Review Article

Measuring Memory-Prediction Errors and their Consequences in Youth at Risk for Schizophrenia

Richard SE Keefe,[1,2]*PhD*, Michael S Kraus,[3]*MA*

Abstract

The largely consistent columnar circuitry observed throughout the cortex may serve to continuously predict bottom-up activation based on invariant memories. This "memory-prediction" function is essential to efficient and accurate perception. Many of the defined cognitive deficits associated with schizophrenia suggest a breakdown of memory-prediction function. As deficits in memory-prediction function are proposed to lie more proximal to the biological causes of schizophrenia than deficits in standard cognitive constructs, tests that more directly probe memory-prediction function may be especially sensitive predictors of conversion in individuals at high-risk for schizophrenia. In this article, we review the conceptual basis for this hypothesis, and outline how it may be tested with specific cognitive paradigms. The accurate identification of cognitive processes that precede the onset of psychosis will not only be useful for clinicians to predict which young people are at greatest risk for schizophrenia, but will also help determine the neurobiology of psychosis onset, thus leading to new and effective treatments for preventing schizophrenia and other psychoses.

Ann Acad Med Singapore 2009;38:414-9

Key words: Cognition, Cortical circuitry, Psychosis, Schizophrenia, Ultra high-risk

Introduction

Despite the common experience of the world as mostly stable and meaningful, the human nervous system continuously engages with a vast array of ambiguous and constantly changing sensory signals. To organise coherent percepts from the fragmented and unstable sensory signals that constitute experience, and to allow for coordinated interaction with the world that these signals represent, the human nervous system must fill in the gaps of sensation, generalise across observations, prioritise stimuli for in-depth processing, and make immediate judgments regarding the meaning of sensory input. The memory-prediction model of cortical function posits that a uniform columnar circuitry throughout the cortex underpins a common algorithm that emphasizes the consistent aspects of experience in memory storage and uses these learned consistencies to make ongoing predictions about bottom-up stimulation across the cortical hierarchy, thus stabilising perception. A recent review suggests that impairments in memory-prediction function may constitute the primary cognitive deficit associated with schizophrenia and may underlie the development of hallucinations and delusions.[1] Here we will briefly review the memory-prediction model and argue that anatomical abnormalities and cognitive deficits associated with schizophrenia suggest widespread and early disruption of the circuitry underlying memory-prediction function. We will also propose that a series of neurocognitive tests described herein which measure these processes may exhibit strong predictive power for later onset of psychosis.

The Memory-Prediction Model of Cortical Function

Although perception has typically been viewed as the result of a bottom-up reconstruction of sensory input, perceptual processes do not simply involve the reproduction of stimuli that impinge upon the sensory receptors, but instead involve far more efficient and adaptive systems of inferring meaning by matching fragmented sensory input to a construct that serves as a working model of the world.[2] Mounting behavioural and physiological evidence suggests that a primary function of the human brain is to encode memories that emphasise the consistent aspects of experience and to use the sum of these "invariant" memories to continuously predict the next moment of experience.[1]

[1] Department of Psychiatry & Behavioral Sciences and Psychology, Duke University Medical Center, USA
[2] Adjunct Professor, Duke-University of Singapore Graduate Medical School, Singapore
[3] Department of Psychiatry and Behavioral Sciences, USA
** the first two authors contributed equally to this article and ordering was determined arbitrarily*
Address for Correspondence: Dr Richard Keefe, DUMC 3270, Durham, NC 27710, USA. Email: richard.keefe@duke.edu

Across multiple sensory systems, neuronal activity in the upper levels of the cortical hierarchy is found to reflect increasingly abstract stimulus properties and to be unaffected by minor deviations.[3-5] Similarly, throughout the cortex, cells are found to fire in anticipation of pain, visual stimulation, self-generated body movement and body movements of other people.[6-9] Continuous prediction based on invariant memories allows regularities in past experience to fill in the missing gaps of imperfect sensation and to facilitate efficient interaction with a complex and constantly changing external world.[10,11] For example, because of our past experiences with stop signs, we are not confused by deviations from the archetypal stop sign; even if the lower left corner of the sign is bent and the "OP" is obscured by a tree branch, we immediately recognise the symbol and step on the brake. Thus, memory-prediction processes are thought to bring a large degree of ease and automaticity to perception.

A recent extension of theories of cortical brain function postulates that the hierarchical structure[12] and consistent columnar architecture[13] seen throughout the cortex underlie the generation of predictive signals and the memories that guide them.[14-16] The memory-prediction model of cortical function posits that the central algorithm of the cortical column serves to form predictions of impending bottom-up activation based on patterns of activity in top-down, horizontal and thalamic loop input to the column. Roughly, these inputs to the column represent: a broad view of the current situation (top-down inputs), the previous moment of experience (thalamic loop connections) and current context (horizontal connections). Synapses from these sources that are reliably activated prior to bottom-up activation are strengthened through the Hebbian processes of "what fires together, wires together;" this strengthening constitutes memory. Eventually, these synapses are fortified sufficiently for top-down and thalamocortical loop signals to drive activity in layers 2, 3 and 5, partially activating columns prior to full activation from bottom-up signals. The overlap in particular columns of top-down activation from invariant memories (the "hypothesis" of the larger picture being experienced) and thalamocortical activation conveying specific information about the last moment of experience constitutes a prediction regarding impending bottom-up stimulation.

Figure 1 outlines the basic elements of the circuitry involved in generating predictions based on invariant memories and current context, using an area of auditory cortex that processes pitch information as an example. A familiar tune sung by an unfamiliar singer is recognisable because the memory of the song is invariant to the actual tones sung. For instance, if one has repeatedly heard Paul McCartney sing "Let it Be" in the key of C, "Let it Be" sung

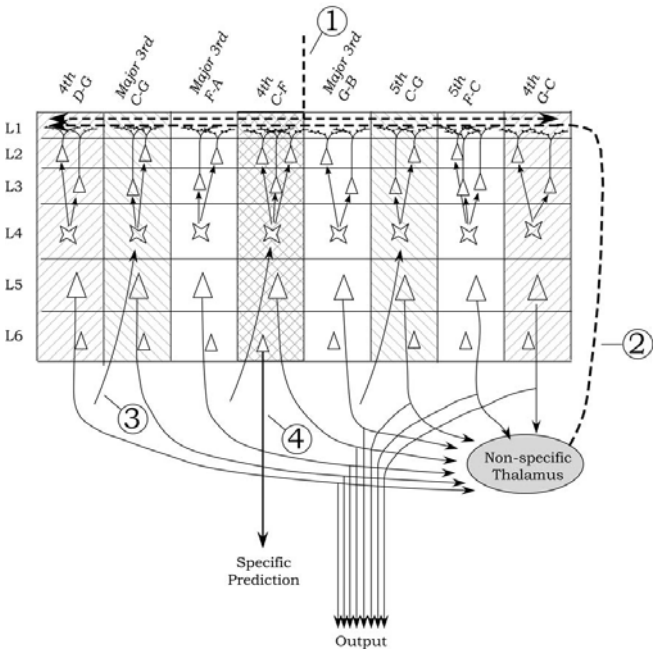

Fig. 1. Columnar circuitry underlying memory-prediction processes. Columns in this hypothetical section of auditory cortex are tuned to specific musical intervals. The circuitry in this area of cortex allows for prediction of the specific upcoming note of a familiar song, even when this song is played in a different key than previously experienced. **1.** Layer 6 cells in a higher cortical region project an invariant "hypothesis" of the identity of the song (or musical phrase) broadly throughout layer one of this area of cortex. **2.** Information regarding the last musical interval experienced is communicated broadly throughout layer 1 via thalmocortical loop input. Cells in layers 2 and 3 have extensive dendritic arbors in layer 1 and learn to anticipate the next musical interval based on the invariant hypothesis and last interval experienced. This initial prediction is invariant to the specific notes involved. Thus, in this example, all columns representing the interval of a fourth are primed (indicated by 45 degree hatch). **3.** Bottom-up input to layer 4 signals the specific current note, activating all columns with "C" as the first tone in the interval (indicated by 315 degree hatch). Processing of this information is facilitated by accurate prediction that primed this column for bottom-up stimulation. **4.** The convergence of the invariant prediction of a 4th and bottom-up signal representing the note C create a specific prediction that the next note will be an F (indicated by cross-hatch). This prediction is communicated broadly to layer 1 of the lower cortical area by the diffuse projection from the output cell in layer 6.

in the key of F by another singer will be easily identified as the same song. It is hypothesized that within the cortical hierarchy processing pitch information lies an area of cortex with columns representing specific musical intervals. This area receives a top-down "hypothesis" regarding the identity of the musical phrase that is currently being experienced. In our example, the hypothesis might roughly correspond to "the beginning of Let it Be." This area of cortex has previously learned the pattern of intervals to expect when this musical phrase is experienced (unison, unison, unison, ascending major 2nd, descending perfect 4th, ascending major 3rd, unison, ascending perfect 4th, ascending major 2nd). Therefore, columns representing these tonal

intervals are partially activated by the top-down hypothesis. Information regarding the last musical interval experienced is communicated broadly to this area of cortex by the thalmocortical loop circuit, partially activating columns corresponding to the next expected interval. The overlap at any given time of the top-down hypothesis (the "name" of the musical phrase) with the specifics of prior activation in that area (where we are within the phrase) forms a prediction. In this example, after hearing the first 7 intervals that begin the melody of "Let it Be," all columns corresponding to perfect fourths become partially activated in anticipation of bottom-up stimulation. Bottom-up stimulation indicating that a "C" was just heard arrives in layer 4. The overlap of the predicted interval with the bottom-up information regarding the specific identity of the first tone in the interval generates a prediction regarding the next specific tone, which is communicated to lower level cortical levels via layer 6 neurons. Thus, this circuitry is capable of translating invariant memories into specific predictions based on current context.

This circuitry underlying memory-prediction processes allows for the efficient use of cortical resources. If bottom-up stimulation conforms to prediction, a steady signal is transmitted to higher cortical areas indicating this compliance. If, however, bottom-up stimulation deviates significantly from prediction, the steady-state signal is halted and the details of experience are transmitted up the hierarchy via thalamocortical pathways. Because minor deviations from expectation are ignored, each cortical area tends to pigeonhole its translation of input to previously established categories of output and signals become more invariant to low level changes in stimulus properties as the cortical hierarchy is climbed. These invariant signals form the basis for the invariant memories upon which future experience is interpreted. Thus these memory-prediction processes constitute an elegant and automatic system by which familiar stimuli are efficiently processed by lower level brain regions, unexpected stimuli are flagged for more deliberate analysis by higher cortical areas and the essential elements of experience are encoded into memory.

Impaired Memory-prediction Function in Schizophrenia

At the core of schizophrenia is a series of cognitive impairments[17] that exist prior to the onset of an acute psychotic episode.[18-20] However, it remains unclear which aspects of cognitive failure are most strongly associated with the core of the psychotic illness. The surprising lack of correlation between the severity of cognitive impairment and positive symptom severity[21] brings into question current conceptualizations of cognitive impairment in schizophrenia. Furthermore, while cognitive impairment is viewed as a risk factor for schizophrenia, there is little current understanding about what aspects of cognitive dysfunction precede psychotic symptoms. We propose that a breakdown in the neural circuitry underlying the formation of invariant representations and the unfolding of predictions from these stored invariant memories places young people at very high risk for schizophrenia.

Histological examination of post-mortem brain tissue from schizophrenic individuals has revealed an abnormal cytoarchitecture throughout much of the cerebral cortex, marked by decreased neuropil, synaptic density and disarray of neuronal location, findings particularly prominent in layers II and III.[22] Cortical thinning has also been observed in prodromal patients who subsequently converted to psychosis.[23] As discussed above, layers II and III sit at a crossroads between bottom-up signaling and top-down contextual predictions and are crucial for detecting patterns in experience that later serve to shape future thought and perception. While some of these alterations appear to be present from birth (such as defects in neuronal migration), others may reflect state dependent alterations (such as changes in neuromodulatory levels).

Although such widespread disruption of cortical architecture would be expected to have wide-ranging effects on cognition, memory-prediction function may be most directly affected. Indeed, considerable evidence suggests that prediction based on invariant memories is disturbed in schizophrenia.[1] Deficits in smooth pursuit eye tracking are largely due to impairments in extra retinal predictive mechanisms used to set pursuit gain.[24-26] Strikingly, when a pursuit target changes directions unpredictably, schizophrenic patients maintain tracking better during the brief period around the change than do healthy controls.[27] Similarly, deficits in physiological responses to deviant stimuli, including MMN and P300 responses, suggest impairment of both pre-attentive and attentive systems of experience-dependent learning.[28,29]

The breakdown of memory-prediction function in schizophrenia is apparent in the difficulty individuals with schizophrenia display in interpreting suboptimal stimuli. Schizophrenia patients are impaired in their ability to identify incomplete images of common objects, suggesting a failure of top-down hypotheses to guide perceptual completion.[30,31] Similarly, schizophrenia patients are impaired in their ability to use the redundancy inherent in speech to meaningfully fill in missing gaps in a standard passage subjected to deletion of every 5th word[32] and compared to healthy controls, patients exhibit less of a decrease in the N400 peaks to semantically primed words compared to unprimed words.[33] In patients, the amplitude of the N400 to a word following a related prime correlates with positive psychotic symptoms, supporting the notion that deficits in memory-prediction underlie psychosis.

The analysis of faces is a particularly important perceptual skill and one with which individuals with schizophrenia struggle. Superficial differences between photographs of identical faces, such as lighting conditions and visual angle, more greatly hamper the ability of schizophrenia patients versus healthy controls to match a target face to a selection of 6 sample faces in the Benton task,[34-36] suggesting an abnormally greater influence of lower level visual properties compared to invariant predictions in face processing in schizophrenia. A decreased influence of invariant memory on perception of human faces is evident in the Binocular Depth Inversion Test (BDIT), in which the images presented to each eye using a stereoscope are reversed, creating a "hollow" face. While a lifetime of experience with convex faces predisposes healthy controls to invert the image, schizophrenia patients are more likely to perceive the veridical "hollow" face (Emrich 1989). Scores on this binocular depth inversion test correlate with the severity of symptoms (Schneider, Borsutzky et al 2002), indicating a more direct relationship with symptomology than more standard tests of cognition.

Use of Tests of Memory-prediction in UHR Studies

Intervention prior to the time that an individual experiences his or her first psychotic episode may offer the best chance for a positive treatment outcome.[37,38] However, while some reports have suggested that behavioural, pharmacologic or combination treatments[39,40] may reduce the risk of psychosis, this work has been hampered by the weak positive predictive value of the identification of individuals at true risk.[41] Recent work has focused on improving this predictive value by supplementing current prodromal symptom criteria for ultra high risk individuals with neurocognitive measures.[42] Among individuals who are at high-risk for psychotic disorders, those who go on to develop schizophrenia have greater cognitive impairment than those who do not develop the illness.[19,43] However, many of these cognitive assessments utilise off-the-shelf cognitive measures that were designed for measuring intelligence or brain damage, and have little direct relationship to schizophrenia. Methodologies investigating the specific cognitive and neurobiological processes that may underlie and possibly precede the conversion to psychosis are likely to yield greater risk prediction specificity. We propose that both permanent (trait) and transitory (state) perturbations of the circuitry underlying memory-prediction function may contribute to risk for developing schizophrenia and thus early detection of risk may be more successful with tasks specifically designed to test memory-prediction function.

We hypothesize that unhealthy development of the neural circuitry that encodes invariant representations and predicts bottom-up activation based on the convergence of top-down, invariant hypotheses and current context may lead to abnormalities of perception, cognition and belief, as well as the tendency to highlight irrelevant information as important.[44,45] Patients with schizophrenia may ascribe great meaning to relatively mundane perceptions and may misunderstand the relevance of highly meaningful events or stimuli. Many of the psychotic experiences of schizophrenia can be seen as being precipitated by this type of cognitive impairment.[44,46] Therefore, cognitive tests that measure memory-prediction function may be especially sensitive predictors of conversion to psychosis. Four such tests are described below:

(i) Binocular Depth Inversion

As discussed above, binocular depth inversion frequently occurs when viewing "hollow" versions of common objects created by switching the images typically viewed by each eye and is especially prevalent when viewing hollow faces.[47] Since the memory of the structure of human faces is invariant in humans, this illusory perception reflects the process by which top-down memory-based predictions override bottom-up sensory information of unlikely stimuli.[48] When viewing hollow presentations of common visual objects, patients with schizophrenia more frequently report perceiving the veridical convex stimuli than do control subjects. Individuals who meet criteria for being at risk for psychosis received binocular depth inversion test (BDIT) scores that were higher (more abnormal) than healthy controls, but not as high as patients with schizophrenia.[49] The specificity of this result to subjects at risk for schizophrenia further suggests that the BDIT may be of value in detection of conversion in high-risk populations.[50]

(ii) Perceptual Closure

Objects in the environment are often partially obscured by other overlapping stimuli, yet the human visual system demonstrates a remarkable ability to identify objects from these fragmented sensory inputs. Functional imaging studies indicate that both low level visual areas[51] and high level visual areas[52] respond similarly to partially occluded objects and their unoccluded counterparts. According to the memory-prediction model, normal maintenance of invariant representations enables an efficient identification of objects with very little information. However, as discussed above, when presented with fragmented line drawings of common objects in a stepwise fashion (whereby each successive presentation of a given stimulus is more complete), individuals with schizophrenia require more complete stimuli before they are able to recognise the figures. As the visual closure task offers a direct measure of the process by which invariant representations affect current perception, it may be especially sensitive to changes that occur early in the conversion to psychosis.

(iii) Learned Irrelevance

Pre-exposure to a conditioned stimulus in the absence of an unconditioned stimulus inhibits conditioning when the stimuli are subsequently paired, a phenomenon termed *latent inhibition*. This paradigm tests the viability of the memory-prediction system in that the development of memories for what is relevant and what is irrelevant helps perceptual systems identify which percepts require attention to more successfully interact with the world. Latent inhibition is decreased in unmedicated and/or acute schizophrenia patients,[53] suggesting that past regularities of experience exhibit weakened influence on current perception and behavior.[54] Additionally, strong correlations between assessments of schizotypal traits and degree of latent inhibition in the general population indicate that latent inhibition is a sensitive measure in sub-clinical populations.[55] Traditional latent inhibition paradigms are designed for between-subject studies and are not easily amenable to repeated measures within subjects. However, a related paradigm termed *learned irrelevance*, in which the conditioned and unconditioned stimuli are presented together in an unpredictable fashion during the pre-exposure phase, has demonstrated comparable results to the latent inhibition literature[56,57] and is amenable to repeated measurements in a within-patient design.[58] This measure may thus be ideal for longitudinal testing of subjects at-risk for psychosis to determine if changes in their ability to gauge the salience of stimuli precedes the onset of psychotic symptoms.

(iv) Spurious Messages from Noise

Auditory hallucinations are one of the most frequent symptoms of early psychosis. When presented with multi-speaker babble consisting of 12 independent streams of speech and given the task of repeating any words or phases that they perceive, patients with early phase psychosis report longer word strings than healthy controls or more chronic schizophrenia patients.[59] As discussed above, deficits in memory-prediction function associated with schizophrenia reduce the automaticity in which the world is perceived and understood, thereby more heavily weighting internally-generated interpretations of reality that then colour perception. As memory-prediction function is hypothesized to be impaired prior to the onset of frank psychosis, the "babble" task may be sensitive to changes in which meaning is assigned to ambiguous stimuli. In fact, this task has recently provided pilot data suggesting that at-risk subjects who later convert to schizophrenia spectrum disorders also report longer word strings in contrast to subjects who fail to convert, suggesting a greater propensity to increase the salience of illusory auditory information perceived from background noise.[60]

Summary and Conclusions

In this article, we have forwarded the hypotheses that dysfunction of the memory-prediction system that underlies efficient and accurate perception and thinking in humans leads to the symptoms of schizophrenia. We have also suggested that this dysfunction will manifest as cognitive impairments on specific tests of memory-prediction functions in young people who are likely to develop schizophrenia. Longitudinal study of youth at risk for schizophrenia will help not only to determine the accuracy of these tests to predict psychosis, but will also help determine the neurobiology of psychosis onset, thus leading to new and effective treatments for preventing schizophrenia and other psychoses.

REFERENCES

1. Kraus MS, Keefe RS, Krishnan KRR. Memory-prediction errors and their consequences in schizophrenia. Neuopsychol Rev 2009 (In press).
2. Helmholtz HV. Concerning the Perceptions in General. Treatise on Physiological Optics. Vol III. 3rd ed. New York: Dover, 1866.
3. Vogels R, Biederman I. Effects of illumination intensity and direction on object coding in macaque inferior temporal cortex. Cereb Cortex 2002;12:756-66.
4. Tovee MJ, Rolls ET, Azzopardi P. Translation invariance in the responses to faces of single neurons in the temporal visual cortical areas of the alert macaque. J Neurophysiol 1994;72:1049-60.
5. Tanaka K, Saito H, Fukada Y, Moriya M. Coding visual images of objects in the inferotemporal cortex of the macaque monkey. J Neurophysiol 1991;66:170-89.
6. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, et al. Placebo-induced changes in fMRI in the anticipation and experience of pain. Science 2004;303:1162-7.
7. Duhamel JR, Colby CL, Goldberg ME. The updating of the representation of visual space in parietal cortex by intended eye movements. Science 1992;255:90-2.
8. Bruce CJ, Goldberg ME. Primate frontal eye fields. I. Single neurons discharging before saccades. J Neurophysiol 1985;53:603-35.
9. Kilner JM, Vargas C, Duval S, Blakemore S-J, Sirigu A. Motor activation prior to observation of a predicted movement. Nat Neurosci 2004;7: 1299-301.
10. Edelman GM. The Remembered Present a Biological Theory of Consciousness. New York: Basic Books, 1989.
11. Snyder AW. Breaking mindset. Mind & Language 1998;13:1.
12. Felleman DJ, Van Essen DC. Distributed hierarchical processing in the primate cerebral cortex. Cereb Cortex 1991;1:1-47.
13. Edelman GM, Mountcastle VB. The Mindful Brain. Cambridge, MA: The MIT Press, 1978.
14. Friston K. A theory of cortical responses. Philosophical Transactions of the Royal Society B: Biological Sciences 2005;360:815-36.
15. Hawkins J, Blakeslee S. On Intelligence. New York: Times Books, 2004.
16. Rao RPN. An optimal estimation approach to visual perception and learning. Vis Res1999;39:1963-89.
17. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 1998;12: 426-45.
18. Davidson M, Reichenberg A, Rabinowitz J, Weiser M, Kaplan Z, Mark M. Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. Am J Psychiatry 1999;156:1328-35.
19. Brewer WJ, Francey SM, Wood SJ, Jackson HJ, Pantelis C, Phillips LJ,

et al. Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. Am J Psychiatry 2005;162:71-8.
20. Keefe RSE, Sweeney JA, Gu H, Hamer RM, Perkins DO, McEvoy JP, et al. Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. Am J Psychiatry 2007;164:1061-71.
21. Keefe RS, Bilder RM, Harvey PD, Davis SM, Palmer BW, Gold JM, et al. Baseline neurocognitive deficits in the CATIE schizophrenia trial. Neuropsychopharmacology 2006;31:2033-46.
22. Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 1999;122:593-624.
23. Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet 2003;361: 281-8.
24. Thaker GK, Ross DE, Cassady SL, Adami HM, LaPorte D, Medoff DR, et al. Smooth pursuit eye movements to extraretinal motion signals: deficits in relatives of patients with schizophrenia. Arch Gen Psychiatry 1998;55:830-6.
25. Thaker GK, Ross DE, Buchanan RW, Adami HM, Medoff DR. Smooth pursuit eye movements to extra-retinal motion signals: deficits in patients with schizophrenia. Psychiatry Res 1999;88:209-19.
26. Hong LE, Turano KA, O'Neill H, Hao L, Wonodi I, McMahon RP, et al. Refining the predictive pursuit endophenotype in schizophrenia. Biol Psychiatry 2008;63:458-64.
27. Hong LE, Avila MT, Thaker GK. Response to unexpected target changes during sustained visual tracking in schizophrenic patients. Exp Brain Res 2005;165:125-31.
28. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. Schizophr Res 2005;76:1-23.
29. Vianin P, Posada A, Hugues E, Franck N, Bovet P, Parnas J, et al. Reduced P300 amplitude in a visual recognition task in patients with schizophrenia. Neuroimage 2002;17:911-21.
30. Doniger GM, Silipo G, Rabinowicz EF, Snodgrass JG, Javitt DC. Impaired sensory processing as a basis for object-recognition deficits in schizophrenia. Am J Psychiatry 2001;158:1818-26.
31. Cavezian C, Danckert J, Lerond J, Dalery J, d'Amato T, Saoud M. Visual-perceptual abilities in healthy controls, depressed patients, and schizophrenia patients. Brain Cogn 2007;64:257-64.
32. Newby D. 'Cloze' procedure refined and modified. 'Modified Cloze', 'reverse Cloze' and the use of predictability as a measure of communication problems in psychosis. Br J Psychiatry 1998;172:136-41.
33. Kiang M, Kutas M, Light GA, Braff DL. An event-related brain potential study of direct and indirect semantic priming in schizophrenia. Am J Psychiatry 2008;165:74-81.
34. Blanchard JJ, Neale JM. The neuropsychological signature of schizophrenia: generalized or differential deficit? Am J Psychiatry 1994;151:40-8.
35. Whittaker JF, Deakin JF, Tomenson B. Face processing in schizophrenia: defining the deficit. Psychol Med 2001;31:499-507.
36. Benton AL, Van Allen MW. Prosopagnosia and facial discrimination. J Neurol Sci 1972;15:167-72.
37. Cornblatt BA, Auther AM. Treating early psychosis: who, what, and when? Dialogues Clin Neurosci 2005;7:39-49.
38. Insel TR, Scolnick EM. Cure therapeutics and strategic prevention: raising the bar for mental health research. Mol Psychiatry 2006;11: 11-7.
39. McGorry PD, Yung AR, Phillips LJ, Yuen HP, Francey S, Cosgrave EM, et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Arch Gen Psychiatry 2002;59:921-8.
40. McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. Am J Psychiatry 2006;163:790-9.
41. Warner R. The prevention of schizophrenia: what interventions are safe and effective? Schizophr Bull 2001;27:551-62.
42. Brewer WJ, Wood SJ, Phillips LJ, Francey SM, Pantelis C, Yung AR, et al. Generalized and specific cognitive performance in clinical high-risk cohorts: a review highlighting potential vulnerability markers for psychosis. Schizophr Bull 2006;32:538-55.
43. Keefe RSE, Perkins DO, Gu H, Zipursky RB, Christensen BK, Lieberman JA. A longitudinal study of neurocognitive function in individuals at-risk for psychosis. Schizophr Res 2006;88:26-35.
44. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 2003;160:13-23.
45. Anscombe R. The disorder of consciousness in schizophrenia. Schizophr Bull 1987;13:241-60.
46. Gilleen J, David AS. The cognitive neuropsychiatry of delusions: from psychopathology to neuropsychology and back again. Psychol Med 2005;35:5-12.
47. Schneider U, Leweke FM, Sternemann U, Emrich HM, Weber MM. Visual 3D illusion: A systems-theoretical approach to psychosis. Eur Arch Psychiatry Clin Neurosci 1996;246:256-60.
48. Gregory RL. Knowledge in perception and illusion. Philos Trans R Soc Lond 1997;352:1121-7.
49. Emrich HM. A three-component-system hypothesis of psychosis. Impairment of binocular depth inversion as an indicator of a functional dysequilibrium. Br Psychiatry Suppl 1989;5:37-9.
50. Koethe D, Kranaster L, Hoyer C, Gross S, Neatby A, Schultze-Lutter F, et al. Binocular depth inversion as a paradigm of reduced visual information processing in prodromal state, antipsychotic-naive and treated schizophrenia. Eur Arch Psychiatry Clin Neurosci 2009;259:195-202.
51. Meng M, Remus DA, Tong F. Filling-in of visual phantoms in the human brain. Nat Neurosci 2005;8:1248-54.
52. Hulme OJ, Zeki S. The sightless view: neural correlates of occluded objects. Cereb Cortex 2007;17:1197-205.
53. Baruch I, Hemsley DR, Gray JA. Differential performance of acute and chronic schizophrenics in a latent inhibition task. J Nerv Ment Dis 1988;176:598-606.
54. Hemsley DR. A simple (or simplistic?) cognitive model for schizophrenia. Behav Res Ther 1993;31:633-45.
55. Baruch I, Hemsley DR, Gray JA. Latent inhibition and "psychotic proneness" in normal subjects. Personality and Individual Differences 1988;9:777-83.
56. Gal G, Mendlovic S, Bloch Y, Beitler G, Levkovitz Y, J. Young AM, et al. Learned irrelevance is disrupted in first-episode but not chronic schizophrenia patients. Behav Brain Res 2005;159:267-75.
57. Gray NS, Snowden RJ. The relevance of irrelevance to schizophrenia. Neurosci Biobehav Rev 2005;29:989-99.
58. Orosz A, Feldon J, Gal G, Simon A, Cattapan-Ludewig K. Repeated measurements of learned irrelevance by a novel within-subject paradigm in humans. Behav Brain Res 2007;180:1-3.
59. Hoffman RE, Rapaport J, Mazure CM, Quinlan DM. Selective speech perception alterations in schizophrenic patients reporting hallucinated "voices". Am J Psychiatry 1999;156:393-9.
60. Hoffman RE, Woods SW, Hawkins KA, Pittman B, Tohen M, Preda A, et al. Extracting spurious messages from noise and risk of schizophrenia-spectrum disorders in a prodromal population. Br J Psychiatry 2007;191:355-6.