nuclei [dorsal and median raphe nuclei, locus coeruleus and ventral tegmental area, which employ 5-HT, noradrenaline and dopamine (DA) as main neurotransmitters, respectively]. These neuronal groups exert an important modulatory role of the excitatory and inhibitory currents in PFC neurons (Steinbusch, 1981; Van den et al., 1987; Seamans and Yang, 2004; Aston-Jones and Cohen, 2005; Puig et al., 2005; Celada and Artigas, 2007). A large population of pyramidal and GABAergic neurons in PFC express receptors sensitive to monoamine neurotransmitters in mammalian brain (Santana et al., 2004, 2009, 2012; de Almeida and Mengod, 2007, 2008). Atypical antipsychotic drugs such as clozapine (CLZ) show high affinity for these monoamine receptors (in particular 5-HT2A/2C, 5-HT1A and α-adrenoceptors, and to a lesser extent, DA D2 receptors), suggesting that the PFC is a key brain structure in their therapeutic action, in addition to the well-known blockade of DA D2 receptors in the ventral striatum (Artigas, 2010).

NMDA receptors; non-competitive antagonists

Strong (ionic) actions of glutamate are mediated by three receptor subtypes, namely the (AMPA), kainate and NMDA receptors. These receptors are ion channels, whose activation by glutamate allows extracellular Na+ and Ca2+ ions to enter (and K+ ions to leave) the neuronal cytoplasm, thus evoking rapid and marked changes of the membrane potential (depolarization in most instances) which subsequently allow for the generation of action potentials. Glutamate can also act on a family of eight G-protein coupled metabotropic receptors, analogous to monoamine receptors, which are suitable targets for drug development in various fields of psychiatry (Swanson et al., 2005; Niswender and Conn, 2010).

NMDA receptors are involved in a large number of key physiological functions, such as long-term potentiation and synaptic plasticity, and play a role in several neurological and psychiatric disorders (Lau and Zukin, 2007; Paoletti and Neyton, 2007). NMDA
receptors are tetrameric ion channels composed of two NR1 and two NR2 (A, B, C, D) subunits. A third type of NMDA subunits (NR3, A and B) has been identified and it changes the ionic sensitivity of the NMDA channel (Cavara and Hollmann, 2008). The NMDA receptor ion channel is voltage-sensitive, i.e. the channel is blocked by Mg$^{2+}$ ions in resting conditions. Only after the depolarization of the cell membrane, Mg$^{2+}$ ions are released to allow for the passage of other ions (Na$^+$, Ca$^{2+}$, K$^+$) through the channel. Thus, in general, AMPA-induced depolarization precedes the functional activity of NMDA receptors.

The NMDA receptor contains several binding sites, including the site for glutamate and competitive antagonists such as AP5 (or AP-V). Likewise, it contains several regulatory sites, such as the glycine site, outside the channel and the Mg$^{2+}$ and the non-competitive antagonist site [also called phencyclidine (PCP) site], inside the channel. The dissociative anaesthetics ketamine and PCP are non-competitive NMDA receptor antagonists. These agents have been used as a pharmacological model of schizophrenia due to their ability to evoke positive and negative symptoms of schizophrenia in healthy individuals and to aggravate them in schizophrenic patients (Javitt and Zukin, 1991; Krystal et al., 2003). Moreover, PCP, ketamine and dizocilpine (MK-801; not available for human use) evoke a series of behavioural alterations in experimental animals characterized by hyperlocomotion, stereotypies and disruption in pre-pulse inhibition of the startle response. These alterations are totally or partly 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 poorly known, although work by different research groups in recent years has started to clarify the actions of NMDA receptors antagonists on PFC function.

Effects of non-competitive NMDA receptor antagonists on neuronal activity in thalamocortical networks

The PFC appears as a target area for these actions since neuroimaging studies show that PCP and ketamine increase PFC activity (Breier et al., 1997). The i.v. administration of PCP to anaesthetized rats exerts a complex effect on the discharge rate of pyramidal neurons of the medial PFC (mPFC), identified by antidromic activation from midbrain (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), reduced the discharge of 35% (to 43% of baseline) and left unaffected the rest (22%). Figure 1 shows an example of a PFC pyramidal neuron excited by PCP. Burst firing was affected in a similar manner (Table 1).

Likewise, the administration of PCP (0.25 mg/kg i.v.) altered the discharge of thalamic neurons projecting to the mPFC, in the centromedial and mediodorsal nuclei increasing (to 424% of baseline) and decreasing (to 41% of baseline) the activity of 57 and 20% of the recorded neurons, respectively (23% remained unaffected; Santana et al., 2011). Figure 1c shows a representative example of the effect of PCP on a thalamic neuron. Figure 2 shows the comparison of the effect of PCP on the discharge rate of pyramidal neurons in mPFC and of thalamic relay neurons in the centromedial and mediodorsal nuclei, reciprocally connected with the mPFC (Berendse and Groenewegen, 1991; Kuroda et al., 1998; Gabbott et al., 2005).

Double in situ hybridization experiments revealed that PCP (10 mg/kg i.p.) markedly increased c-fos expression in glutamatergic neurons of several cortical areas (prefrontal, somatosensory, retrosplenial, entorhinal; 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. PCP also increased c-fos expression in the amygdala and had a small effect in the hippocampal formation of the same animals (Figs 1 and 3).

Recent evidence from other groups also supports the involvement of thalamic nuclei in the action of NMDA receptor antagonists. Hence, ketamine administration increased the discharge rate in the nucleus reuniens of the thalamus and subsequently, in the cornu ammonis 1 (CA1) subfield of the hippocampus, to which the nucleus reuniens projects (Zhang et al., 2012). The same team also reported that NMDA receptor blockade with the competitive antagonist AP-V 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 later) in the PFC was mimicked by the local application of lidocaine in the mediodorsal nucleus of the thalamus (Kiss et al., 2011a). Furthermore, the motor hyperactivity and behavioural stereotypies induced by MK-801 in rats were prevented by the local (bilateral) application of the GABA$\textsubscript{A}$ agonist muscimol in the anterior nucleus of the thalamus, suggesting that MK-801 reduces GABA$\textsubscript{A}$-mediated neurotransmission in the thalamus (Hill and Scorza, 2012). Overall, these observations clearly support the implication of thalamic nuclei in the behavioural, perceptual and possibly cognitive alterations induced by non-competitive NMDA receptor antagonists.
Fig. 1. Effect of phencyclidine (PCP) administration on the activity of thalamocortical networks in rat brain. (a) Macroscopic dark-field images from emulsion-dipped coronal sections at two different anteroposterior (AP) coordinates from control and treated rats showing the localization of cells expressing c-fos messenger RNA (mRNA). Upper row correspond to AP+3.7 mm and lower row to AP –2.5 mm from bregma. Columns correspond to the treatments indicated in the figure (Sal, saline; PCP, phencyclidine 10 mg/kg i.p.; CLZ, clozapine 5 mg/kg i.p.). Note the marked expression of c-fos mRNA in various cortical and thalamic areas of PCP-treated rats together with the relative absence of a significant increase in hippocampal areas. In prefrontal cortex, a particularly remarkable increase was observed in dorsal anterior cingulate, prelimbic and infralimbic areas. ACAd, dorsal anterior cingulate; CM, central medial thalamic nucleus; Hyp, hypothalamus; ILA, infralimbic area of prefrontal cortex; M, motor cortex; MD, mediodorsal thalamic nucleus; PIR, piriform cortex; PL, prelimbic cortex; RS, retrosplenial cortex; S1, somatosensory cortex. Bar: 1 mm. Panels (b) and (c) show extracellular recordings of a pyramidal and thalamic neuron showing the effect of PCP (0.25 mg/kg i.v.) on the discharge rate. Note the marked increase of the discharge produced by PCP in both neurons, as well as the reversal of this effect by the subsequent administration of CLZ (1 mg/kg i.v.). Arrows mark the time of injections (abscissa in s).
PCP action on corticothalamic or thalamocortical pathways?

Despite these marked alterations of PFC function induced by PCP, it is still unclear whether NMDA receptor antagonists primarily affect PFC or whether other cortical and subcortical areas reciprocally connected with the PFC are also involved, in particular the hippocampal formation and the thalamus. The opposite effects of the systemic MK-801 administration on the activity of putative pyramidal and GABAergic neurons (increase and decrease, respectively) led to the proposal of a preferential blockade of NMDA receptors on cortical GABAergic interneurons and a subsequent disinhibition of pyramidal neurons (Jackson et al., 2004; Homayoun and Moghaddam, 2007). However, the local application of PCP or MK-801 in mPFC reduced the discharge of putative pyramidal neurons (Suzuki et al., 2002; Jodo et al., 2005) and the study by Jodo et al. (2005) reported a facilitation of pyramidal neuron activity in mPFC by the local application of PCP in the hippocampal formation. Moreover, the systemic, but not local, administration of non-competitive NMDA receptor antagonists increased neurotransmitter release in PFC (Amargos-Bosch et al., 2006; Lopez-Gil et al., 2007) suggesting that NMDA receptor blockade in other brain areas may also contribute to increased PFC activity.

Table 1. Effect of phencyclidine (PCP) on pyramidal cell activity in the medial prefrontal cortex

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal</th>
<th>PCP (0.25 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Firing rate (spikes/s)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>2.2±0.3</td>
<td>3.4±0.4*</td>
</tr>
<tr>
<td>E</td>
<td>2.1±0.3</td>
<td>6.0±0.7**</td>
</tr>
<tr>
<td>I</td>
<td>2.8±0.8</td>
<td>1.2±0.4**</td>
</tr>
<tr>
<td></td>
<td>Spikes in bursts (2 min)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>177±36</td>
<td>238±35</td>
</tr>
<tr>
<td>E</td>
<td>117±25</td>
<td>386±61**</td>
</tr>
<tr>
<td>I</td>
<td>288±99</td>
<td>100±37*</td>
</tr>
<tr>
<td></td>
<td>Burst episodes (2 min)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>72±12</td>
<td>101±14</td>
</tr>
<tr>
<td>E</td>
<td>54±11</td>
<td>169±24**</td>
</tr>
<tr>
<td>I</td>
<td>109±31</td>
<td>39±12*</td>
</tr>
<tr>
<td>n</td>
<td>A 80</td>
<td>E 36</td>
</tr>
<tr>
<td></td>
<td>I 26</td>
<td></td>
</tr>
</tbody>
</table>

A, All neurons; E, excited neurons; I, inhibited neurons. *p<0.05, **p<0.01, vs. baseline.

A putative effect of PCP on hippocampal-PFC neurons appears unlikely to explain the PCP-induced changes in PFC since PCP had a minimal effect on c-fos expression in the various hippocampal subfields (CA1, CA3, somatosensory cortex (S)), as previously observed (Santana et al., 2011; see also Fig. 3). Alternatively, c-fos-expressing cells in the CA1 subfield are GABAergic (Santana et al., 2011), an observation discordant with a putative increase of the hippocampal excitatory output to mPFC.

Fig. 2. Comparison of the effect of phencyclidine (PCP, 0.25 mg/kg i.v.) on the discharge rate of pyramidal neurons in medial prefrontal cortex (mPFC) and relay neurons of the centromedial and dorsomedial nuclei of the thalamus (CM/MD). Each colour sector corresponds to one of the three neuronal responses to PCP (excitations, EXC; inhibitions, INH, no effect, NE). The percentage inside each sector shows the average magnitude of the effect; n=80 for PFC and n=50 for CM/MD (one neuron per rat). Data reproduced from Kargieman et al. (2007) and Santana et al. (2011).
that the increase in PFC activity can solely drive the massive c-fos expression observed in cortical and thalamic areas as well as the marked increase in thalamic discharge. Thalamic relay cells are subjected to direct monosynaptic corticothalamic excitatory inputs plus bisynaptic, reticular nucleus-mediated, feed-forward inhibitions (Steriade, 2001; Jones, 2002). Nearly 70% of excitatory synapses on Rt cells are from corticothalamic fibres (Jones, 2002). Thus, under certain conditions, the cortex can exert an inhibitory influence over the thalamus via Rt-mediated inhibitions (Steriade, 2001). This suggests that a PCP-mediated activation of PFC should result in a more moderate effect in thalamic neurons from the centromedial and mediodorsal nuclei than that observed (Fig. 2). Moreover, given the corticothalamic connectivity (see earlier), a PFC-driven increase of thalamic activity should have also activated c-fos expression in GABA cells of the reticular nucleus.

A bottom-up (e.g. thalamocortical) increase of cortical activity may also contribute to the overall activation of cortical and thalamic regions. PCP did not increase c-fos expression in the reticular nucleus (Fig. 3) nor in basal ganglia such as the substantia nigra reticulata or ventral pallidum, which send inhibitory afferents to thalamic relay neurons. Alternatively, PCP markedly increased c-fos expression in layers IV and VI of S1, indicating the existence of an increased thalamocortical (layers IV and VI) and corticothalamic (layer VI) functional connectivity [see Shipp (2007) for review of thalamocortical connectivity]. Likewise, PCP increased c-fos in a narrow band of cells between layers III and V in PFC (Kargieman et al., 2007) which receive thalamic inputs (Kuroda et al., 1998), since the rat PFC lacks layer IV. Interestingly, unlike in PFC (Kargieman et al., 2007), GABAergic neurons in S1 and retrosplenial cortices expressed c-fos in response to PCP treatment, which agrees with the dual projection of thalamocortical fibres to cortical glutamatergic and GABAergic neurons (Sun et al., 2006) and the preferential thalamocortical inputs on fast-spiking cortical interneurons (Hull et al., 2009).

Irrespective of the primary target area(s) affected by PCP, its overall excitatory effects on thalamocortical pathways is clearly indicative of a preferential action on NMDA receptors located on inhibitory GABAergic neurons. The reason(s) for this cellular selectivity are unclear and may involve a different
subunit composition of the NMDA receptor (Monyer et al., 1994; Wenzel et al., 1997; Karavanova et al., 2007) which would confer different pharmacological properties from other regions rich in excitatory neurons. In support of this possibility, the competitive NMDA receptor antagonist AP-V hyperpolarized Rt cells, but not PFC cells, in vitro (Zhang et al., 2009).

An alternative explanation lies on the mechanism of action of non-competitive NMDA receptor antagonists, including PCP. These agents require the release of Mg²⁺ ions to penetrate the NMDA channel. Hence, PCP may preferentially block NMDA receptor inputs on fast-spiking GABAergic neurons (e.g. cortical interneurons, Rt neurons or basal ganglia projection neurons), which are depolarized for more prolonged periods of time than PFC pyramidal or thalamic relay neurons, which fire at lower rates. Further work is required to examine this possibility.

**Fig. 4.** Schematic representation of two potential sites of action of phencyclidine (PCP) on N-methyl-D-aspartate receptor (NMDAR) in cortical and subcortical GABAergic neurons. (a) PCP blockade of NMDAR in fast-spiking cortical GABAergic interneurons would reduce tonic GABAₐ-mediated inputs onto prefrontal cortex (PFC) pyramidal (Pyr) neurons. Given the widespread projections of PFC pyramidal neurons to many subcortical areas (including the thalamus), the increase in pyramidal discharge would result in an enhanced excitatory input onto thalamic neurons. (b) PCP blockade of NMDAR in inhibitory inputs to glutamatergic thalamic nuclei [e.g. reticular nucleus (Rt), substantia nigra reticulata (SNR) or ventral pallidum (VP)] would disinhibit thalamic relay neurons leading to increased excitatory thalamocortical inputs in various cortical areas. The relative weight of options a and b in the overall effects of PCP may differ among cortical areas. CM/MD, centromedial and dorsomedial nuclei of the thalamus; GABA, Modified from Santana et al. (2011).

**Brain oscillations: relevance to schizophrenia**

Higher cognitive functions and executive functions emerge from the coordinated activity of different neuronal networks and brain areas. This is reflected in an oscillatory activity, a characteristic feature of cortical dynamics. Brain oscillations can be evidenced through electroencephalographic (EEG) recordings which detect the integrated activity of neuronal networks surrounding the electrodes (Nunez and Srinivasan, 2006). EEG oscillatory activity depends on the synchrony at which local and distal networks operate. Since the discovery of the EEG by Berger (1929) and the first description of the most prominent rhythm (α, 8–12 Hz), multiple oscillatory activities have been described: slow (<1 Hz); δ (1–4 Hz); θ (4–7 Hz); β (12–30 Hz); γ (30–80 Hz) oscillations. Brain oscillations are important in codifying neural
### Table 2. Oscillatory activity in animal models of schizophrenia

<table>
<thead>
<tr>
<th>Model</th>
<th>Studied parameters</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological NMDA hypofunction</td>
<td>FC and sensorimotor cortex EEG power in conscious rats</td>
<td>PCP and MK-801 ↑ FC 1–3 Hz power and ↑ or ↓ 9–30 Hz power depending on dose</td>
<td>Sebban et al. (2002)</td>
</tr>
<tr>
<td></td>
<td>mPFC pyramidal neuron firing and low frequency cortical oscillations power in anesthetized animals</td>
<td>PCP increases pyramidal firing and decreases low frequency oscillations</td>
<td>Kargieman et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Hippocampal EEG in freely moving rats</td>
<td>Ketamine and MK-801 ↑ hippocampal γ power Antagonized by pre-perfusion of muscimol into the medial septum or supramammillary area.</td>
<td>Ma and Leung (2007)</td>
</tr>
<tr>
<td></td>
<td>Neocortical spontaneous γ oscillations in freely moving rats</td>
<td>Ketamine and MK-801 ↑ γ power</td>
<td>Pinault (2008)</td>
</tr>
<tr>
<td></td>
<td>In vivo recordings from CA3 regions of mouse during a paired-click auditory task</td>
<td>Ketamine ↓ θ frequency band in background activity and in poststimulus evoked activity</td>
<td>Lazarewicz et al. (2010)</td>
</tr>
<tr>
<td></td>
<td>Interactions between high and low-frequency γ oscillations in layers III and V of rat visual cortex in vitro</td>
<td>Ketamine, PCP, selective NR2B subunit-containing receptor antagonism and reduced α-serine levels caused cross-layer phase coupling of γ oscillations</td>
<td>Anver et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>Oscillatory activity in hippocampus, dorsal striatum and nucleus accumbens</td>
<td>Ketamine ↑ high frequency oscillations power in all structures, ↑ γ oscillations in hippocampus and ↓ in nucleus accumbens</td>
<td>Hunt et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>Subiculum stimulation, MUA and local field potential recordings of mPFC in urethane-anaesthetized rats</td>
<td>Systemic and local microinfusions of MK-801 in MD changed 2 Hz oscillation to a less regular δ rhythm ↓ paired-pulse facilitation, ↓ overall MUA</td>
<td>Kiss et al. (2011a, b)</td>
</tr>
<tr>
<td></td>
<td>Mediodorsal and centromedial thalamic single unit and local field potential recordings in anesthetized rats</td>
<td>PCP increases overall neuronal firing and decreases low frequency oscillations</td>
<td>Santana et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>Effects of acute and chronic NMDA antagonist administration on oscillatory hippocampal activity in freely moving rats</td>
<td>Acute injection of MK-801 or ketamine ↑ γ power in CA1 and DG, shifted θ peak to higher frequencies and ↓ θ power in CA1 Chronic ketamine administration ↓ θ and γ oscillations ↑ aberrant γ after systemic administration of nonselective NMDAR antagonists and by NR2A-prefering antagonists</td>
<td>Kittelberger et al. (2012)</td>
</tr>
<tr>
<td></td>
<td>Oscillatory activity (EEG) in frontal and occipital cortices</td>
<td>Ketamine and MK-801 ↑ high frequency evoked and total power, ↑ baseline high frequency power, ↓ high frequency intertrial coherence</td>
<td>Kocsis (2012)</td>
</tr>
<tr>
<td></td>
<td>Mouse EEG during repeated auditory stimuli</td>
<td>Ketamine and MK-801 ↑ high frequency evoked and total power, ↑ baseline high frequency power, ↓ high frequency intertrial coherence</td>
<td>Saunders et al. (2012)</td>
</tr>
<tr>
<td></td>
<td>Oscillatory activity and neuron firing rate in PFC I freely moving rats</td>
<td>MK-801 causes an overall ↑ neuron firing and ↓ correlation between spike rate and γ band.</td>
<td>Wood et al. (2012)</td>
</tr>
<tr>
<td>Serotonergic drugs</td>
<td>mPFC pyramidal neuron single unit recordings and local field potential recordings in choral hydrate anesthetized rats</td>
<td>DOI caused an overall ↑ pyramidal neuron firing and ↓ slow cortical oscillations</td>
<td>Celada et al. (2008)</td>
</tr>
<tr>
<td></td>
<td>Oscillatory activity and neuron firing rate in PFC I freely moving rats</td>
<td>DOI causes an overall ↓ neuron firing and ↓ correlation between spike rate and γ band.</td>
<td>Wood et al. (2012)</td>
</tr>
<tr>
<td>Dopaminergic drugs</td>
<td>Neocortical spontaneous ( \gamma ) oscillations in freely moving rats</td>
<td>d-Amphetamine and apomorphine ( \uparrow ) cortical ( \gamma ) power</td>
<td>Pinault (2008)</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Cannabinoid-1 receptor activation</td>
<td>Hippocampus, entorhinal cortex and mPFC recordings in freely moving rats</td>
<td>CP-55940 ( \downarrow ) ( \theta ) power in the hippocampus and ( \downarrow ) ( \gamma ) power in the hippocampus and entorhinal cortex</td>
<td>Hajos et al. (2008)</td>
</tr>
<tr>
<td>Developmental MAM</td>
<td>mPFC single-unit and local field potential recordings in anesthetized adult rats</td>
<td>Absent slow and fast field potential oscillations, more regular spike firing activity</td>
<td>Goto and Grace (2006)</td>
</tr>
<tr>
<td></td>
<td>mPFC and ventral hippocampus local field potential recordings in a latent inhibition paradigm (adult rats)</td>
<td>No significant alterations in spontaneous activity. MAM attenuates effects on conditioned-stimuli evoked oscillatory activity.</td>
<td>Lodge et al. (2009)</td>
</tr>
<tr>
<td></td>
<td>Visual and motor cortex EEG recordings in behaving adult rats</td>
<td>Visual cortex ( \gamma ) oscillations and ( \uparrow ) motor cortex high frequency oscillations in MAM treated animals in response to NMDAR antagonism</td>
<td>Phillips et al. (2012)</td>
</tr>
<tr>
<td>Neonatal ventral hippocampal lesion</td>
<td>Spontaneous frontal and parietal EEG recordings in prepuberal and adult rats</td>
<td>Prepuberal rats: ( \uparrow ) ( \delta ), ( \theta ) and ( \alpha ) power Adult rats: ( \uparrow ) ( \delta ) and ( \theta ) power</td>
<td>Ahnaou et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Spontaneous frontal and parietal EEG recordings in prepuberal and adult rats</td>
<td>Prepuberal rats: ( \uparrow ) ( \delta ), ( \theta ) and ( \alpha ) power Adult rats: ( \uparrow ) ( \delta ) and ( \theta ) power</td>
<td>Ahnaou et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>Frontal, parietal and occipital EEG recordings in behaving adult rats</td>
<td>( \downarrow ) parietal and occipital at 1–30 Hz</td>
<td>Valdes-Cruz et al. (2012)</td>
</tr>
<tr>
<td>Genetic</td>
<td>PV-Cre/NR1f/f mice</td>
<td>CA1 local field potential and unitary neuronal recordings in freely behaving mice ( \downarrow ) and altered ( \theta ) oscillation, ( \uparrow ) ( \gamma ) oscillation and less modulated by ( \theta ) rhythm</td>
<td>Korotkova et al. (2010)</td>
</tr>
<tr>
<td></td>
<td>Somatosensory single unit and local field potential recordings in anesthetized and awake mice ( \uparrow ) baseline cortical ( \gamma ) band and ( \downarrow ) sensitivity to NMDAR antagonists-induced effects on ( \gamma ) oscillations</td>
<td>Carlen et al. (2012)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Df(16)A(^{+/-}) mice</td>
<td>Single unit and local field potential recordings in behaving mice during working memory task ( \downarrow ) phase locking of PFC neurons to hippocampal ( \theta ) rhythm and ( \downarrow ) coherence between PFC and hippocampal local field potentials</td>
<td>Sigurdsson et al. (2010)</td>
</tr>
<tr>
<td></td>
<td>ErbB4(^{MHC-ExB4-/-}) mice</td>
<td>Rat, WT and KO mice hippocampal slices Mutation ( \downarrow ) kainate-induced ( \gamma ) oscillations and avoids the potentiating effect of NRG1 on these oscillations</td>
<td>Fisahn et al. (2009)</td>
</tr>
<tr>
<td></td>
<td>Dys1(^{-/-}) mice</td>
<td>EEG recordings in hippocampus during auditory processing ( \downarrow ) evoked high ( \gamma ) power and deficit suppressing late ( \gamma ) activity</td>
<td>Carlson et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>GCLM(^{-/-}) mice</td>
<td>Hippocampal slices \textit{in vitro} recordings ( \downarrow ) kainite induced ( \beta ) and ( \gamma ) oscillations</td>
<td>Steullet et al. (2010)</td>
</tr>
<tr>
<td></td>
<td>DAT(^{-/-}) mice</td>
<td>Hippocampal and prelimbic PFC local field potential during spontaneous activity and during the exploration of a novel environment ( \uparrow ) ( \gamma ) phase signalling</td>
<td>Dzirasa et al. (2009)</td>
</tr>
<tr>
<td></td>
<td>NRI KD</td>
<td>Hippocampal and prelimbic PFC local field potential during spontaneous activity and during the exploration of a novel environment ( \downarrow ) ( \theta-\gamma ) phase coupling</td>
<td>Dzirasa et al. (2009)</td>
</tr>
</tbody>
</table>

CA, Cornu ammonis; DG, dentate gyrus; DOI, 1-(2,5-dimethoxy-4-iodophenyl-2-aminopropane); EEG, electroencephalogram; FC, frontal cortex; KD, knock down; KO, knock out; MAM, methylazoxymethanol acetate; MUA, multi-unit activity; NMDAR, \( N \)-methyl-\( D \)-aspartate receptor; NRG1, neuregulin 1; PFC, prefrontal cortex; PCP, phencyclidine; WT, wild-type.
information and to allow for coordinated activity between different neuronal networks in the temporal plane: information is encoded by spiking activity, but also by the time at which they are produced.

The generation of brain oscillations involves a balance between excitatory and inhibitory transmission in the network, which depends on the individual properties of the components. Hence, slow oscillations result from the interaction of cortical, thalamo-cortical and reticular nucleus oscillators (Crunelli and Hughes, 2010), whereas δ oscillations depend upon cortical and thalamocortical components (Petsche et al., 1984; Leresche et al., 1990; McCormick and Pape, 1990; Steriade et al., 1993; Llinas and Steriade, 2006). Low frequency oscillations (slow and δ oscillations) are involved in several brain functions per se, including short- and long-term memory (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 (Steriade, 2006).

The γ oscillations (30–80 Hz) deserve special attention due to their implication in multiple cognitive processes through the phylogenetic scale (Engel and Singer, 2001): sensory and perceptual processing; short and long-term memory; attention; executive functions, among others. Parvalbumin positive GABAergic interneurons are strongly involved in the generation of γ oscillations. They are fast-spiking interneurons, with special electrical properties, which are able to control large populations of pyramidal neurons via large networks connected by gap junctions (Traub et al., 2000, 2001; Galarreta and Hestrin, 2001). These properties make them excellent candidates to spread fast oscillations through neuronal networks, although other cells and neurotransmitter systems have been also involved (Belforte et al., 2010; Korotkova et al., 2010; Carlen et al., 2012).

Since brain oscillations mirror neuronal and network dynamics, they may provide a valuable tool to study the aetiology 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 (Hoffman and McGlashan, 1993; Skelly et al., 2008; Camchong et al., 2011). Brain oscillations have also been examined in a variety of animal models of schizophrenia (Table 2).

Recent studies show an increase of resting state γ activity in schizophrenic patients compared to healthy controls (Venales et al., 2009; Kikuchi et al., 2011; Spencer, 2012). This disruption agrees with the reported alterations on GABAergic neurotransmission in schizophrenic patients (Lewis et al., 2005), especially in fast-spiking interneurons, as well as deficits in NMDA glutamatergic neurotransmission (Krystal et al., 2003; Konradi and Heckers, 2003; Woo et al., 2008). Likewise, abnormalities in cortico-subcortical communications (e.g. thalamocortical) may be examined via EEG sleep recordings. Slow wave sleep deficits have been reported in schizophrenic patients, associated with negative symptoms. Specifically, schizophrenia patients show decreased δ wave counts, reductions in δ and θ power and alterations in the laterality of these measures compared with healthy controls (Keshavan et al., 1998; Sekimoto et al., 2007). Alterations in α activity during sleep have also been correlated with positive and negative symptom scores (Poulin et al., 2008). Likewise, enhanced slow wave, δ, θ and β activity and decreased α activity in the resting state has been associated with schizophrenia (Rockstroh et al., 2007; Bates et al., 2009; Begic et al., 2011). Alterations in the δ band frequency have been associated with negative symptoms of the illness (Iloh et al., 2011).

Moreover, EEG patterns allow distinction between patients with schizophrenia and other psychiatric disorders (Rockstroh et al., 2007; Venales et al., 2009; Begic et al., 2011) and between different groups of schizophrenic patients (violent and non-violent schizophrenic patients: Schug et al., 2011) and positive vs. negative type schizophrenia (Begic et al., 2000, 2009).

Finally, different strategies have been used to model schizophrenia in healthy subjects. One of them is the administration of psychotomimetic drugs such as NMDA antagonists (Krystal et al., 2003). Using this approach, it has been shown that the administration of subanaesthetic doses of ketamine to healthy subjects augmented high frequency oscillations (40–85 Hz) and reduced low frequency oscillations (1–5 Hz) mimicking some of the oscillatory alterations of schizophrenia (Hong et al., 2010). Similar results have been reported using other hallucinogenic drugs disrupting serotonergic neurotransmission (Oughourli et al., 1971; Riba et al., 2002).

Effects of psychotomimetic agents on low frequency cortical oscillations

The cellular effects of PCP described earlier were accompanied by a simultaneous and marked alteration
Fig. 5. Reduction of low frequency cortical oscillations (LFCO) by phencyclidine (PCP) and 1-(2,5-dimethoxy-4-iodophenyl-2-aminopropane; DOI). (a1): local field potential recording in basal conditions (left), after the administration of PCP (0.25 mg/kg i.v.; middle) and after the subsequent administration of clozapine (CLZ, 1 mg/kg i.v.). Note the marked reduction of the magnitude of the LFCO by PCP and the reversal of this action by CLZ. (a–d): spectrograms showing the effect of PCP (a2, b) and DOI (c, d) on LFCO, as well as the reversal of these actions by CLZ and haloperidol (Hal). Note the marked loss of the power of LFCO by PCP and DOI, denoted by a reduction of the colour intensity (red) at low frequencies. Ordinate range is 0–10 Hz; abscissa is a 1-min period during each treatment. (e) and (f): bar diagrams showing average effects of PCP (e) and DOI (f) on the power of LFCO as well as the reversal by CLZ and Hal; n=20 for PCP and n=51 for DOI. Data taken from Kargieman et al. (2007) and Celada et al. (2008). * p<0.05 vs. basal; # p<0.05 vs. PCP or DOI.
of low frequency cortical oscillations (LFCO; 0.3–4 Hz) in mPFC and of δ waves in the thalamus (Kargieman et al., 2007; Santana et al., 2011). PCP administration dramatically reduced the power of LFCO, recorded in parallel with neuronal discharge, 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 the anaesthetized rat. Interestingly, PCP also produced very marked desynchronization of the neuronal discharge from the active (or ’up’) phases of LFCO. Spikes are typically fired during the active phases of LFCO, corresponding to ’up’ or depolarized states recorded intracellularly. The percentage of spikes fired in active phases of the LFCO was 90±3% in baseline conditions. PCP reduced this value to 59±11% (note that maximal reduction is to 50%; i.e. a random distribution between active and inactive phases; Kargieman et al., 2007).

In addition to NMDA receptor antagonists, serotonergic hallucinogens are considered pharmacological models of schizophrenia due to their ability to evoke some psychotic symptoms, such as hallucinations and perceptual disturbances. In addition, these agents activate 5-HT2A receptors (Nichols, 2004) whereas atypical antipsychotic drugs are antagonists of the same receptors (Meltzer, 1999). 1-(2,5-Dimethoxy-4-iodophenyl-2-aminopropane; DOI) is a partial 5-HT2A agonist that evokes long-lasting alterations in consciousness and perception (Nichols, 2004), an effect mediated by activation of 5-HT2A receptors (Schreiber et al., 1994; Martin-Ruiz et al., 2001).

The systemic administration of DOI (50–300 μg/kg i.v.) produced a marked alteration of the discharge of pyramidal neurons in mPFC, which was similar to that produced by PCP (Fig. 6). Hence, DOI administration increased the discharge rate of 39% of the recorded neurons (to 481% of baseline), reduced that of 27% (to 11% of baseline) and left unaffected 34% of the recorded pyramidal neurons, producing an overall increase of 240% of the pyramidal discharge in mPFC (Puig et al., 2003). In all instances, DOI produced a marked and concurrent reduction of LFCO to 56% of baseline, an effect slightly less marked than that evoked by PCP (Fig. 4). All these effects were antagonized by the subsequent administration of the selective 5-HT2A receptor antagonist M100907, indicating the exclusive participation of 5-HT2A receptors. The inhibitory effect of DOI appears to depend on the activation of 5-HT2A receptors in GABAergic interneurons, as it was reversed by the subsequent administration of the GABA_A receptor antagonist picrotoxinin (Puig et al., 2003). Interestingly, this inhibitory effect appears to increase with dose, as recently reported (Wood et al., 2012).

Reversal by antipsychotic drugs: mechanisms involved

Behavioural alterations induced by non-competitive NMDA receptor antagonists and 5-HT2A agonists are reversed by antipsychotic drugs, in particular by second generation or atypical antipsychotic drugs (Geyer et al., 2001). Given the similar disruption of PFC activity produced by the two different models of schizophrenia used (NMDA receptor antagonist and 5-HT2A receptor agonist) we examined whether PCP- and DOI-induced alterations could be antagonized by classical (haloperidol) and atypical (CLZ) antipsychotic drugs. As shown in Fig. 1, the administration of CLZ completely reversed the increase in firing rate produced by PCP in PFC pyramidal neurons and in thalamic neurons (Kargieman et al., 2007; Santana et al., 2011). Likewise, CLZ pre-treatment prevented the increase in c-fos expression in all brain areas examined, including the PFC and thalamic nuclei (Fig. 1).

CLZ also reversed the fall in low frequency oscillation produced by PCP in PFC and thalamic nuclei.
It also reversed the alteration induced by the serotonergic halucinogen DOI in PFC (Celada et al., 2008). Figure 5 shows representative examples of the reversal by CLZ of the alterations in LFCO induced by PCP and DOI as well as the average data from all recordings. When examined, the administration of haloperidol also reversed PCP and DOI effects. Hence, haloperidol was equally able to reverse the effect of PCP and DOI on LFCO (Fig. 5) as well as the effect of PCP on pyramidal neuron discharge in PFC.

The mechanisms involved in the reversal of PCP and DOI actions are not fully elucidated. At cellular level, the reversal by CLZ of PCP effects may depend on an increased GABA input onto pyramidal neurons, given the opposite effects of PCP + CLZ on c-fos expression in GABAergic neurons (increase vs. PCP alone) and pyramidal neurons (decrease vs. PCP alone; Kargieman et al., 2007). However, this possibility requires further experimental testing.

The reversal by CLZ of PCP effects appears to require the activation of 5-HT1A receptors. Hence, PCP was equally effective in reducing LFCO in the PFC of wild-type (WT) mice and of mice lacking 5-HT1A or 5-HT2A receptors [1A-knock out (KO) and 2A-KO, respectively; Kargieman et al., 2012]. However, the subsequent administration of CLZ reversed the effects of PCP in WT mice and in 2A-KO, but failed to do so in 1A-KO (Kargieman et al., 2012), indicating the requirement of 5-HT1A receptors (Fig. 7). On-going pharmacological studies also support the involvement of 5-HT1A receptors in the reversal of PCP effects on LFCO. Hence, the selective 5-HT1A agonist BAY×3702 completely reversed the fall in LFCO power produced by PCP in rat PFC and the subsequent administration of CLZ did not produce any additional effect (L. Lladó-Pelfort, P. Celada, E. Troyano-Rodríguez and F. Artigas, unpublished observations). These results cannot be explained by the in vitro affinity of CLZ for 5-HT1A receptors. However, atypical antipsychotic
drugs, including CLZ, behave as agonists at 5-HT\textsubscript{1A} receptors in vivo to increase PFC DA release (Rollema et al., 1997; Ichikawa et al., 2001; Diaz-Mataix et al., 2005; Bortolozzi et al., 2010).

5-HT\textsubscript{1A} and 5-HT\textsubscript{2A} receptors are highly co-expressed in PFC neurons (Amargos-Bosch et al., 2004). Thus, 5-HT\textsubscript{2A} receptor blockade by CLZ might alter the physiological balance between both receptors, resulting in an increase of 5-HT\textsubscript{1A} receptor-mediated neurotransmission. However, these results, together with additional data using also 5-HT receptor KO mice (Bortolozzi et al., 2010) do not support this view, since CLZ reversed the effects of PCP on LFCO in KO-2A mice whereas it did not in KO-1A mice. Thus, the effect of CLZ may depend on some still unknown pharmacological property, perhaps resulting from its in vivo occupancy of 5-HT\textsubscript{1A} receptor (Chou et al., 2003). Alternatively, the reversal by CLZ of the effects of DOI may depend on the direct competition of both drugs at PFC 5-HT\textsubscript{2A} receptors.

Given the almost exclusive high affinity of haloperidol for DA D\textsubscript{2} receptors, the reversal of PCP and DOI effects by haloperidol is likely dependent on the in vivo blockade of such receptors which participate in the excitatory–inhibitory balance in PFC (Tseng et al., 2006). Given the role of PFC in cognitive functions, the normalization of its function by antipsychotic drugs might be viewed as an electrophysiological signature of potential pro-cognitive actions. However, the pro-cognitive action of antipsychotic drugs is far from being established and actually, many drugs show deleterious effects on cognition likely due to the blockade of DA actions in PFC. In addition to cognitive processes, the PFC participates in affective control and higher brain functions such as sensory integration, attention, decision-making, behavioural inhibition, language etc., whose alterations contribute to psychotic symptoms. Therefore, it is very likely that the antipsychotic reversal of PCP and DOI actions in PFC are related to the antipsychotic effect rather than to potential pro-cognitive actions of first and second generation antipsychotic drugs.

Concluding remarks

Data obtained in recent years has revealed that psychotomimetic agents markedly disrupt neuronal activity in the PFC and anatomically-connected thalamic areas, such as the centromedial and dorsomedial nuclei. In parallel, these agents alter the power of low frequency oscillations in PFC and in the thalamus, when examined. Given the crucial role of these brain networks in adapting behavioural responses to external sensory inputs, among others, it is likely that the observed abnormalities underlie, at least in part, the psychotomimetic action of these agents. The link with schizophrenia symptoms is strengthened by the observation that antipsychotic agents reverse the disruption of thalamic and cortical activity evoked by PCP and DOI. Overall, the alterations of thalamo-cortical activity induced by psychotomimetic agents can be successfully used to gain further insight into the neurobiological basis of schizophrenia symptoms and to examine the potential antipsychotic activity of new drugs in development.

Acknowledgements

Supported by the Innovative Medicines Initiative Joint Undertaking (IMI) under Grant Agreement No. 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 2012-35183 (Ministry of Economy and Competitiveness and European Regional Development Fund), PI10/1245 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, 11NT3). Support from the Generalitat de Catalunya (SGR20093) is also acknowledged. P.C. is supported by the Researcher Stabilization Program of the Health Department of the Generalitat de Catalunya. M.R. is recipient of an IDIBAPS fellowship.

Statement of Interest

None.

References


serotonin(2A) receptors in pyramidal neurons of prefrontal cortex. Cereb Cortex 14:281–299.


Fuster JM (2001) The prefrontal cortex


Keshavan MS, Reynolds CF, Miewald JM, Montrose DM, Sweeney JA, Vasko RC, Kupfer DJ (1998) Delta sleep...
deficits in schizophrenia – evidence from automated analyses of sleep data. Arch Gen Psychiatry 55:443–448.
Lewis DA, Hashimoto T, Volk DW (2005) Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 6:312–324.
Lisman JE, Pi HJ, Zhang YC, Otmakhova NA (2010) A thalamo-hippocampal-ventral tegmental area loop may produce the positive feedback that underlies the psychotic break in schizophrenia. Biol Psychiatry 68:17–42.


