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Review article

Glutamate and modeling of schizophrenia symptoms: Review of our Findings: 1990–2014

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ABSTRACT

In the early 90s, we studied the role of perception disturbances in schizophrenia in our first clinical approaches, using the Bender test in schizophrenic patients. Results were clear, showing a shape discrimination failure. Following this initial results, we reproduced nuclear symptoms of schizophrenia in animal models, showing that perceptual disturbances, acquisition disturbances, decrease in affective levels and working memory disturbances can be induced by specific N-methyl-D-aspartic acid (NMDA) glutamatergic blockade within the nucleus accumbens septi (NAS). We studied also another glutamatergic and dopaminergic drugs, finding that a decrease in glutamatergic transmission within NAS led to cognitive disturbances and affective flattening. An increase in glutamatergic transmission fully enhances cognition in the tasks used. Dopaminergic D-2 antagonists partially improved cognition. Our results link the proposed corticostriatal dysfunction with the thalamocortical disturbances underlying perceptual problems, but also influencing affective levels and cognitive variables. According to our translational findings, core schizophrenia symptoms may be translationally reproduced antagonizing NMDA receptors within NAS, and improved blocking the glutamate auto-receptor. Dopaminergic transmission appears to have a role in therapeutic but not in the early pathophysiology of schizophrenia.

Contents

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Introduction

Translational research has a relevant place in psychiatry. These experimental lines allow understanding mechanisms underlying illness, and by this way they contribute to the possibility of new treatments [1]. Since a long time ago animal models have been used in psychiatry [2–4]. Even today, these lines have a high strength in the field of psychiatry [5,6]. Translational research is considered today an appropriate tool to correlate brain circuitries and psychiatric disorders, aiming to study the pathophysiology of these illnesses, and, when possible, to try new therapeutical approaches [6].

Taking into account only the most recent studies, animal models have been used to study anxiety [7–10], panic attack [11,12], depressive disorders [13,14], and even mania [15]. Other approaches focused on schizophrenia and mania [16]. The risk factors of psychosis and affective disorders have been also studied using animal models [17]. Indoleamine derived hallucinogens have been also studied using translational approaches with animal models [18,19]. Furthermore, animal models of schizophrenia have been recently reviewed [20]. All these studies and evidences attest to the validity of the concept of models in psychiatry and give relief to translational research in this field.

The schneiderian's criteria have an influence even today [21]. In this conception, psychotic states must be "explained" by biological causes, and not merely "understood", in a traditional center European schedule ("erklaren" vs. "verstehen"), following the concepts of Jaspers, Schneider and, in the same way, Popper [21]. We are here studying efficient causes acting on the brain, explaining the consecutive behavioral disorders. These concepts have been largely vindicated [22]. In this way, it is correct to try studies on brain activity aiming to "explain" the so-called "caused" disorders. The problem here does not refer to human personality; the problem here leads to brain disturbances causing cognitive and behavioral disorders.

Translational research in schizophrenia

Considering the causal origin of psychoses, they may be referred to brain dysfunctions. The schizophrenia puzzle has been always an intriguing and attractive object for researchers since an important time ago because of its complexity. A large number of very different theories have been proposed along time. Theories started from clinical descriptions, followed by psychoanalytic conceptions and systemic approaches, and dopamine theory was prevalent between 1969 and 2000 [23]. Our findings allow thinking in a possible next glutamatergic explanation of main schizophrenic phenomena.

In all cases, nucleus accumbens septi (NAS) was identified as an important brain structure involved in schizophrenia [24–29]. Early evidences came from the fact that NAS receives dopaminergic inputs, is related to the mechanism of action of antipsychotic drugs, and, finally, all these evidences fit in an adequate manner with the dopaminergic hypothesis of schizophrenia [30,27]. An important number of neurochemical evidences were reviewed in the early 80s, giving strength to the idea that this nucleus shows biochemical differences in schizophrenic patients when compared to controls. In these pioneer articles, the relevance and promises of the animal models use was emphasized, saying that indirect but very important evidences could be obtained by this way [28]. It was said there that NAS lesions have an effect on "behavioral switching", a disorder that has been related to the attentional impairment described in schizophrenic patients [28]. Further studies on attention problems in animal models mimicking schizophrenic cognition deficits were relevant or initiate understanding of schizophrenic pathophysiology [24].

Schizophrenic symptoms: our translational approaches

Classically, schizophrenic symptoms have been divided in primary and secondary symptoms [31], or positive and negative symptoms [32,33]. Historically, positive symptoms have been attributed to a neurotransmitter over activity, and negative symptoms to structural changes [32,33]. Recently, cognitive symptoms have been pointed as very relevant and in an independent manner to positive and negative symptoms [34].

We have proposed experimental approaches to the schizophrenic main manifestations (Table 1), considering the most essential symptoms in each group. In this way, delusional perception was considered by us the most prominent, characteristic and representative primary symptom, since some of the others cannot be observed only in schizophrenia [35–39]. Considering negative symptoms, affective flattening is one of the most relevant of the group [32,33], and it was modeled also in our lab [40]. Ideoaffective rigidity is also a relevant secondary symptom, and some homologies have been proposed in our models [35–39]. Finally, cognitive symptoms, considered today as very relevant schizophrenic manifestation, were also modeled in our laboratory in both, punished [41] and not punished tests [42]. All evidences led to a glutamatergic neurotransmitter dysfunction within the nucleus accumbens septi (NAS) as a common fact (Table 1) [43]. We shall explain our evidence lines in this short review.

Primary or positive symptoms: perceptual disorders

The perceptual disorders have been widely remarked by our team in the field of psychoses [43–47]. This topic has been recently taken as a central fact of this illness [48], since perceptual cognitive distortions are a core symptom of schizophrenic psychoses [37,49].

Table 1
We propose here a classification for schizophrenic symptoms categories and corresponding experimental approaches of our group. In all cases the pharmacological manipulation was an intra-accumbens injection of the NMDA glutamatergic antagonist AP-7, 1 μg/1 μl).

Symptoms categories	Main symptoms of the category	Experimental approaches
Primary symptoms	Delusional perception	Gargiulo et al. [24] Acerbo et al. [1] Gargiulo et al. [29]
Secondary symptoms	Ideoaffective rigidity Affective flattening	Gargiulo et al. [24] Acerbo et al. [1] Gargiulo et al. [29] Martínez et al. [60,61]
Cognitive symptoms	Acquisition deficit Working memory disturbance	Martínez et al. [60] Baiardi et al. [4]

As we said in our early papers [44] and ulterior reviews [46,47], more than half a century ago Conrad attempted to analyze the symptoms of incipient schizophrenia appealing to Gestalt theory using a phenomenological descriptive methodology [36]. Continuing Matussek's assertion [36,44,46,47,50], who argued that there is a delusional perception loosening or relaxation of the natural structure of perception, stated that in delusional states. In the opposite way to what happens in normal psychology, a prevalence of the essential properties of objects, in the sense of Metzger, on this structure is observed. Details have prevalence over the contextual nature of objects. Thus, unlike Gruhle, Conrad felt that the perception would be altered, and this would result in difficulties in integration of perceptual globalities [36,43–47]. A perceptual similar phenomenon could be observed with hallucinogenic drugs such as mescaline [51].

Following the same line, Conrad thought that interpretation of interpersonal communication was more affected than perceptions of external objects, because their characteristics linked to a higher degree of subtlety. This fact makes more difficult this kind of perceptions, and at this level failures are observed easier constituting most frequent forms of delusional perceptions. These facts have been considered as suggesting that cognitive deficits may lie at the heart of schizophrenia [48]. We followed here the ideas of Conrad about a gestaltic dysfunction in schizophrenia that allow explaining delusional perceptions [36]. We had clear results using the gestaltic Bender test (Fig. 1) [44,45]. These studies showed statistically significant differences between controls, acute and chronic schizophrenic patients, in global scores and time employed (Fig. 2). We attributed it to a loss of objective structure of perception in schizophrenic patients [43–47]. Other studies have shown failure to perform correctly in visual backward masking tasks in schizophrenic patients [52]. These perception disturbances have been related to failures to establish cortical oscillations (gamma range) in response to sensory stimulation [52]. As it may be observed, the perception disorder is very relevant, and, in some senses, is related to cognition deficits. The problems in distinguishing facial expressions of emotion [48] are related to the integration and the evaluation of perception, and closely related to the ideas of Conrad [36]. Following this background, we studied perception in close relationship with cognition and anxiety in animal models, taking into account the current primary conceptions about the pathophysiology of schizophrenia.

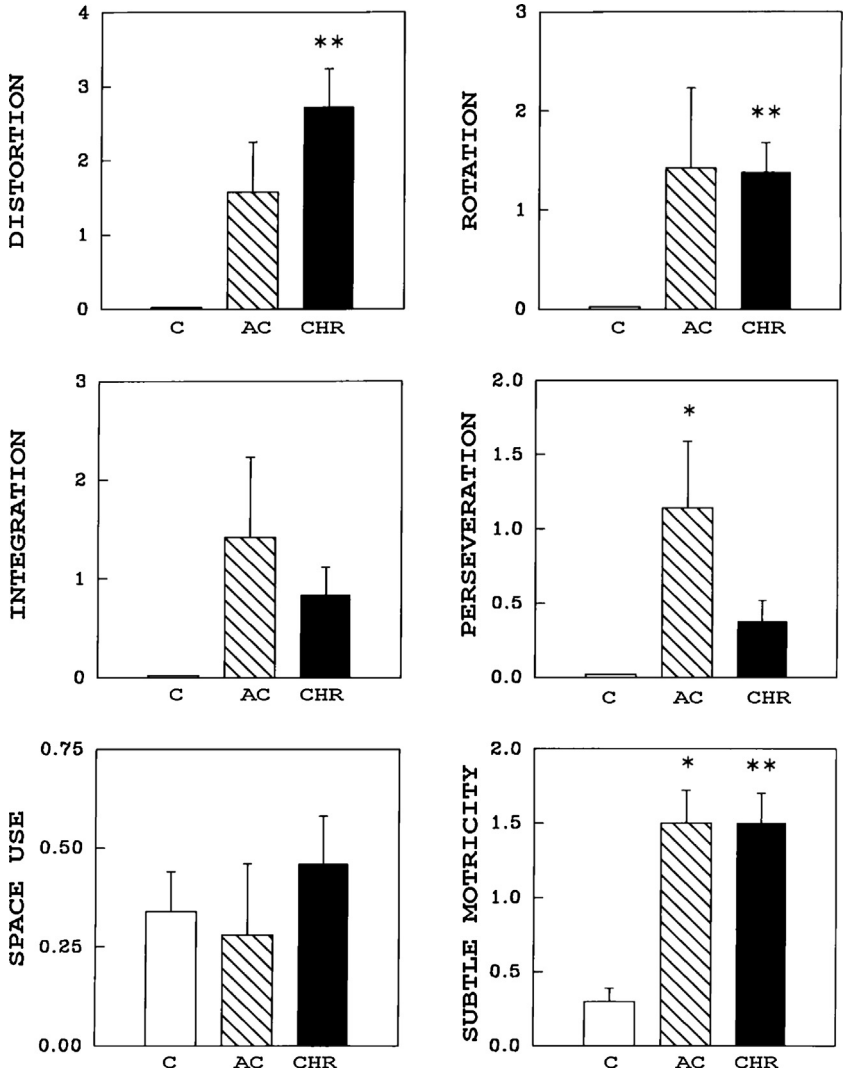

Fig. 1. Results of the studies in schizophrenic patients using gestaltic Bender test [15,23,26–28]. Parameters considered are here separately detailed. Three groups were studied: Controls (C, $n = 26$), acute schizophrenic patients in the first episode, in absence of any initial treatment (AC, $n = 7$) and chronic schizophrenic patients (CHR, $n = 26$). Data are presented as mean ± standard error of the mean (SEM). Non parametric Dunn's test was used in all cases and a $p < 0.05$ was considered significant ($^{*}p < 0.05$; $^{**}p < 0.01$). We observed a significant difference between controls and chronic patients in distortion, rotation and subtle motricity ($p < 0.01$). Acute schizophrenic patients differed from controls in perseveration and subtle motricity ($p < 0.05$).

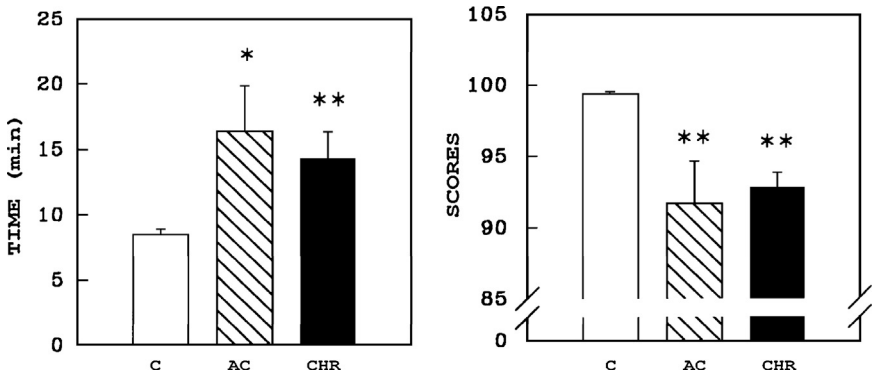

Fig. 2. Results of the studies in schizophrenic patients using gestaltic Bender test [15,23,26–28]. Main resultant parameters are here considered. Three groups were studied: Controls (C, $n = 26$), acute schizophrenic patients in the first episode, in absence of any initial treatment (AC, $n = 7$) and chronic schizophrenic patients (CHR, $n = 26$). Data are presented as mean ± standard error of the mean (SEM). Non parametric Dunn's test was used in all cases and a $p < 0.05$ was considered significant ($^{*}p < 0.05$; $^{**}p < 0.01$). We observed a highly significant difference between controls and acute and chronic patients in scores ($p < 0.01$). Time of execution of the task showed significant differences between controls and acute patients ($p < 0.05$), and a highly significant difference between chronic patients and controls ($p < 0.01$).

We studied perception in an animal model using pigeons (Figs. 3 and 4). The opportunity of perform the experiments in the Laboratory of Professor Delius, in Konstanz, was an exceptional possibility, taking into account the tradition of this group in perception comparative studies in human and animal shape perception [53]. In the designed schedule, pigeons were trained in a visual discrimination task, in which reward was linked to recognition of shapes (Fig. 5), requiring a high level of attention. We stimulated dopamine receptors and blocked N-methyl-D-aspartic (NMDA) glutamatergic receptors within NAS, which is classically linked to schizophrenia [9,28], with an aim to produce an homologous "psychotic-like state," with loss of "gestaltic" discrimination function [38]. Negative findings were seen with apomorphine or lidocaine injections, but a significant and reversible performance disruption to near chance levels was obtained after 7-aminophosphonoheptanoic acid (AP-7, Fig. 6) injection into the NAS [38]. After it, using other NMDA blockers (5-aminophosphonoheptanoic acid, AP-5, and CGS-19975, cis-4-(phosphonomethyl)-piperidine-2-carboxilic acid) the same phenomenon was observed, suggesting a specific action on the receptor. In all cases, a decrease in the percent of correct trials and an increase in correcting trials (exposition to the same stimulus in the case of a wrong choice, aiming to correct it) were observed (Fig. 6) [35,39]. The increases in correcting trials evidenced in present experiments were interpreted as a secondary or negative symptom since it could be considered as a manifestation of ideoaffective rigidity (see next point) [35,38,39]. A failure in acquisition could be deduced from these results, and it was predictable in the corresponding tests, since perception is clearly linked to these parameters (see cognitive models, at the end). Additional evidences showed that an increase in glutamatergic transmission within NAS induced by the glutamate auto-receptor blockade improves the task efficiency in a very clear manner, enhancing the percent of correct trials and decreasing the number of correcting trials in the execution of the task (Fig. 6) [39]. The dopamine D-2 receptor blockade led to a partial improvement, maintaining the same level in the percent of correct trials, but decreasing the number of correcting trials (Fig. 6) [39]. We said at

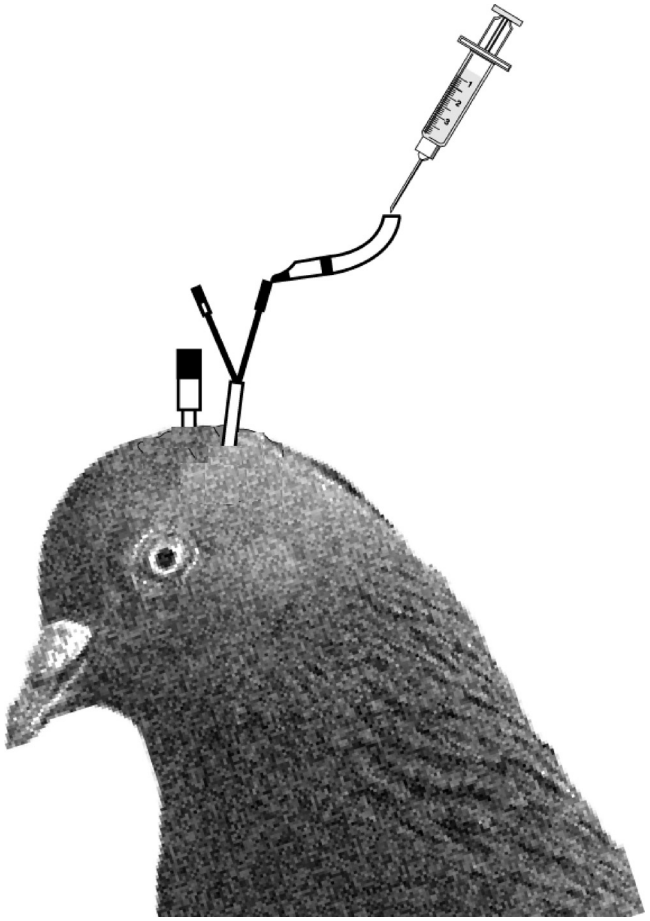

Fig. 3. Schematic representation of cannula placement in the skull of the pigeon and injections procedure. Pigeons were gently manually restrained during injection.

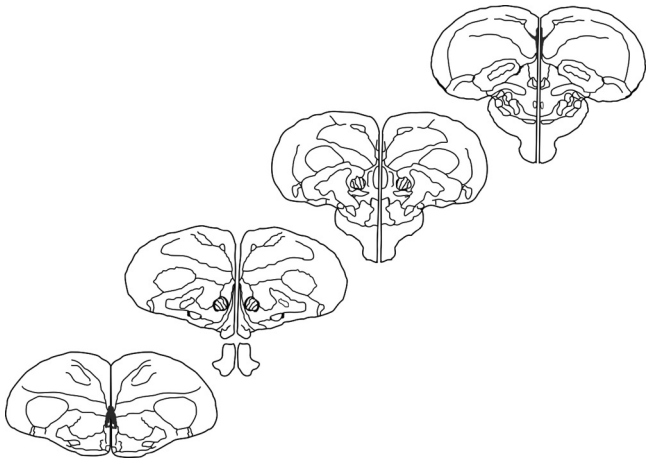

Fig. 4. Histological scheme of Nucleus Accumbens Septi (NAS, crossed lines) in the pigeon schematically represented in serial slices. Note its central and periventricular position.

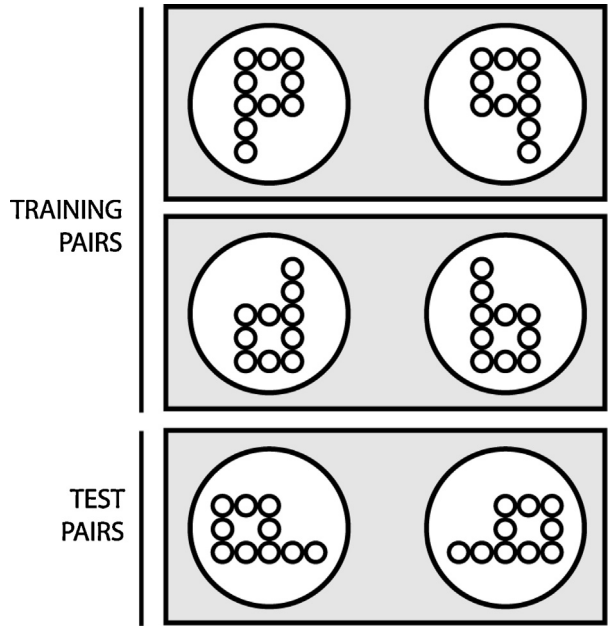

Fig. 5. Image of shapes used as training pairs ant test pairs. One stimulus of each pair was reinforced by a reward. Stimulus like "p" and "d" were reinforced, but not "q" and "b". This condition was maintained along the training and the test. Training pairs were presented in the training and test, and test pairs were presented only in test conditions, aiming to evaluate generalization.

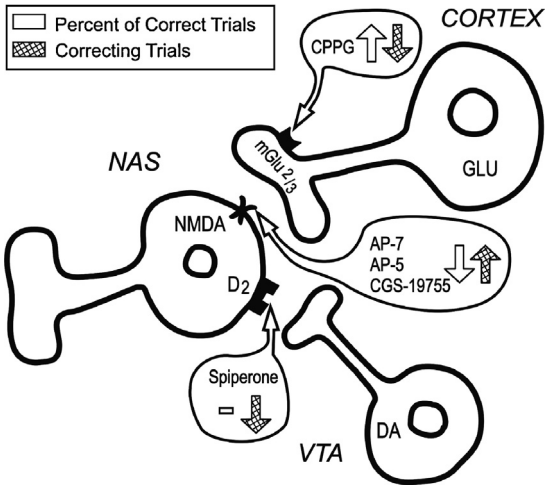

Fig. 6. Interactions of neurotransmitter systems within NAS in the pigeon according to the findings of our experiments in the proposed model. Antagonists of NMDA receptors acting within the NAS decrease the performance. This phenomenon was observed with all N-methyl-D-aspartic (NMDA) receptor blockers AP-7 (7-amino-phosphono-heptanoic acid), AP-5 (5-amino-phosphono-heptanoic acid), and CGS-19755, (cis-4-(phosphonomethyl)-piperidine-2-carboxilic acid) [1,24,29]. The results were in all cases significant decreases in percent of correct trials and significant increases in correcting trials. The use of a dopamine D-2 like receptor antagonist (Spiperone) led to a significant decrease of correcting trials, with no effects on percent of correct trials [29]. Very interesting results were obtained with the auto-receptor antagonist mGlu2/3, CPPG (RS-alpha-cyclopropyl-4-phospho-nophenylglycine) [29]. These findings clearly showed that the glutamate auto-receptor blockade within NAS led to a significant increase in the percent of correct trials and a significant decrease in the correcting trials [29]. These evidences led us to suppose that glutamate neurotransmission management within NAS is more efficient than dopamine D-2 blockade improving the cognitive task here proposed. It could be over lighted that D-2 blockade is the classical treatment proposed for schizophrenia [29], and that early stages of this illness appears to be produced by glutamate dysfunction and not by dopamine initial dysfunctions, according to our findings [24–29]. The brain areas are: Cortex, Nucleus Acumbens Septi (NAS) and Ventral Tegmental Area (VTA). GLU: glutamate, DA: dopamine.

this opportunity that dopaminergic transmission, according to this model, has a role in therapeutic but not in the early pathophysiology of schizophrenia [38].

Secondary or negative symptoms: ideoaffective rigidity and affective flattenening

Ideoaffective rigidity is also classically considered a relevant secondary symptom, and some homologies have been proposed in our models. In our experiments in pigeons the number of correcting trials was clearly increased by injection of NMDA glutamatergic antagonists. It was considered by us a problem in reversal learning [35,38,39], a phenomenon classically related to difficulties in "behavioral switching" [28]. In these conditions, the pigeon perseverates in the wrong stimuli, pecking on the same key without the possibility of changing of stimulus. The repetitive demands of schizophrenic patients following a wish, with impossibility to change facing environmental demands, assume a form very similar to the phenomenon observed here. We said at this opportunity that positive (perceptual disorder) and negative symptoms (increase in correcting trials as mimicking ideoaffective rigidity) could be experimentally induced with the same procedure, blocking NMDA glutamatergic transmission [35,38,39]. Interestingly, correcting trials were significantly decreased injecting a D-2 dopaminergic antagonist within the pigeon's NAS [39]. It suggests an additional parallelism between our model in pigeons and clinical facts. According with the hypothesis, an improvement could be expected enhancing glutamatergic transmission. This improvement in neurotransmission could be induced blocking glutamatergic auto-receptors or antagonizing inhibitory D-2 dopaminergic influences on glutamatergic transmission. Actually, both phenomena were observed. Glutamatergic auto-receptor blockade injecting CPPG (RS-alpha-cyclopropyl-4-phospho-nophenylglycine) [39] within the NAS significantly increased the percent of correct trials and decreased the number of correcting trials, showing by this way a modification of both cognitive parameters [48], and Spiperone reduced correcting trials [39].

Other observed phenomena were related to affective flattening. In previous punished experiments, fecal boli were diminished during retrieval, suggesting a decrease in anxiety levels during acquisition. It led us to use a specific anxiety test, the Plus Maze. In this schedule, we observed that AP-7 clearly decreases anxiety levels when injected within the NAS, suggesting homologies with the affective flattening observed in schizophrenia [22]. Taking all these findings as a whole, it appears that NAS integrates cognition and affective levels, and a dysfunction in this nucleus could underlie schizophrenic illness, giving a basis to the explanation of cognitive (working memory failure), positive (perception and acquisition disturbances) and negative (affective flattening) symptoms. Clinically, it has been postulated that some amygdala abnormalities dysregulate brain, leading to emotional disturbances [54]. Recent evidences surged from research on emotional disturbances in schizophrenia led to the idea of an abnormal emotional driving in schizophrenia. It was previously postulated by Grace and attributed to a hippocampal functional defect leading to disturbances in emotional driving [9]. Posterior revisions of studies using tasks of emotional recognition led to postulate also an amygdala functional defect [54]. It has been postulated from experimental evidences showing anatomical reduction of the amygdala using structural magnetic resonance images (MRI). Additional studies using functional MRI (fMRI) have shown that the amygdala reaction decreased in response to emotional stimuli when compared to neutral stimuli [54]. It has been postulated that a lesion of the amygdala, when associated to a reduced interconnectivity with the prefrontal cortex could lead to a reduced emotional expression (affective flattening), associated to

emotion recognition deficits. Central and basolateral nuclei of the amygdala may be influencing in different modes in these abnormal emotionality driving [54]. In our experiments, the glutamatergic projection from amygdala to the NAS [9] is experimentally blocked, inducing an anxiolytic like state, which we referred as a homologous state of affective flattening [40]. Grace proposed an interesting circuitry aiming to integrate and explain several schizophrenic symptoms. His hypothesis is that schizophrenia is related to a dysfunction in afferent projections, glutamatergic in nature, converging onto the NAS. He suggested that goal-directed motor plans produced by the prefrontal cortex, the contextual constraints specified by the hippocampus, and the affective evaluation provided by the amygdala are all integrated in the NAS, a structure in which all these brain regions converge sending glutamatergic projections. This integration leads to goal-directed behavior bounded by contextual information and emotional significance. Conversely, in schizophrenia this integration is disturbed, and this fact leads to an abnormal affective driving with an inadequate utilization of contextual cues, resulting in impulsive and disorganized behavior [36]. We have recently explored the differential action of these brain areas inhibiting these structures with benzodiazepines. We observed different interactions between them, expressed in modifications in anxiety levels, and leading to explanation possibilities for benzodiacepines expected and paradoxical effects [55].

Cognitive symptoms: acquisition and working memory

If the glutamatergic transmission within NAS mediates the cognitive processes involved in shape recognition in the pigeon, it could be expected that antagonists disrupt performance in this task. Inversely, drugs that improve glutamatergic transmission into this structure would have an optimizing effect in these cognitive tasks. As previously said, it was the case of the effects observed with NMDA glutamatergic antagonists. In this sense, we have observed that different drugs with this profile: AP-7, AP-5 and CGS-19755 used in different instances [35,38,39] produced a clear decrease in perceptual performance, disrupting the shape recognition task used. By the inverse way, drugs that blocked the autoreceptor (mGlu 2/3, CPPG) [39] clearly improved the task execution. These cognitive effects were also observed in other paradigms in rats, in punished [56,41] and not punished cognitive tasks [42]. Passive avoidance and working memory tests were disrupted by NMDA glutamatergic blockade [41,42,56].

In rats, we observed that injecting AP-7 within the NAS, acquisition, which requires a high level of attention, is disturbed, with no effects on consolidation [41,56]. These findings were related by us to perceptual disturbances during acquisition but also to cognitive disturbances [48]. These cognitive disturbances induced by described glutamate blockade were also observed in non-punished cognitive tasks. In a working memory test we observed a clear disruptive effect with the same pharmacological procedure, indicating that cognitive disturbance was not attributable to the stress or pain component of the avoidance task [42]. After our previous findings, other groups found, in the same way, that cognitive tasks that involve cognitive flexibility, processing speed, response inhibition and attention, are affected by NMDA antagonists, resembling cognitive disorders that are present in schizophrenic patients, and are attenuated by antipsychotic drugs [1].

Dopamine, glutamate, schizophrenia and the mechanism of action of neuroleptics

An interesting model of psychotogenesis has been proposed by Carlsson [57]. He postulates that a neurotransmitter interaction

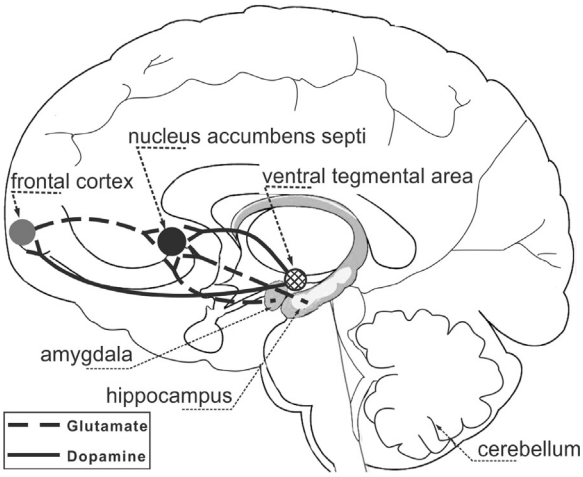

Fig. 7. Brain structures involved in schizophrenia schematically represented. Meso-cortico-limbic dopaminergic system is represented here by an unbroken line, and dashed lines represent the glutamatergic corticostriatal projections. A problem in the interplay of both systems is here proposed as the base of schizophrenia. We proposed that early stages of the illness could be attributed to a deficiency of glutamate neurotransmission [24–29].

takes place within NAS (Fig. 7), and that dopamine and glutamate systems, projecting to the striatum from the lower brainstem and the cortex, respectively, evidence interactions. These projections regulate a striatal GABAergic neuron system that projects to the thalamus constituting the indirect striatothalamic pathway. They exert an inhibitory action on thalamocortical glutamatergic neurons, protecting the cortex of sensory overload and consecutive cortical hyperarousal. The inverse situation can be observed when the corticostriatal glutamate pathways fall in hypoactivity. Furthermore, the protection exerted by this system is reduced when dopaminergic pathways increase their firing. These dysfunctions lead to psychotic states. In these conditions, direct glutamatergic pathway exerts excitatory influences, and glutamatergic corticostriatal fibers may be acting by both pathways. Thus, both systems may operate as brakes and accelerators, respectively [57].

Dopaminergic and glutamatergic afferences within NAS have also interactions, converging in a very close proximity on NAS neurons and establishing a closely related contact on dendritic spines [9,58]. D-2 receptors appear to exert a presynaptical inhibition on cortical afferent terminals [9,59]. Following these evidences, it has been proposed that D-2 dopaminergic receptors could have an inhibitory effect on corticostriatal terminals. This affirmation is based in the fact that D-2 antagonists increased the excitatory post-synaptic potentials (EPSP) amplitude in NAS neurons, enhancing the effects of excitatory afferent projections from prefrontal cortex, hippocampus and amygdala [9,60–64]. A presynaptic effect of D-2 dopaminergic receptors has also been described [65].

The mechanism of action of antipsychotic drugs cannot be merely explained by a D-2 receptor antagonism or by decreases in dopamine absolute levels [9]. The acute antipsychotic administration leads to an increase in dopamine neurons firing and is accompanied by a simultaneous elevation of dopamine release and turnover [66,67], suggesting that additional mechanisms related to chronic administration are possibly underlying therapeutic effects.

The D-2 receptor blockade is present in a rapid time course after drug administration. However, the therapeutic effect starts two or three weeks later. It strongly suggests neuronal adaptation mechanisms. Antipsychotics exert a time-dependent firing inactivation in dopaminergic neurons. It has been postulated that this effect is mediated by over excitation or depolarizing block (DB) [66,68]. DB is a state of dopamine neuron inactivation induced by antipsychotic drugs chronically administered [69]. It has been

postulated that DB mediates the therapeutic effects in schizophrenic patients blunting hyper activation of dopamine neurons firing, induced by external stimuli, leading to an attenuation of dopamine systems responsivity [66].

The DB generation mechanism involved is actually matter of discussion [69]. Evidences suggest that antipsychotic drugs induce an "offsetting deficit" but not an etiological treatment directed to the schizophrenia primary pathology [69]. Different hypothesis have been proposed regarding the acute effect of antipsychotic drugs. One of them sustains that it could be due to the blockade of dopamine auto-receptors. The other hypothesis postulates a post-synaptic blockade involving a wide circuitry, leading to a feedback mechanism. Several recent findings strongly suggest the intervention of the last one [67]. The chronic effect of antipsychotic drugs is studied using repeated administration, aiming to induce a depolarization block. This induced state has a close correlation with the therapeutic efficacy of the drug, and, depending of the drug, with the ability of the drug to produce extrapyramidal side effects in humans. Acute and chronic administration of neuroleptics leads to a decrease in spontaneous active dopamine neurons. This decrease appears to restore the balance within the NAS. It has been postulated a decrease in facilitator actions of hippocampus afferent pathways on frontal cortex inputs. Decreasing action of inhibitory dopaminergic afferent pathways, a new balance is established [9].

According to our experimental findings and the present state of evidences, a glutamatergic deficiency on NAS afferent pathways could be at the base of the main schizophrenic symptoms because perceptual disturbances [35,38,39], acquisition disturbances [41,45], decrease in affective levels [40] and a disturbance in working memory tasks [42] can be induced by glutamatergic blockade within the NAS in animal models. An over activation of the frontal cortex was observed by us with the same pharmacological procedure [42]. It fits with the idea that psychosis is produced by a cortical overload. Our results link the proposed corticostriatal glutamatergic dysfunction related to thalamocortical disturbances underlying the perceptual, affective and working memory problems in schizophrenia. It suggests that new treatments could be expected exerting new modulations of glutamate systems. In the same way, it has been proposed that drugs acting on particular glutamate receptors could lead to new treatments for schizophrenia [70].

Starting from these evidences, we may conclude that our results link the proposed corticostriatal dysfunction with the thalamocortical disturbances underlying perceptual problems, but also influencing affective levels and cognitive variables. Dopamine transmission has a role in therapeutic but not in the early pathophysiology of schizophrenia [38].

Final synthesis of our thought line and its relation with recent evidences

Our present findings have a clear coherence with those obtained by other experimental approaches. Some reviews have widely fulfilled the present state of the art [71,72]. It is our intention to describe our thought line, more than review the findings of another groups. Our initial approach was a neuropsychological one. As previously said, we experimentally demonstrated that the shape perception was affected in early schizophrenic states (Figs. 1 and 2) [43–45,47]. An important number of evidences showed neurophysiological and neuropsychological disturbances in schizophrenia [73–75]. However, visual perception disturbances are recognized in recent studies as a valid way to study information processing deficits in schizophrenia [49,76,77]. We elected this way, and we applied our clinical findings to a pigeon shape discrimination model initially based on the dopaminergic hypothesis of schizophrenia [38]. In it, we initially tried to disrupt the mesolimbic system, classically linked to schizophrenia [see 102], stimulating dopamine receptors. Since corresponding experiment clearly failed, we tried to use the model applying to the postulated glutamatergic theory, blocking the NMDA receptors within NAS. It led to clear results, and we postulated that the early pathogenesis of schizophrenia could be explained by a reduced glutamatergic tone within NAS, and not to an increase in dopamine release in NAS [35,38,39]. It was coincident with previous findings of Carlsson [79], reporting specific effects of dizocilpine in monoamine depleted mice, suggesting an effect directly mediated by glutamatergic transmission, and new trends in the hypothesis of schizophrenia pathophysiology [80]. Furthermore, positive, negative and cognitive symptoms were reproduced by glutamatergic blockade (Table 1) [35,38–42]. We postulated these acute experimental pharmacological procedures could be mimicking a decrease in glutamatergic afferent pathways to NAS, as it has been postulated for hippocampus glutamate projections to NAS [see 36]. It has been recently postulated that a NMDA glutamatergic hypofunction may be considered as a suitable convergence point aiming to explain symptoms and even progression of schizophrenia [81]. A convergent number of evidences appear to show today a coincident pathophysiology for the NMDA-schizophrenia relation, suggesting a decrease in glutamatergic tone and leading to NMDA antagonist models mimicking schizophrenia [82–85]. This decrease appears to be expected within NAS [9]. A failure could be acting also postsynaptically. Recent findings coming from molecular biology showed that NMDA receptor encephalitis may originate a symptomatic schizophrenic psychosis [see 51]. Furthermore, recent genetic findings give additional support to this idea, suggesting a NMDA hypofunction [87–89]. Aberrant genes have been proposed as genetic disorders underlying NMDA receptor formation [90]. If something could be said of our lines along these years, it is that they contributed to this convergence using translational models.

Therapeutic approaches derived from gluatamate theory

Some therapeutic approaches have been developed starting from early evidences. As previously said, on 1998, we proposed that glutamate is related to the initial schizophrenic dysfunctions, and not dopamine, since dopaminergic stimulation had no effect on visual cognitive tasks as translational models [38]. We suggested that dopaminergic transmission management could be linked to therapeutic effects, but not to the initial pathophysiology of schizophrenic illness [38]. Even more, the dopaminergic D-2 like antagonists used partially improved cognition in the proposed model [39]. An interaction between dopaminergtic and glutamatergic transmission has been postulated within striatum, and dopaminergic transmission has an inhibitory role on glutamate excitatory action on striatal neurons [see 50]. In this way, in our translational model, we found that interference in glutamate transmission within NAS led to perceptual tasks disruption (Fig. 6) [35,38,39]. D-2 antagonists, that block the inhibitory effect of dopamine on striatal glutamate terminals, partially improved cognition decreasing correcting trials in a clear manner (Fig. 6) [29], inhibiting an inhibitory effect. By the opposite way, the autoreceptor glutamate blockade led to a clear improvement in the task, producing a significant increase in the percent of correct trials, and a significant decrease of the correcting trials (Fig. 6) [39].

We have here displayed a translational approach. It was an experimental, acute decrease in glutamatergic tone using NMDA antagonists. This decrease could be emulating the illness condition, which could be considered a presynaptic dysfunction. It could be the case of a chronic lowered glutamatergic tone due to failure in

glutamatergic projections, such as those coming from hippocampus [see 36]. But it could be also a dysfunction of the postsynaptic site, due to a failure of NMDA receptors (see previously).

Other basic and clinical approaches

Aiming to suggest some future development of lines, a brief analysis could be drawn. A significant effect has been reported modifying NMDA allosteric sites states. It has been postulated that NMDA receptor activity could be improved or at least partially restored by a pharmacological manipulation of the glycine site of the NMDA receptor [91,92]. It is coherent with the idea that an optimization of the NMDA glutamate transmission appears to improve schizophrenic patients. A decrease in NMDA function antagonizing this receptor leads to cognitive dysfunctions [35,38,39] and an increase or facilitation of the activity of this receptor within NAS leads to an optimization of a cognitive task [39].

A special attention should be paid to the question of the metabotropic auto-receptor, the mGLU 2/3 receptor. These findings are opposed to our experimental evidences, and we consider that the interpretation of experiments realized in this way may be conditioned or questioned. A basic approach proposed that stimulation of this receptor could have an antipsychotic effect based in the decrease of the locomotion induced in rats by phencyclidine [93]. In this experimental translational approach, stimulation of the auto-receptor should be enhancing the glutamatergic blockade, decreasing the cortical overactivity, but also decreasing the NAS glutamatergic activity. Last condition is postulated by all our evidences as the pathophysiological basis of schizophrenia. Taking it into account, the resultant effect in the commented experiment, a decrease in the locomotor activity previously induced by phencyclidine, cannot be strictly and univocally considered as a psychosis reversion [93]. Furthermore, the glutamatergic blockade, due to the previous phencyclidine administration, and the additional decrease of glutamate release due to the auto-receptor stimulation could be considered as a convergent action against glutamatergic transmission. The same may be obtained with high doses of ketamine. It must be noted that the decrease in locomotor activity is classically considered as a sign of sedation in the rat models [94]. Synergistic potentiation by two different ways (glutamate antagonist plus glutamate release interference) could be exerting the same blocking mechanism. It could lead to sedation and, even, anesthesia (ketamine), but not strictly or necessary to an antipsychotic effect.

Following with this idea, it has been reported that the target of mGLU 2/3 receptor stimulation is blocking glutamatergic firing of secondary but not primary glutamatergic neurons involved in this circuitries [95]. The primary neuron hypofunction in schizophrenia could be increased by this treatment. In our translational experimental schedules, we obtained a clear improvement in the performance of cognitive tasks using an antagonist of the auto-receptor, in an inverse strategy than here mentioned [39]. In the basic [93] and clinical [96] studies, agonists of mGLU 2/3 receptor could be counteracting secondary cortex activation. This cortical activation is a phenomenon that we have observed in frontal cortex using NMDA antagonists within NAS [42], as a consequence. The primary fact is the NAS glutamate blockade that we experimentally used. The secondary event is the cortical activation.

The clinical approaches based on mGlu 2/3 receptor stimulation may be also questioned. A study represented an attempt to use a glutamate mGLU 2/3 receptor agonist as a therapeutic tool in schizophrenia [96]. This study could be matter of discussion in some points. When positive symptoms were studied, it must be considered that the used drug was compared versus olanzapine. Even when atypical antipsychotics have been considered an interesting tool for cognitive problems in schizophrenia [97], it could better to try in the acute state a comparison with some recognized incisive neuroleptics, such as trifluoperazine [98,99] or haloperidol [100]. Some atypical antipsychotic drugs, directed to serotonin 5HT-2A receptors have demonstrated to have not efficacy, or to have at least an inferior efficacy when the comparison was made with a classic antipsychotic like haloperidol [71,101,102]. It indicates the convenience of a comparison with incisive classical antipsychotics. Furthermore, a new study using mGlu2/3 agonists reported failure versus placebo in efficacy, but also no results were obtained here with olanzapine, an established antipsychotic drug [103]. And even more, it has been reported in a small group of patients that they worsened after 3 months of mGlu 2/3 receptor agonists [see 72], as it may be expected because of the blockade of striatal glutamate release.

In the same clinical study [96], the postulation of an improvement of negative symptoms may be considered in detail. First of all, it is very difficult to expect an important reversion of this kind of symptoms by definition. Schizophrenia is classically considered as a psychosis with defect states related to brain structural changes, and no clear improvements were obtained with drugs in the present state of the art [32,33]. Second, improvement of secondary symptoms may be confounded here with an antidepressant-like effect. Ketamine acts antagonizing NMDA glutamate receptors and appears to have antidepressant effects [105,106]. It could be expected that a similar phenomenon of this antidepressant-like effect could be induced here. If instead of the Ketamine NMDA glutamate blockade, the auto-receptor is stimulated and glutamate release acutely decreased by this stimulation, it could be acting in the same way, acutely decreasing the glutamate tone. Ketamine produces a clear antidepressant effect in basic [106] and clinical approaches [105], and here the stimulation of the auto-receptor could be mimicking a NMDA blockade. Thus, auto-receptor stimulation cannot be strictly considered as a specific treatment for schizophrenic negative symptoms, and may be related to an antidepressant-like effect.

Final conclusion

Even recognizing some successful applications [91,92], our results and today recent evidences [81,86,95] lead to the idea that at the present, results of these lines should be mainly considered in the way of a comprehensive approach to schizophrenia pathophysiology, but not, at least today, to a direct and current therapeutic application of the present knowledge. There is an important number of studies in progress [see 82], and they could lead to a successful clinical use of glutamate based treatments.

Conflict of interest

There is no known conflict of interest associated with this publication.

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