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Coupling in the cortico-basal ganglia circuit is aberrant in the ketamine model of schizophrenia

Ivan Cordon[a], María Jesús Nicolás[a], Sandra Arrieta[a], Eneko Lopetegui[a], Jon López-Azcárate[a], Manuel Alegre[a,b], Julio Artieda[a,b,*,1], Miguel Valencia[a,*,1]

[a]*Neurophysiology Laboratory, Neuroscience Area, CIMA, Universidad de Navarra, Pamplona, Spain*
[b]*Neurophysiology Service, Clínica Universidad de Navarra, Universidad de Navarra, Pamplona, Spain*

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Abstract
Recent studies have suggested the implication of the basal ganglia in the pathogenesis of schizophrenia. To investigate this hypothesis, here we have used the ketamine model of schizophrenia to determine the oscillatory abnormalities induced in the rat motor circuit of the basal ganglia. The activity of free moving rats was recorded in different structures of the cortico-basal ganglia circuit before and after an injection of a subanesthesic dose of ketamine (10 mg/kg). Spectral estimates of the oscillatory activity, phase-amplitude cross-frequency coupling interactions (CFC) and imaginary event-related coherence together with animals' behavior were analyzed. Oscillatory patterns in the cortico-basal ganglia circuit were highly altered by the effect of ketamine. CFC between the phases of low-frequency activities (delta, 1–4; theta 4–8 Hz) and the amplitude of high-gamma (~80 Hz) and high-frequency oscillations (HFO) (~150 Hz) increased dramatically and correlated with the movement increment shown by the animals. Between-structure analyses revealed that ketamine had also a massive effect in the low-frequency mediated synchronization of the HFO's across the whole circuit. Our findings suggest that ketamine administration results in an aberrant hypersynchronization of the whole cortico-basal circuit where the tandem theta/HFO seems to act as the main actor in the hyperlocomotion shown by the animals. Here we stress the importance of the basal ganglia circuitry in the ketamine model of schizophrenia and leave the door open to further investigations devoted to elucidate to what extent these abnormalities also reflect the prominent neurophysiological deficits observed in schizophrenic patients.

*Correspondence to: Neurophysiology Laboratory (2.33) CIMA, Avda. Pío XII 55, 31008 Pamplona (Navarra), Spain. Tel.: +34 948 194700.
E-mail addresses: jartieda@unav.es (J. Artieda), mvustarroz@unav.es (M. Valencia).
[1]These authors coordinated equally this work.

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1. Introduction

Schizophrenia is a mental disorder characterized by positive (hallucinations and paranoia) and negative symptoms (social withdrawal, poverty of speech and blunted affect), together with alterations in working memory and attention (Carter et al., 2010). To date, the antipsychotic medication (mostly D2 dopamine receptors antagonists) is able to treat the positive symptoms, but it has poor efficacy against the negative and cognitive ones.

Much research has been carried out on the idea that dopaminergic dysfunction could lead to schizophrenia (Howes and Kapur, 2009). Although the initial findings pointed towards a general hyperactivity of dopamine receptors, more recent studies have found that, while striatal regions suffer from hyperdopaminergia (Abi-Dargham et al., 1998), the prefrontal cortex suffers from hypodopaminergia (Abi-Dargham et al., 2002). Newer theories suggest an origin related to misregulations in the glutamatergic system (Javitt, 2007). This is supported by the fact that in humans the administration of N-methyl-D-aspartate receptors (NMDAR) antagonists, such as phencyclidine (PCP) and ketamine, induce symptoms and cognitive deficits similar to schizophrenia (Lahti et al., 2001; Murray, 2002).

In rodents, different NMDAR models of schizophrenia have been developed. One of the most common consists of the acute injection of subanesthetic doses (5–10 mg/kg) of ketamine (Kocsis et al., 2013). Ketamine injection produces hyperlocomotion, altered social interaction and impaired cognitive function. In particular, rodents hyperlocomotion has been associated with cognitive and perceptive disturbances that would mimic the cognitive dysfunction observed in humans (Adler et al., 1999). Among the NMDAR antagonists, ketamine is of particular interest due to its D2 dopamine affinity (Kapur and Seeman, 2002), having the potential to converge the dopaminergic and glutamatergic hypothesis into the same model (Frohlich and Van Horn, 2013). Many electrophysiological works have characterized this model in the hippocampus (Ehrlichman et al., 2009), cortex (Phillips et al., 2012) and nucleus accumbens (Hunt et al., 2006). These studies together with those carried out in patients have led to a general consensus about the idea of schizophrenia as a disorder where the synchronization of neural activity is altered. Likewise in Parkinson's or Alzheimer's disease, abnormalities in the oscillatory regime have been detected in schizophrenia (Alonso-Frech et al., 2006; Jeong, 2004; Uhlhaas and Singer, 2010). Among them, phase-amplitude cross-frequency coupling interactions (CFC) – where the phase of a slower activity determines the amplitude of higher frequency oscillations – have received much attention in the last years. CFC has been proposed as a potential mechanism to mediate into neural computation and synchronization between distant regions (Canolty and Knight, 2010). While it has been related to cognitive processing in humans (Canolty et al., 2006) and rodents (Tort et al., 2008), it has also been associated with the pathophysiology of different diseases (Ibrahim et al., 2014; López-Azcárate et al., 2010), including schizophrenia (Kocsis, 2012; Lakatos et al., 2013).

Motivated by those studies which highlight the relevance of the basal ganglia circuits in the pathogenesis of schizophrenia (Perez-Costas et al., 2010; Simpson et al., 2010), here we set out to determine the CFC alterations produced by a subanesthetic dose of ketamine (10 mg/kg) on the motor circuit of the rat basal ganglia and relate them with the hyperlocomotion effects shown by the model. We show that the oscillatory architecture of the cortico-basal network is strongly affected by the effect of ketamine that seems to be closely related to the hyperlocomotion experienced by the animals. Specifically, we detect a strong correlation between the increase of locomotion and the alterations in the CFC interactions between the phase of delta (theta) oscillations and the amplitude of high-frequency activities ($>$ 50 Hz) that may be of relevance for understanding schizophrenia.

2. Experimental procedures

Here we studied a subset of recordings obtained from the experiments previously described in (Nicolás et al., 2011). During these recordings, we evaluated the effect of a low dose of ketamine (10 mg/kg) on the oscillatory activity of 13 male Wistar rats (250–300 g) measured on the motor cortex and three nuclei of the basal ganglia.

2.1. Ethics statement

Animal care and surgery procedures were approved by the animal ethics committee; Comité de Ética para la Experimentación Animal, Universidad de Navarra, approval ID 088-06.

2.2. Surgical electrode implantation

Recording electrodes were implanted along the basal ganglia motor circuit. They were located in motor cortex (Cx), caudate-putamen (CPU), subthalamic nucleus (STN) and substantia nigra pars reticulata (SNr). Stereotactic coordinates were calculated according to the Paxinos and Watson neuroatlas (Paxinos and Watson, 2007). Coordinates were Cx (anterior (AP): 2.70 mm and lateral (L): 3.20 mm); CPU (AP: 0.20 mm, L:2.5 mm; ventral (V): −6 mm); STN (AP: −3.80 mm; L: 2.5 mm; V: −7.8 mm); SNr (AP: −5.80 mm, L:2 mm, V: −8 mm).

Two different types of electrodes were used to record LFP from the different brain structures. Concentric microelectrodes with two contacts (SNE-100, Kopf Instruments, Tujunga, California, USA) were used for CPU, STN and SNr. Cortical activity was recorded by means of stainless steel screws placed in the skull. The active electrode was placed in the primary motor cortex and was referenced to an electrode placed in the auditory cortex.

2.3. Recording procedure

The recordings started 5 days after surgery and took place inside a custom-made Faraday cage. Recordings started 45 min after connecting the cables in order to let the animals habituate to the Faraday cage. Then, the basal condition activity (before injection of ketamine) was recorded for 15 min. After that time, rats were injected a ketamine dose (10 mg/kg; Ketolar, Pfizer, Madrid, Spain) and activity was recorded along 60 min after injection. Animal's movement was tracked using a webcam placed on the top of the cage. Videos were analyzed semi-automatically with custom-made software running under Matlab (Mathworks, Natick, MA, USA). To rule out any possible sleep or awake-but-inactive effects on brain activity, only active periods (i.e. with locomotion) were selected for further analyses.

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