For the past half-century or so, the US Food and Drug Administration (FDA) has licensed drugs for use in schizophrenia only if they reduced the positive symptoms of psychosis. This limitation was identified as a bottleneck preventing the identification and development of novel treatments for the problems experienced by schizophrenia patients. Implicitly, the FDA operated from the assumption that one must treat the entire disorder with one compound, rather than treat specific clinical problems with specific compounds. It has become widely accepted that a cluster of cognitive deficits—which have been long recognized as being important aspects of schizophrenia—are not treated adequately, if at all, by existing antipsychotic treatments. Furthermore, evidence has accumulated that these cognitive deficits are largely responsible for the disappointingly poor functional outcome demonstrated...
by antipsychotic-treated patients with schizophrenia. Thus, despite the fact that many antipsychotic treatments have been identified and licensed, the cognitive deficits remain as clinical problems in schizophrenia, and most patients cannot work.

The MATRICS program

MATRICS: moving beyond antipsychotics

In response to the identification of the bottleneck limiting the development of treatments specifically directed at the cognitive deficits in schizophrenia, the US National Institute of Mental Health (NIMH) developed the Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program. MATRICS set out to develop a broad consensus regarding the nature of the cognitive impairments in schizophrenia and how they might best be assessed and treated. The MATRICS approach to the problem is to treat cognitive deficits and psychotic symptoms separately. The NIMH awarded the MATRICS contract to the University of California Los Angeles (UCLA) (Drs Stephen Marder and Michael Green, Co-principal Investigators) in 2002. Over the subsequent 2 years, MATRICS gathered the relevant stakeholders in both industry and academia to achieve a consensus and establish a clear path that would enable the FDA to consider registering compounds intended to treat cognitive deficits in schizophrenia, independently of treating psychosis per se. The typical anticipated use of such compounds would be as cotreatments in schizophrenia patients who were already treated with antipsychotic medications. Hence, the assumption has been that these patients would be relatively free of the positive symptoms of schizophrenia that might complicate the assessment of cognitive deficits and impede the ability of patients to benefit from cognitive enhancers.

The MATRICS consensus process

MATRICS consisted of a series of conferences organized by corresponding committees of experts. The first step was taken by the MATRICS Neurocognition Committee, which organized a 2-day consensus meeting in April 2003 in order to identify the critical domains of cognitive deficits that characterize patients with schizophrenia. The seven domains of cognition deemed most relevant in schizophrenia were: working memory; attention/vigilance; verbal learning and memory; visual learning and memory; speed of processing; reasoning and problem-solving; and social cognition. At the second MATRICS meeting, held at the National Institutes of Health (NIH) in June of 2003, the Neuropharmacology Committee assembled clinicians and psychopharmacologists from academia and industry to identify the most intriguing molecular targets, promising compounds, relevant human test measures, and potentially predictive animal models for use in the discovery of treatments that target basic mechanisms related to complex cognitive operations. The presentations at that meeting were gathered in a special issue of *Psychopharmacology*. A third MATRICS conference then used the consensus process developed by RAND Health to develop recommendations for the appropriate cognitive tests to be used in clinical assessments of potential cognitive enhancers. The meeting resulted in a beta version of the MATRICS Consensus Cognitive Battery for Clinical Trials, which is listed on the MATRICS Web site. The next MATRICS meeting was held at the NIH in January 2004 and focused on collaborations between the NIMH and industry. The fifth MATRICS conference involved a joint meeting between the FDA and the NIMH, and addressed the processes needed for assessment of cognition as an end point in clinical trials. This meeting was held at the NIH in April 2004 and was summarized in Buchanan et al. Once the primary consensus-building goals of MATRICS were accomplished, a concluding meeting called “New Approaches to Assessing and Improving Cognition in Schizophrenia” was held in Potomac, Md, in September 2004. This meeting was designed to look ahead in order develop a research agenda that would foster improved methods for the discovery, validation, and assessment of procognitive cotreatments for schizophrenia (for transcripts of the presentations, see the MATRICS Web site). The proceedings of this last MATRICS conference were summarized in a special issue of *Schizophrenia Bulletin*. Throughout the 2-year process, the MATRICS conferences included participants from the NIMH, the NIH, and the FDA, as well as academic and industry representatives, and were very effective in establishing a broad consensus regarding the appropriate criteria and opportunities for discovering and evaluating cotreatments for the cognitive impairments in schizophrenia.
Sensorimotor gating measures in schizophrenia

Gating deficits in schizophrenia

Measures of sensory or sensorimotor gating are among the most widely studied physiological markers used in laboratory studies of schizophrenia. For example, the auditory “sensory gating” paradigm pioneered by Freedman’s group involves a condition-test, paired-stimulus paradigm in which the P50 event-related potential (ERP) elicited by the second of two audible clicks is normally reduced relative to the ERP elicited by the first click. In schizophrenia patients, however, this suppression of the P50 is diminished, apparently due to a reduction in short-term habituation. An analogous paradigm has been developed for use in rodents. This cross-species ERP paradigm has been critical in the identification of the α7-nicotinic receptor as a potential target for procognitive cotreatments in schizophrenia.

Another cross-species gating paradigm, prepulse inhibition of startle (PPI) is the focus of this review and differs qualitatively from the P50 ERP paradigm. Since it involves both sensory stimuli and motor responses, PPI is considered a measure of “sensorimotor gating” rather than sensory gating. In PPI, the startle response elicited by a strong sudden stimulus, usually acoustic or tactile, is measured in the presence or absence of a weak prepulse stimulus, which may be in the same or a different modality. The weak prepulse robustly inhibits the response to the subsequent startling stimulus. In contrast to P50 suppression, PPI is clearly not a form of habituation. In humans, startle is usually assessed via the eyeblink component of startle, using electromyography. In animals, the whole-body flinch aspect of the startle response is quantified using an accelerometer that is sensitive to dynamic movements.

As was first noted by Braff and colleagues in 1978 and confirmed in many subsequent reports, PPI is reduced in schizophrenia patients. The early demonstrations of PPI deficits in schizophrenia were based on groups of patients who were, for the most part, treated with first-generation or so-called typical antipsychotic drugs. More recent studies have demonstrated similar deficits even in first-break patients who had never been treated with any antipsychotics. Thus, deficient PPI in schizophrenia is not attributable to medications or the course of illness, but it is also not reversed by first-generation antipsychotic treatments.

Sensorimotor gating deficits in psychiatric disorders

Studies of PPI as an operational measure of sensorimotor gating were originally intended to test the general theory that failures of inhibitory filtering mechanisms can lead to sensory overload and consequent cognitive fragmentation in schizophrenia. Nevertheless, subsequent research has demonstrated that PPI is reduced not only in schizophrenia, but also in patients suffering from a variety of neuropsychiatric disorders characterized by deficits in the gating of motor, sensory, and/or cognitive information. Thus, PPI deficits have also been found in obsessive-compulsive disorder (OCD), Tourette’s syndrome, Huntington’s disease, panic disorder, and manic patients with bipolar disorder. These disorders are all characterized by PPI deficits and abnormalities of gating in sensory, motor, or cognitive domains. It should also be noted, however, that deficient PPI is not found in several other psychiatric disorders.

Antipsychotic effects on PPI in animals

PPI models in rodents

The cross-species nature of startle and PPI enables the use of animal models of induced deficits that are extremely similar to the gating deficits seen in schizophrenia. Beginning with the initial demonstrations of the ability of dopamine agonists to disrupt PPI in rats, the rodent PPI models have evolved into at least four distinct models. These models have PPI measures in common, but are differentiated by the manipulations used to disrupt PPI: (i) psychostimulant dopamine agonists; (ii) hallucinogenic serotonin agonists; (iii) psychotomimetic N-methyl-d-aspartate (NMDA) receptor antagonists; and (iv) developmental manipulations, such as isolation rearing or neonatal lesions of the ventral hippocampus. The first three models are based on changes induced by acutely administered psychotomimetic drugs. While pharmacological approaches that alter PPI help identify relevant neural substrates, they do not assess environmental or developmental contributions to PPI deficits. In contrast, the fourth PPI model is based on the loss of PPI in adult rats subsequent to social isolation during development. Although this isolation rearing model has proven to be of value in testing antipsychotic treatments, only the dopamine and NMDA models are particularly relevant for the present discussion.
The dopamine PPI model

As reviewed in detail elsewhere, PPI disruptions that mimic those seen in schizophrenia were first produced in animals by the administration of direct or indirect dopamine agonists, such as apomorphine or d-amphetamine. The original dopamine model focused primarily on testing the ability of antipsychotic drugs to block the PPI-disruptive effects of apomorphine in rats. In brief, these effects of apomorphine in rats are reliably prevented by virtually all antipsychotics that have appreciable affinity for dopamine D2 receptors. There is an excellent correlation between the clinical potency of an antipsychotic and its ability to block the PPI-disruptive effects of the dopamine agonist apomorphine in rats. Although this finding provides important validation of the predictive validity of the dopamine PPI model, it primarily reflects the importance of D2 receptor antagonism in antipsychotic drug action and therefore only recapitulates in a behavioral paradigm what was already known from simple ligand-binding assays. Thus, the dopamine agonist PPI model is an example of what might be termed “receptor tautology,” insofar as the receptor mechanism of the agonist used to induce the schizophrenia-like PPI deficit predicts the antagonists that the behavioral test will identify. The serotonin agonist PPI model suffers from the same logical limitation; PPI disruptions by hallucinogenic serotonin agonists largely provide only a model to identify antagonists at the serotonin (5-hydroxytryptamine) 5-HT2A receptor because that is the receptor upon which the agonists act. While such information may well be germane to the actions of most second-generation antipsychotics, such agonist-induced phenomena lead to circular models that are not likely to lead to the identification of novel mechanisms or treatments.

The NMDA antagonist PPI model

The rodent PPI model that shows the greatest potential to provide insight into the unique effects of second- rather than first-generation antipsychotics is the NMDA antagonist model. As reviewed elsewhere, both competitive and noncompetitive NMDA antagonists (eg, phencyclidine, dizocilpine, and ketamine) produce robust deficits in PPI in rats, mice, or infra-human primates. Many studies of the effects of antipsychotics on the PPI-disruptive effects of NMDA antagonists have confirmed that first-generation antipsychotics such as haloperidol do not attenuate the PPI-disruptive effects of NMDA antagonists in rats. Similarly, the effects of NMDA antagonists on PPI are maintained in mice treated with dopamine antagonists or in mutant mice lacking specific subtypes of dopamine receptors. In contrast, clozapine and some other second-generation antipsychotics have been demonstrated to reduce the disruption in PPI produced by NMDA antagonists in both rats and mice. This interaction between clozapine and NMDA antagonists is seen only with a limited range of doses and has been confirmed in many, but not all, studies in rats. Complementing the studies in rodents, clozapine has been demonstrated to attenuate the effects of phencyclidine on PPI in monkeys, while haloperidol was ineffective. These results in experimental animals are consistent with the observations in humans that the psychotic symptoms produced by NMDA antagonists are not reduced by typical antipsychotics but are blocked by clozapine. Such findings led to the suggestion that the phencyclidine-PPI model might enable the specific identification of atypical rather than typical antipsychotic treatments. The interactions between second-generation antipsychotics and NMDA antagonists with regard to their effects on PPI are not likely to be mediated by competition for a common receptor, because these antipsychotics do not have appreciable affinity for NMDA receptors. Rather, the reductions in NMDA antagonist-induced PPI deficits following clozapine-like antipsychotics likely reflect interactions within the complex forebrain circuitry that modulates PPI. Thus, the NMDA antagonist PPI model does not appear to be another instance of receptor tautology and may, therefore, provide a pathway to identification of novel molecular targets for treatments of schizophrenia.

PPI in the post-MATRICS era

By virtue of the MATRICS program, the new focus of drug discovery in schizophrenia is on the identification of potential procognitive cotreatments. In contrast, the work discussed above addressed the effects of antipsychotic treatments on PPI in animal models. In the post-MATRICS era, the question arises as to the possible utility of PPI models in the discovery process for procognitive cotreatments. The previous work in rodents indicated that the dopamine PPI model is reliably predictive of existing antipsychotics, while the NMDA PPI model is insensitive to first-generation antipsychotics, but
responsive to clozapine and some other second-generation compounds. Since the anticipated application is for cotreatments to be used in patients already stably treated with antipsychotic drugs, any animal model that is responsive to first-generation antipsychotics is likely to be uninformative. Given that the patients will already be treated with antipsychotics having antagonist actions at dopamine D$_2$ receptors, dopamine agonist models are inappropriate. In contrast, the PPI models based on the effects of NMDA antagonists may be of considerable value in this context.

**Antipsychotic effects on PPI and cognition in patients**

The fundamental difficulty in evaluating the potential applicability of any animal model for the prediction of procognitive agents in schizophrenia is the absence of any established positive control compound. That is, in the absence of any path to registration of procognitive treatments that do not also treat positive symptoms of schizophrenia, virtually no studies have been done in this specific area. What we do have some information about, however, are comparisons of different classes of antipsychotic drugs on both cognition and PPI in patients with schizophrenia. As summarized recently by Hagan and Jones,$^{35}$ it is clear that first-generation antipsychotics, which are principally dopamine D$_2$ antagonists, have no beneficial effects on cognition. Similarly, as evident from the many early demonstrations of deficient PPI in antipsychotic-treated patients, first-generation compounds do not normalize PPI in schizophrenia.$^{21,36}$ With respect to second-generation antipsychotics, and in particular clozapine, the evidence is less clear, but indicates that clozapine and some other multireceptor antagonist antipsychotics may have some salutary influences on cognition$^{37}$ and appear to be associated with relatively normal PPI.$^{38}$ Of particular interest in this regard is a cross-sectional study indicating that clozapine treatment, relative to typical antipsychotic treatments, is associated with reduced PPI deficits in patients with schizophrenia.$^{38}$ While the evidence indicating that second-generation antipsychotics, especially clozapine, may ameliorate PPI deficits in schizophrenia is based largely on cross-sectional studies,$^{35,38}$ some longitudinal studies are now suggesting that PPI deficits may be reversed in groups of schizophrenia patients treated primarily with second-generation compounds.$^{39}$ Although much more work is needed to clarify the effects of newer antipsychotics on both cognitive and PPI deficits in schizophrenia, it is clear that first-generation antipsychotics fail to normalize either class of deficits.

**NMDA antagonist effects**

The original suggestion that glutamatergic systems may contribute to symptoms of schizophrenia derived from the observation that NMDA receptor antagonists, such as phencyclidine or ketamine, produce psychotic symptoms that resemble those seen in schizophrenia.$^{26,40,41}$ In contrast to effects produced by dopamine agonists such as amphetamine, which primarily resemble only the positive symptoms of schizophrenia, the effects of NMDA antagonists have been suggested to mimic the positive, negative, and cognitive symptoms of schizophrenia.$^{38,40,42}$ Further, administration of the NMDA receptor antagonist ketamine to schizophrenia patients exacerbates both psychotic symptoms and cognitive impairments.$^{38}$ With respect to the cognitive deficits, it appears that, within groups of schizophrenia patients, the most robust correlates of the deficits in PPI are abnormalities in distractibility$^{43}$ and thought disorder.$^{44}$ As noted above, the PPI-disruptive effects of NMDA antagonists in rats and mice are clearly insensitive to most first-generation antipsychotic treatments, but are attenuated by clozapine and some other second-generation antipsychotics.$^{21,29}$ Similarly, the psychotomimetic effects of ketamine in humans are insensitive to first-generation antipsychotics such as haloperidol, but are reduced in patients treated with clozapine.$^{31,32}$ Hence, the rodent model based on the disruption of PPI produced by NMDA antagonists may reveal information that is specifically relevant to the responsiveness of some neuroleptic-resistant patients to second-generation antipsychotics such as clozapine.

**Conclusions**

The NIMH-funded MATRICS program has ushered in a new era in the development of treatments for cognitive deficits in schizophrenia, independently of treating psychotic symptoms. Compounds to be used as cotreatments in schizophrenia patients already treated with antipsychotic drugs may now be registered. Animal models having predictive validity for identifying existing antipsychotics, including first-generation compounds, would not appear to be useful here; these drugs do not ameliorate the cognitive deficits in schizophrenia and most patients...
will already be treated with them. Although PPI cannot be considered to be a cognitive process per se, abnormalities in preattentive information processing may be predictive of or even lead to complex cognitive deficits. Rodent models mimicking the deficits in PPI seen in schizophrenia, bipolar mania, and other disorders are used to identify antipsychotics. Indeed, both first- and second-generation antipsychotics reliably block the PPI deficits induced by dopamine agonists. Hence, the dopamine agonist PPI model is not useful in identifying cognitive enhancers of relevance to schizophrenia. In contrast, the PPI deficits caused by NMDA antagonists, like the exacerbation of symptoms they produce in patients, are insensitive to first-generation antipsychotics, but are attenuated by clozapine. Similarly, PPI deficits in schizophrenia patients, like cognitive deficits, are not reversed by first-generation antipsychotics, but may be attenuated by clozapine. Hence, treatment-induced reversals of deficits in PPI produced by NMDA antagonists may provide animal, and human, models to aid in the discovery of treatments of cognitive deficits in patients already treated with existing antipsychotics. Given the absence of positive control compounds having known efficacy in the treatment of cognitive deficits in schizophrenia or bipolar disorder, especially when used as cotreatments with existing antipsychotics, it is premature to establish the predictive validity of related animal models. Nevertheless, the NMDA antagonist PPI model may have heuristic value in this context due to its construct validity related to cognitive deficits in attention and information processing.

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¿Son útiles las mediciones de la selección de impulsos sensomotores a través de las especies para el descubrimiento de coterapias procognitivas en la esquizofrenia?

La inhibición del alerta preestímulo (IAP), una medida de la selección de impulsos sensomotores utilizada para identificar los antipsicóticos, está reducida en los pacientes esquizofrénicos y en roedores tratados con agonistas de dopamina o antagonistas de glutamato. El programa MATRICS (Measurement And Treatment Research to Improve Cognition in Schizophrenia) financiado por el Instituto Nacional de Salud Mental (NIMH) ha iniciado una nueva era en el desarrollo de las coterapias procognitivas en la esquizofrenia, independiente del tratamiento de los síntomas positivos. Aunque la IAP no es un proceso cognitivo per se, tales anormalidades en la atención pueden ser predictoras de o conducir a déficits cognitivos. Ya que los antipsicóticos de primera generación bloquean los déficits de la IAP inducidos por agonistas de dopamina, este modelo no puede identificar reforzadores cognitivos para su empleo como coterapias con antipsicóticos. Tanto los déficits de IAP provocados por antagonistas de glutamato, como la exacerbación de síntomas que ellos producen en los pacientes, son insensibles a los antagonistas de dopamina, pero se reducen con clozapina. Del mismo modo, la IAP y los déficits cognitivos de los pacientes esquizofrénicos son insensibles a los antipsicóticos de primera generación, pero son atenuados por clozapina. En consecuencia, la reversión de los efectos de antagonistas de glutamato inducida por el tratamiento sobre la IAP puede proveer modelos animales y humanos para identificar terapias para los déficits cognitivos en los pacientes que ya han sido tratados con antipsicóticos existentes.

Les mesures interespèces de modulation des afférences sensorimotrices sont-elles utiles pour la découverte des coterapiest procognitifs dans la schizophrénie ?

L’inhibition du sursaut par prépulse (IPP), un outil de mesure de modulation des afférences sensorimotrices, utilisé pour identifier les antipsychotiques, est diminuée chez les patients schizophrènes et les rongeurs traités par des agonistes dopaminergiques ou des antagonistes du glutamate. Le programme MATRICS (Measurement And Treatment Research to Improve Cognition in Schizophrenia) financé par le NIMH (National Institute of Mental Health), a inauguré une nouvelle ère dans le développement de coterapiest procognitifs dans la schizophrénie, indépendamment du traitement des symptômes positifs. Bien que l’IPP ne soit pas un processus cognitif en soi, des déficits de l’attention peuvent être prédictifs de, ou mener à des déficits cognitifs. Les antipsychotiques de première génération bloquent les déficits d’IPP induits par les dopaminergiques, ce modèle ne reconnaît pas les stimulateurs de la cognition comme traitements associés aux antipsychotiques. Les déficits d’IPP induits par les antagonistes du glutamate, comme l’exacerbation des symptômes qu’ils provoquent chez les patients, ne sont pas sensibles aux antagonistes de la dopamine mais sont diminués par la clozapine. De façon identique, l’IPP et les déficits cognitifs chez les patients schizophrènes ne sont pas sensibles aux antipsychotiques de première génération mais sont diminués par la clozapine. Par conséquent, des inversions des effets antagonistes du glutamate sur l’IPP induites par un traitement peuvent constituer des modèles animaux et humains pour identifier des traitements des déficits cognitifs chez les patients déjà traités avec des antipsychotiques existants.

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