THIS IS THE THIRD WHITE PAPER IN A SERIES OF 3 ON COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA.

White Paper 1 | Cognitive Impairment in Schizophrenia: Understanding Prevalence, Magnitude, and Scope
White Paper 2 | Cognitive Impairment and Poor Functional Outcomes in Schizophrenia
White Paper 3 | Cognitive Impairment in Schizophrenia: Understanding the Neurobiology and Its Implications for Future Management

SUPPLEMENT TO Current PSYCHIATRY

Cognitive Impairment in Schizophrenia:
Understanding the Neurobiology and Its Implications for Future Management

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Three panels of experts in the field of schizophrenia were convened in May and June 2014 in Chicago, Los Angeles, and New York by FORUM Pharmaceuticals to discuss the current state of knowledge and practice around cognitive impairment in schizophrenia, including the prevalence, magnitude, and scope of this disorder; its impact on patient outcomes and functioning; and the neurobiology behind it. This is the third paper in a series of 3 papers that were derived, in large part, from the proceedings of those meetings.

"Given the high rates of disability seen with schizophrenia, it is important for clinicians to have some conceptualization of the theorized neurobiology of this disorder."

— Seth Cohen, M.D., Puget Sound Psychopharmacology Service, Seattle, Washington

In spite of the widespread use of antipsychotics, rates of recovery in schizophrenia remain as low as 1% to 2% per year.[1] Two-thirds of patients with schizophrenia never marry, less than 15% hold competitive employment, and 20% are homeless at any given time.[2-4] Moreover, the World Health Organization has ranked schizophrenia as the third most disabling illness, globally, among adolescents and young to middle-aged adults.[5]

What is behind the dismal functional outcomes in this population?

The answer that has emerged from dozens of studies over the past 2 decades resurrects what used to be a key tenet in the description of schizophrenia: cognitive impairment.[2,6-8]

Cognition, defined as the ability to plan, attend to stimuli, filter out irrelevant stimuli, remember new information, engage in social interactions, and perform many other higher-order thought processes, is critical to successfully navigating the world.[9] Yet, an estimated 98% of patients with schizophrenia exhibit cognitive impairment, as demonstrated when their neurocognitive scores are compared with those predicted by maternal education levels.[10] Further, it has been well established that cognitive deficits in schizophrenia are predictive of patient functioning.[7,11-14] *(To learn more about the ties between cognition and function, please see the second paper in this series.)*

98% of patients with schizophrenia exhibit cognitive impairment.[10]

Cognitive deficits are associated with dysfunction in many brain pathways and regions, including the basal ganglia; the frontal cortex; the auditory and parietal cortexes; the magnocellular visual system (which is involved in attention capture and rapidly conducting low-resolution visual information, eg, the occurrence of motion, to the cortex); and the limbic system, including the hippocampus **(Figure 1)**.[15-24]

Postmortem neuroimaging studies reveal decreased gray matter, white matter, and whole brain volume—as well as a reciprocal increase in ventricular volume—in patients both with recent-onset and with chronic schizophrenia.[25] Further, these analyses have uncovered evidence that suggests disrupted or altered synaptic connectivity, such as that seen in the systems that may affect cognition—for example, the glutamatergic, gamma-aminobutyric acid–ergic (GABAergic), and acetylcholinergic systems.[19,26]

A Closer Look at the Neurobiology of Cognitive Impairment in Schizophrenia

"Understanding the neurobiology associated with specific symptom domains in schizophrenia allows us to target therapeutic interventions that may address these symptoms at the molecular level."

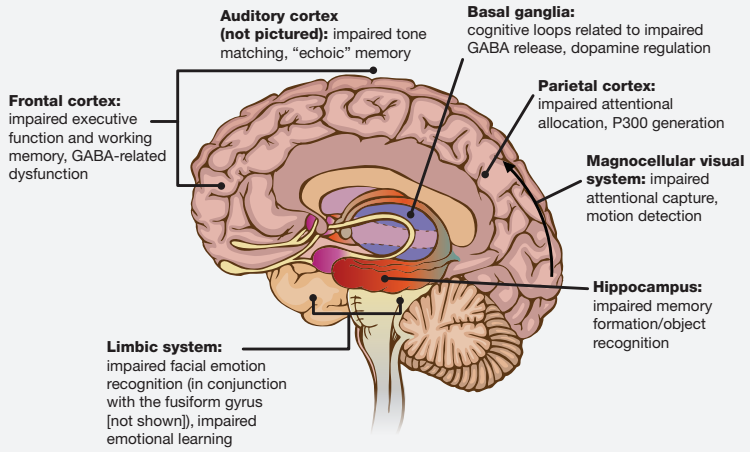
— Anissa Abi-Dargham, M.D., Columbia University Medical Center; Columbia University and New York State Psychiatric Institute, New York, New York

The 3 areas currently receiving the greatest interest in cognitive impairment in schizophrenia are those involved in the dopaminergic, glutamatergic, and cholinergic systems **(Figure 2)**.[27] Abnormalities in these pathways have been implicated in the pathophysiology of schizophrenia, with evidence supporting their role in cognitive function.[27-29]

THE MOST FAMILIAR PIECE OF THE NEUROBIOLOGICAL PUZZLE IN SCHIZOPHRENIA: THE DOPAMINE SYSTEM

Data from studies of patients with schizophrenia have demonstrated elevated levels of dopamine in the cortical region, with modest increases seen in presynaptic and striatal D_2 receptors.[28] In the prefrontal cortex, dopaminergic transmission is

Figure 1. Areas Implicated in Neurocognitive Dysfunction in Schizophrenia[15-24,30-34]



GABA, gamma-aminobutyric acid.

Figure 2. MATRICS: Potential Mechanistic Targets for Treatment of Cognitive Impairment in Schizophrenia[35]

CHOLINERGIC
- α7 Receptor
- Muscarinic M1 mAChR

DOPAMINERGIC
- Dopamine D_1 receptor

GLUTAMATERGIC
- AMPA glutamatergic receptor
- NMDA glutamatergic receptor
- Metabotropic glutamate receptor
- Glycine reuptake

OTHER
- α2 Adrenergic receptor
- $GABA_A$ R subtype

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, gamma-aminobutyric acid; mAChR, muscarinic acetylcholine receptor; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; NMDA, *N*-methyl-D-aspartate.

mediated primarily by D_1 receptors; therefore, given the substantial role that the prefrontal cortex plays in cognition, it has been suggested that D_1 receptor dysfunction may mediate some cognitive impairments and negative symptoms.[28]

These observations support findings that currently approved antipsychotics, which have a strong affinity for D_2 receptors, reduce positive symptoms of the disease but have no effect on cognitive impairment or negative symptoms.[28,36] This was shown in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which found no significant differences in cognitive improvement in any of the treatment groups (those receiving a first-generation antipsychotic and those receiving 1 of 4 second-generation antipsychotics) after 2 months of treatment.[37]

Dopamine has proved a viable target for ameliorating positive symptoms.[38,39] However, "targeting dopamine has not adequately alleviated cognitive impairment in schizophrenia," said Anil K. Malhotra, M.D., of Hofstra North Shore-LIJ School of Medicine in Hempstead, New York, and The Zucker Hillside Hospital in Glen Oaks, New York.

> "Targeting dopamine has not adequately alleviated cognitive impairment in schizophrenia."
>
> — **Anil K. Malhotra, M.D., Hofstra North Shore-LIJ School of Medicine, Hempstead, New York; The Zucker Hillside Hospital, Glen Oaks, New York**

GROWING EVIDENCE ALSO IMPLICATES THE GLUTAMATE SYSTEM

A growing body of evidence suggests that abnormalities in glutamate transmission also contribute to the pathogenesis of schizophrenia, particularly cognitive and sensory processing deficits.[29] This theory is predicated on the fact that glutamatergic *N*-methyl-D-aspartate (NMDA) antagonists, such as phencyclidine (PCP) and ketamine, can induce psychosis and dull cognitive function, producing effects similar to the disturbances seen with schizophrenia.[32,40]

Research shows that the NMDA system plays a key role in neuroplasticity, neuronal synchronization, and synaptic connectivity. A key effect is the modulation of GABAergic input to interneurons and, ultimately, the control of pyramidal cells, which are thought to be integral to cognitive function.[19,40-43] Dysfunction can significantly disrupt interneuron-dependent network synchrony in schizophrenia, which may then lead to impaired neuroplasticity.[19,43]

This makes sense, noted Gerald Maguire, M.D., D.F.A.P.A., of the University of California, Riverside,

School of Medicine. "Although the discussion previously focused on treating anxiety in patients with schizophrenia, we have always talked about a GABAergic approach to the illness."

Accumulating research shows that the glutamatergic-mediated cognitive deficits may, in turn, be regulated by the acetylcholine (ACh) system and, specifically, by the α7 receptor.[16,44]

THE ACETYLCHOLINE SYSTEM: AN ESSENTIAL MEDIATOR OF COGNITIVE FUNCTION?

"Understanding the pathophysiology and etiology of illnesses is critical to developing a way of effectively interfering with or correcting such processes. That is true whether we are trying to stop an infection or improve cognitive function in individuals with schizophrenia."

— Sheldon Preskorn, M.D., World-Wide Psychopharmacology Consultants, Wichita, Kansas; Laureate Institute for Brain Research, Tulsa, Oklahoma

Within the central nervous system, acetylcholinergic neurotransmission is integrally involved in aspects of memory formation, affect, and motivational and volitional behaviors, all of which are impaired in schizophrenia.[16] These cognitive and behavioral functions are thought to be modulated by the α7 ACh receptor. Therefore, altered ACh neurotransmission may contribute to the cognitive and behavioral symptoms of schizophrenia.[27]

Figure 3 shows a schematic diagram of cholinergic circuits (in red) and their projections within key brain areas implicated in schizophrenia. Specifically, it depicts the potential for direct and indirect interactions of the cholinergic system with dopaminergic, glutamatergic, and GABAergic projections in these brain regions.[16] As shown, the α7 receptor appears to be involved in the modulation of neurotransmission related to cognitive function.[16,44]

α7 Receptors and Cognitive Impairment

The α7 nicotinic ACh receptor (nAChR) is an ACh-gated ion channel receptor that is abundantly expressed in the hippocampus and cortex—key brain areas involved in cognition.[45] The α7 receptor has several characteristics that distinguish it from other nAChRs (eg, α4β2), including more rapid desensitization (ie, reversible loss of functionality after an initial period of activation) and higher calcium permeability (ie, an increased capability to allow calcium to flow through the receptor).[27,45-48]

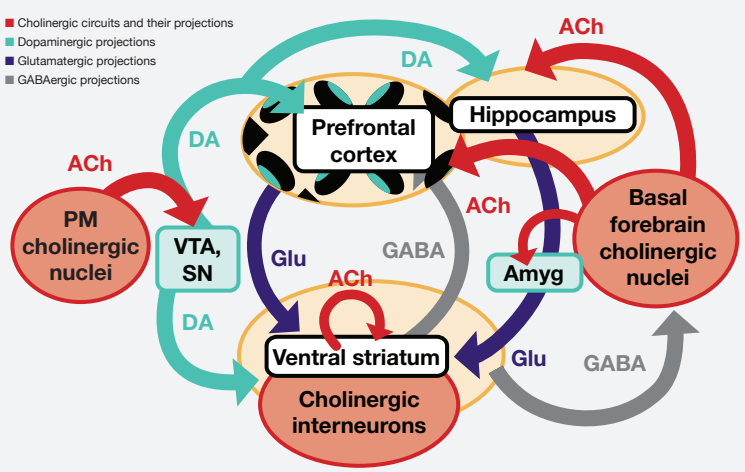
The α7 receptor is also less sensitive than α4β2 is to the agonist effects of nicotine. The observation of an increased rate of smoking in patients with schizophrenia did lead to an initial interest in nicotinic receptors. However, circulating levels of nicotine from cigarette use do not reach levels believed to be needed to stimulate α7 receptors.[49]

α7 Receptors as an Important Target in Cognitive Impairment

"We want to get a handle on cognition, and this is the path that is promising. There may be others in the future, but this is the first one that looks very promising."

— Henry A. Nasrallah, M.D., Saint Louis University School of Medicine; University Hospital, Saint Louis University, Missouri

Figure 3. Role of ACh in Schizophrenia[16]



ACh, acetylcholine; Amyg, amygdala; DA, dopamine; GABA, gamma-aminobutyric acid; Glu, glutamate; PM, pontomesencephalic; SN, substantia nigra; VTA, ventral tegmental area.

Berman JA, Talmage DA, Role LW. Cholinergic circuits and signaling in the pathophysiology of schizophrenia. *Int Rev Neurobiol*. 2007;78:193-223. Reprinted with permission from Elsevier. Copyright 2007.

The α7 receptor is thought to play a role in the cholinergic modulation of glutamate and GABA activity that is important to neuroplasticity and cognition.[44]

Research finds that stimulating α7 receptors may enhance cognition via effects on glutamate release and on NMDA-mediated prefrontal cognitive processing.[50,51] The stimulation of α7 receptors enhances glutamatergic and GABAergic transmission in both the hippocampus and the midbrain.[45,52,53] Binding of ACh to the α7 receptor induces glutamate and GABA release, as well as the release of additional ACh.[44] As previously noted, regulating the synaptic connectivity of all of these systems may potentially enhance cognition in patients with schizophrenia.[19,28,45]

Despite the seemingly essential role of this receptor, postmortem studies have demonstrated decreases in α7 receptor density in the striatum, frontal cortex, and hippocampus of patients with schizophrenia.[26] Therefore, it is not surprising that researchers postulate that the α7 receptor may be a potential target for improving cognition in schizophrenia.[45,50,51]

Given the widespread distribution of cholinergic receptors throughout so many areas of the brain that are involved in cognition, said Steven G. Potkin, M.D., of the University of California, Irvine, "targeting the α7 receptor may be a promising approach to improving many cognitive domains."

Ongoing Clinical Research

"We don't have an effective intervention for cognitive impairment yet, but we do have several promising pharmacologic targets."

— Gregory Mattingly, M.D., Washington University School of Medicine in St. Louis; Midwest Research Group, Missouri

Recognition of the need for effective treatments for cognitive impairment in schizophrenia led to the MATRICS initiative, or the Measurement and Treatment Research to Improve Cognition in Schizophrenia program. This National Institute of Mental Health (NIMH)–led collaboration between academia, industry, and government regulators established the first framework for conducting clinical trials of drugs designed to treat cognitive impairment in schizophrenia.[35,54] It also ranked the most promising neurotransmitter targets, with α7 identified as a top target **(Figure 2)**.[35]

From Brain Circuits to Impaired Functioning

The dysfunctional neurobiological processes affecting cognitive function in patients with schizophrenia can be observed in differences in mismatch negativity (MMN) between patients with schizophrenia and healthy controls.[32,55]

Mismatch negativity, a measure of early auditory processing, is a component of the event-related potential (ERP) that is sensitive to small changes in the acoustic environment, such as a tone change.[56,57] Mismatch negativity is reduced in patients with schizophrenia compared to healthy controls, reflecting a sensory processing deficit that has been connected with impairment in cognitive and social function.[32,58]

Deficits in MMN may underlie dysfunctional auditory communication by impairing speech perception, contributing to deficits in auditory short-term memory (which may make it difficult to follow conversation) and reducing a patient's ability to direct attention toward relevant stimuli.[56]

Mismatch negativity impairment in patients with schizophrenia is well established by at least 18 months into the disorder and, in patients with chronic schizophrenia, correlates with the severity of negative symptoms and functional outcomes, including such cognitive components as verbal memory deficits, executive functioning, and degree of social skills acquisition.[32,55] Typical and atypical antipsychotics have no effect on MMN deficits.[32]

Mismatch negativity depends on intact NMDA receptor signaling, with multiple studies finding that NMDA receptor antagonists such as ketamine can induce MMN deficits in animals and healthy controls.[32,57,59] Thus, therapeutic approaches that target NMDA receptors may restore full MMN, possibly improving cognitive processing and negative symptoms, and ultimately, a patient's ability to function.

It is worth noting that preliminary research supports the potential for pharmacologic-driven improvements of MMN in patients with schizophrenia.[60]

With parameters in place for clinical trials to evaluate compounds that target cognitive impairment, the pharmaceutical industry has engaged in a robust clinical investigation for potential therapies. An August 2014 search of ClinicalTrials.gov, for instance, identified more than 60 completed, terminated, or ongoing studies in this area.[61]

"Although we don't have an approved medication for treating cognitive impairment, a number of promising compounds and targets are being evaluated by industry and academia," said Stephen R. Marder, M.D., of the University of California, Los Angeles, and the Desert Pacific Mental Illness Research, Education and Clinical Center of the VA Greater Los Angeles Healthcare System.

"There are a number of different neurotransmitter receptor systems that have been implicated in both schizophrenia and cognitive function," concluded Dr Malhotra. "If we knew which one was the key, I think we would be much further along in what we're doing. However, these systems play very prominent roles, and one should not forget the ACh system when considering both schizophrenia as a whole and the neurocognitive function associated with it."

Thank you for your interest in this white paper. The other 2 papers in this series, which address the prevalence, magnitude, and scope of cognitive impairment in schizophrenia and the relationship of this impairment with functional outcomes, can be found at **www.CurrentPsychiatry.com/Cognition**.

For more information, please see www.CurrentPsychiatry.com/Cognition.

References

1. Jääskeläinen E, Juola P, Hirvonen N, et al. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull*. 2013;39(6):1296-1306.
2. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. *Schizophr Res*. 2009;110 (1-3):1-23.
3. Rosenheck R, Leslie D, Keefe R, et al; CATIE Study Investigators Group. Barriers to employment for people with schizophrenia. *Am J Psychiatry*. 2006;163(3):411-417.
4. Folsom DP, Hawthorne W, Lindamer L, et al. Prevalence and risk factors for homelessness and utilization of mental health services among 10,340 patients with serious mental illness in a large public mental health system. *Am J Psychiatry*. 2005;162(2):370-376.
5. World Health Organization. *The World Health Report 2001. Mental Health: New Understanding, New Hope*. Geneva, Switzerland: World Health Organization; 2001.
6. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry*. 1996;153(3):321-330.
7. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull*. 2000;26(1):119-136.
8. Green MF, Harvey PD. Cognition in schizophrenia: past, present, and future. *Schizophr Res Cogn*. 2014;1(1):e1-e9.
9. Sabbe B. Cognitive and motor disorders in schizophrenia. *Proc Belg Roy Acad Med*. 2012;1:77-88.
10. Keefe RS, Eesley CE, Poe MP. Defining a cognitive function decrement in schizophrenia. *Biol Psychiatry*. 2005;57(6):688-691.
11. Carrión RE, Goldberg TE, McLaughlin D, Auther AM, Correll CU, Cornblatt BA. Impact of neurocognition on social and role functioning in individuals at clinical high risk for psychosis. *Am J Psychiatry*. 2011;168(8):806-813.
12. Robinson DG, Woerner MG, McMeniman M, Mendelowitz A, Bilder RM. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2004;161(3):473-479.
13. August SM, Kiwanuka JN, McMahon RP, Gold JM. The MATRICS Consensus Cognitive Battery (MCCB): clinical and cognitive correlates. *Schizophr Res*. 2012;134(1):76-82.
14. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res*. 2004;72(1):41-51.
15. Perez-Costas E, Melendez-Ferro M, Roberts RC. Basal ganglia pathology in schizophrenia: dopamine connections and anomalies. *J Neurochem*. 2010;113(2):287-302.
16. Berman JA, Talmage DA, Role LW. Cholinergic circuits and signaling in the pathophysiology of schizophrenia. *Int Rev Neurobiol*. 2007;78:193-223.
17. Goghari VM, Sponheim SR, MacDonald AW 3rd. The functional neuroanatomy of symptom dimensions in schizophrenia: a qualitative and quantitative review of a persistent question. *Neurosci Biobehav Rev*. 2010;34(3):468-486.
18. Potkin SG, Turner JA, Brown GG, et al; FBIRN. Working memory and DLPFC inefficiency in schizophrenia: the FBIRN study. *Schizophr Bull*. 2009;35(1):19-31.
19. Gonzalez-Burgos G, Lewis DA. GABA neurons and the mechanisms of network oscillations: implications for understanding cortical dysfunction in schizophrenia. *Schizophr Bull*. 2008;34(5):944-961.
20. Oades RD, Wild-Wall N, Juran SA, Sachsse J, Oknina LB, Röpcke B. Auditory change detection in schizophrenia: sources of activity, related neuropsychological function and symptoms in patients with a first episode in adolescence, and patients 14 years after an adolescent illness-onset. *BMC Psychiatry*. 2006;6:7.
21. Fujimoto T, Okumura E, Takeuchi K, et al. Changes in event-related desynchronization and synchronization during the auditory oddball task in schizophrenia patients. *Open Neuroimag J*. 2012;6:26-36.
22. Butler PD, Javitt DC. Early-stage visual processing deficits in schizophrenia. *Curr Opin Psychiatry*. 2005;18(2):151-177.
23. Tan H, Ahmad T, Loureiro M, Zunder J, Laviolette SR. The role of cannabinoid transmission in emotional memory formation: implications for addiction and schizophrenia. *Front Psychiatry*. 2014;5:73.
24. Wiescholleck V, Manahan-Vaughan D. Persistent deficits in hippocampal synaptic plasticity accompany losses of hippocampus-dependent memory in a rodent model of psychosis. *Front Integr Neurosci*. 2013;7:12. doi:10.3389/fnint.2013.00012.

25. Meyer-Lindenberg A. From maps to mechanisms through neuroimaging of schizophrenia. *Nature*. 2010;468(7321):194-202.
26. Bencherif M, Stachowiak MK, Kucinski AJ, Lippiello PM. Alpha7 nicotinic cholinergic neuromodulation may reconcile multiple neurotransmitter hypotheses of schizophrenia. *Med Hypotheses*. 2012;78(5):594-600.
27. Jones CK, Byun N, Bubser M. Muscarinic and nicotinic acetylcholine receptor agonists and allosteric modulators for the treatment of schizophrenia. *Neuropsychopharmacology*. 2012;37(1):16-42.
28. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophr Bull*. 2009;35(3):549-562.
29. Kantrowitz J, Javitt DC. Glutamatergic transmission in schizophrenia: from basic research to clinical practice. *Curr Opin Psychiatry*. 2012;25(2):96-102.
30. Kawasaki H, Tsuchiya N, Kovach CK, et al. Processing of facial emotion in the human fusiform gyrus. *J Cogn Neurosci*. 2012;24(6):1358-1370.
31. Faria MA Jr. Violence, mental illness, and the brain—a brief history of psychosurgery: part 2—from the limbic system and cingulotomy to deep brain stimulation. *Surg Neurol Int*. 2013;4:75.
32. Javitt DC, Spencer KM, Thaker GK, Winterer G, Hajós M. Neurophysiological biomarkers for drug development in schizophrenia. *Nat Rev Drug Discov*. 2008;7(1):68-83.
33. Bartels A, Zeki S. The chronoarchitecture of the cerebral cortex. *Philos Trans R Soc Lond B Biol Sci*. 2005;360(1456):733-750.
34. Corradi-Dell'acqua C, Schwartz S, Meaux E, Hubert B, Vuilleumier P, Deruelle C. Neural responses to emotional expression information in high- and low-spatial frequency in autism: evidence for a cortical dysfunction. *Front Hum Neurosci*. 2014;8:189.
35. Marder SR. Neurocognition as a treatment target in schizophrenia. *Focus*. 2008;6(2):180-183.
36. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;36(1):71-93.
37. Keefe RS, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. *Arch Gen Psychiatry*. 2007;64(6):633-647.
38. Carpenter WT, Koenig JI. The evolution of drug development in schizophrenia: past issues and future opportunities. *Neuropsychopharmacology*. 2008;33(9):2061-2079.
39. Foster DJ, Jones CK, Conn PJ. Emerging approaches for treatment of schizophrenia: modulation of cholinergic signaling. *Discov Med*. 2012;14(79):413-420.
40. Javitt DC. Glutamatergic theories of schizophrenia. *Isr J Psychiatry Relat Sci*. 2010;47(1):4-16.
41. Homayoun H, Moghaddam B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J Neurosci*. 2007;27(43):11496-11500.
42. Tsapakis EM, Travis MJ. Glutamate and psychiatric disorders. *Adv Psychiatr Treat*. 2002;8:189-197.
43. Paoletti P, Bellone C, Zhou Q. NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat Rev Neurosci*. 2013;14(6):383-400.
44. Albuquerque EX, Pereira EF, Alkondon M, Rogers SW. Mammalian nicotinic acetylcholine receptors: from structure to function. *Physiol Rev*. 2009;89(1):73-120.
45. Coyle JT, Balu D, Benneyworth M, Basu A, Roseman A. Beyond the dopamine receptor: novel therapeutic targets for treating schizophrenia. *Dialogues Clin Neurosci*. 2010;12(3):359-382.
46. Ley CK, Kuryatov A, Wang J, Lindstrom JM. Efficient expression of functional ($\alpha6\beta2$)$2\beta3$ AChRs in xenopus oocytes from free subunits using slightly modified $\alpha6$ subunits. *PLoS One*. 2014;9(7):e103244.
47. Papke RL, Kem WR, Soti F, López-Hernández GY, Horenstein NA. Activation and desensitization of nicotinic alpha7-type acetylcholine receptors by benzylidene anabaseines and nicotine. *J Pharmacol Exp Ther*. 2009;329(2):791-807.
48. Decker ER, Dani JA. Calcium permeability of the nicotinic acetylcholine receptor: the single-channel calcium influx is significant. *J Neurosci*. 1990;10(10):3413-3420.
49. Buchanan RW, Freedman R, Javitt DC, Abi-Dargham A, Lieberman JA. Recent advances in the development of novel pharmacological agents for the treatment of cognitive impairments in schizophrenia. *Schizophr Bull*. 2007;33(5):1120-1130.
50. Konradsson-Geuken A, Gash CR, Alexander K, et al. Second-by-second analysis of alpha 7 nicotine receptor regulation of glutamate release in the prefrontal cortex of awake rats. *Synapse*. 2009;63(12):1069-1082.
51. Yang Y, Paspalas CD, Jin LE, Picciotto MR, Arnsten AF, Wang M. Nicotinic $\alpha7$ receptors enhance NMDA cognitive circuits in dorsolateral prefrontal cortex. *Proc Natl Acad Sci U S A*. 2013;110(29):12078-12083.
52. Banerjee J, Alkondon M, Pereira EF, Albuquerque EX. Regulation of GABAergic inputs to CA1 pyramidal neurons by nicotinic receptors and kynurenic acid. *J Pharmacol Exp Ther*. 2012;341(2):500-509.
53. Gray R, Rajan AS, Radcliffe KA, Yakehiro M, Dani JA. Hippocampal synaptic transmission enhanced by low concentrations of nicotine. *Nature*. 1996;383(6602):713-716.
54. Buchanan RW, Davis M, Goff D, et al. A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schizophr Bull*. 2005;31(1):5-19.
55. Rissling AJ, Makeig S, Braff DL, Light GA. Neurophysiologic markers of abnormal brain activity in schizophrenia. *Curr Psychiatry Rep*. 2010;12(6):572-578.
56. Mondragón-Maya A, Bernal-Hernández J, Yáñez-Téllez G, Rodríguez-Agudelo Y. Mismatch negativity (MMN) and schizophrenia: a revision. *Actas Esp Psiquiatr*. 2011;39(6):363-373.
57. Garrido MI, Kilner JM, Stephan KE, Friston KJ. The mismatch negativity: a review of underlying mechanisms. *Clin Neurophysiol*. 2009;120(3):453-463.
58. Gold R, Butler P, Revheim N, et al. Auditory emotion recognition impairments in schizophrenia: relationship to acoustic features and cognition. *Am J Psychiatry*. 2012;169(4):424-432.
59. Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. *Arch Gen Psychiatry*. 2000;57(12):1139-1147.
60. Preskorn SH, Gawryl M, Dgetluck N, Palfreyman M, Bauer LO, Hilt DC. Normalizing effects of EVP-6124, an alpha-7 nicotinic partial agonist, on event-related potentials and cognition: a proof of concept, randomized trial in patients with schizophrenia. *J Psychiatr Pract*. 2014;20(1):12-24.
61. Search for *cognitive impairment in schizophrenia* (Interventional Studies, NIH, U.S. Fed, Industry, Other). Clinical Trials.gov Web site. http://clinicaltrials.gov/ct2/results?term=cognitive+impairment+schizophrenia&type=Intr&fund=0123&pg=1. Accessed August 25, 2014.

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