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Cholinergic Mechanisms, Early Brain Development, and Risk for Schizophrenia

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Abstract

Neuropsychiatric diseases are complex illnesses where the onset of diagnostic symptomology is often the end result of a decades-long process of aberrant brain development. The identification of novel treatment strategies aimed at normalizing early brain development and preventing mental illness should be a major therapeutic goal; however, there are few models for how this goal might be achieved. This report uses the attentional deficits of schizophrenia as an example and reviews data from genetic, anatomical, physiological, and pharmacologic studies to hypothesize a developmental model with translational primary prevention implications. Specifically, the model suggests that an early interaction between $\alpha 7$ nicotinic receptor density and choline availability may contribute to the development of schizophrenia-associated attentional deficits. Translational implications, including perinatal dietary choline supplementation, are discussed. It is hoped that presentation of this model will stimulate other efforts to develop empirically-driven primary prevention strategies.

Most psychiatric illnesses are complex diseases. Like most complex diseases (e.g. heart disease, diabetes, asthma, etc.), the complexity is found in multiple domains: 1) the diseases are heterogeneous in that the symptoms vary from individual to individual; 2) the diseases are multi-factorial with etiologic factors are both genetic and environmental and these etiologic factors are likely interactive rather than additive; and 3) the diseases are developmental suggesting that many of the brain changes that lead to disease are present years to decades prior to onset of the diagnostic symptomology. The development of new and better treatments for psychiatric illnesses is a critical goal for the field; however, for complex illnesses, successful strategies to decrease morbidity and mortality also often include efforts in primary prevention. However, because primary prevention, by definition, includes intervention before onset of disease, efforts need to focus not on the disease itself, but on risk factors for the disease; and often, when the disease is symptomologically complex, on risk factors for components of the disease. Primary prevention has not been a major focus of psychiatric research; and thus there are few models for psychiatric-illness primary prevention research. This manuscript attempts to decrease that gap by focusing on a single component (attentional dysfunction) in a single illness (schizophrenia). The approach uses multiple levels of analyses, from neural circuits to symptomatic behavior (see Figure 1), to describe a neurodevelopmental model which includes an interaction between genetic and environmental factors and a biological marker of risk. Preclinical studies which support the potential for a primary prevention strategy are also reviewed.

Schizophrenia has often been conceptualized as a disorder of at least 3 symptom domains: positive symptoms (such as hallucinations and delusions), negative symptoms (such as lack of strong affect and motivation), and cognitive dysfunction (such as problems in attention and working memory). Chronic presentation of the positive symptoms, and to a large extent the negative symptoms, are relatively specific to schizophrenia. The diagnostic criteria for schizophrenia reflect this specificity being heavily weighted towards these two symptom domains. The onset of chronic positive symptoms suggestive of schizophrenia has been documented in a child as young as 3 years of age (Beresford, Hepburn, & Ross, 2005) and in individuals over 75 years of age (Barak, Aizenberg, Mirecki, Mazeh, & Achiron, 2002; Howard, Castle, Wessely, & Murray, 1993). However, the majority of cases have onset of hallucinations and delusions between 15 and 35 years of age (Morgan, Castle, & Jablensky, 2008), leading to multiple research efforts focused on early identification (McKenna, Gordon, & Rapoport, 1994; Miller et al., 1999; Preda et al., 2002; Ross et al., 2003; Schaeffer & Ross, 2002; Yung et al., 2003), neurocognitive presentation (Davalos, Compagnon, Heinlein, & Ross, 2004; Cornblatt, Obuchowski, Roberts, Pollack, & Erlenmeyer-Kimling, 1999; Seidman et al., 2006), brain changes (Giedd et al., 1999; Thompson et al., 2001; Vidal et al., 2006) and treatment efforts (Cornblatt, McGorry, McGlashan, & Ross, 2000) in the timeframe preceding the period of highest risk, generally between about 7 and 19 years of age.

While positive symptoms generally develop in late adolescence or early adulthood, the cognitive symptoms of schizophrenia, including problems in attention, develop much earlier. Schizophrenia-associated cognitive impairments are stable across the course of the disease (Rund, 1998; Heaton et al., 2001; Censits, Ragland, Gur, & Gur, 1997; Hill, Schuepbach, Herbener, Keshevan, & Sweeney, 2004) and present at the same level of impairment at first episode (Bilder et al., 2000; Hill et al., 2004; Hoff et al., 1999; Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999; Saykin et al., 1994). Because the diagnostic (positive) symptoms do not generally present until adolescence or later, inferences about onset of cognitive deficits are generally drawn from groups with higher risk for later developing schizophrenia. For example, having a parent with schizophrenia increases the risk a child will later develop schizophrenia by approximately 10 times, so a parental history of schizophrenia is often used as a marker of risk. Neuropsychological, behavioral, and symptomatic assessments of children with a parent with schizophrenia demonstrate that schizophrenia-associated attentional difficulties are fully present as young as 6 years of age (Rieder & Nichols, 1979; Cornblatt et al., 1999; Rosenberg et al., 1997; Jones, Rodgers, Murray, & Marmon, 1994; Niendam et al., 2003; Erlenmeyer-Kimling et al., 2000) and those who develop the psychotic symptomology come from this group of children who have attentional deficits (Erlenmeyer-Kimling et al., 2000; Marcus, Hans, Auerbach, & Auerbach, 1993; Gheorge, Baloesu, & Grigorescu, 2004; Davidson et al., 1999). Attentional deficits can be thought of as an early expression of risk for the disorder.

Standardized, well-accepted assessments of attention are generally only available for children 6 years of age and older and the majority of work on age-of-onset of attentional dysfunction has focused on children age 6 years and above. As a result, until recently, there has been little attempt to determine if the attentional problems are present at even younger ages such as in preschoolers or even infants. However, delays in infant motor development correlate with later cognitive performance and infants who later develop schizophrenia have delays in early motor development (Ridder et al., 2006) suggesting that schizophrenia-associated cognitive dysfunction may be present by early infancy.

While attentional tests for adults and older children can be verbally based, neither verbally-based instructions nor verbally-based outcomes are possible with young infants. In young infants, attentional measures are limited to those that can be inferred from physiological measurements such as auditory evoked potentials (e.g. P50 auditory evoked potential sensory

gating, mismatch negativity), heart rate (e.g. heart rate changes in response to visual stimuli and heart rate variability), autonomic responsivity (e.g. prepulse inhibition of startle), and visual-based attention tasks (such as the visual expectation task). We use P50 sensory gating here as a illustrative example because of its association with the genetics (Leonard et al., 2002; Flomen et al., 2006) and cognitive deficits of schizophrenia (described below) and its applicability to infant populations (Kisley, Polk, Ross, Levisohn, & Freedman, 2003b).

P50 sensory gating

Physiological tests of attention are based on the concepts that (a) selective attention toward one stimulus requires the inhibition of attention towards other stimuli and (b) that much of this inhibitory process is automatic. For example, when a hippocampal pyramidal cell is tuned to specific stimulus characteristics, this also leads to increased activity in surrounding inhibitory interneurons. The inhibitory interneurons both inhibit activity in neighboring pyramidal cells (maximizing spectral discrimination) and loop back to inhibit the initial pyramidal cell (maximizing temporal discrimination; see Figure 2B).

The P50 sensory gating paradigm tests the local inhibitory circuit by presenting two identical auditory stimuli 500 milliseconds apart. For most individuals, there is a strong evoked potential approximately 50 milliseconds after the first stimulus, and a much reduced or “gated” response to the second stimulus. The ratio of the amplitude of the second P50 wave to the first P50 wave is the dependent measure. (A ratio of 0 represents complete suppression of the second response and is considered optimal inhibitory circuit performance; most adults have ratios below 0.4; see Figure 3A).

There is adrenergic input into the local inhibitory circuit and increased adrenergic tone (as might be caused by anxiety or stress) temporarily blocks sensory gating, increasing the P50 ratio (Adler et al., 1990). Infants are affectively volatile, with frequent unpredictable agitation, including high effort motor activity and crying. Older infants, with their improved motor control, will also often interfere with physiological recording by unintentionally grabbing recording wires and removing them from the body surface. The combination of agitation, motor activity, and unintentional interference makes reliable electrophysiological recording difficult. In addition, high adrenergic tone can create false positives for abnormal P50 sensory gating (Adler et al., 1990); thus, agitation creates a confounding variable in interpreting evoked potential results. Rapid eye movement (REM) sleep (termed active sleep in an infant) is a period where motor activity, agitation, and adrenergic tone are decreased or absent. In adults, we have demonstrated that both normal and schizophrenia-associated abnormalities in P50 sensory gating are unchanged between waking and REM sleep (Kisley, Olincy, & Freedman, 2001; Kisley et al., 2003a), so REM sleep provides an optimal environment to assess infants. Figure 4 presents examples of both intact and impaired infant sensory gating recorded during REM sleep (Kisley et al., 2003b). Recording infants during REM sleep is also reliable with a test-retest reliability of 0.87 (Hunter, Corral, Ponicsan, & Ross, 2008).

P50 sensory gating is correlated with other measures of attention, for example with performance on the digit vigilance task (Cullum et al., 1993) and with a self-report of the ability to selectively attend (Kisley, Noecker, & Guinther, 2004). As a physiological correlate of aspects of attentional function, P50 sensory gating shows promise as a surrogate for infant development of attention.

P50 sensory gating in schizophrenic subjects and their relatives

Consistent with their known attentional deficits, individuals with schizophrenia have elevated (impaired) P50 sensory gating ratios (Figure 3B). Schizophrenia-associated P50 sensory gating deficits have been reliably demonstrated across laboratories (Table 1). Meta-analyses suggest

an overall effect size of 1.28-1.56 (de Wilde, Bour, Dingemans, Koelman, & Linszen, 2007b; Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004), which can be increased to 1.8 with careful attention to sound levels, subject position, and filter settings (de Wilde et al., 2007b). Like their affected relatives, around 50% of unaffected first-degree relatives have impairments in attention (Laurent et al., 2000; Ma et al., 2007; Birkett et al., 2007) and abnormalities in P50 sensory gating (Freedman et al., 2000); the attentional and P50 sensory gating deficits co-segregate in families with schizophrenia (Harris et al., 1996; Ross et al., 1999). For these unaffected relatives, a meta-analysis identified an effect size for the P50, relative to controls, of 0.85 (de Wilde et al., 2007b). The impact of having a first-degree relative with chronic psychosis is already present by a few weeks after birth (Hunter, Kisley, Freedman, & Ross, 2008), suggesting that, for vulnerable individuals, the perinatal period may be a time of particular malleability.

Animal models: $\alpha 7$ nicotinic receptor density and sensory gating

The development of physiological (non-verbal) correlates of attention, such as P50 sensory gating, are not only necessary for the study of preverbal children, but are also of utility in developing convergent animal models.

Mice demonstrate a similar auditory sensory gating phenomenon to humans: when presented with two identical auditory stimuli, the early evoked response (the N40) to the second (test) auditory stimulus is dramatically reduced compared to response to the first (conditioning) stimulus the response is gated). Notably, when compared across several inbred mouse strains, the degree of gating is correlated with the amount of hippocampal α -bungarotoxin binding, a measure of genetically-mediated $\alpha 7$ nicotinic receptor expression (95). For example, the C3H mouse expresses a high level of hippocampal $\alpha 7$ nicotinic receptors and has a high degree of sensory gating (the N40 evoked response is lower to the second sound than the first). The DBA/2 mouse has a strain-specific restriction fragment length polymorphism in the $\alpha 7$ receptor gene locus (79) associated with decreased density of $\alpha 7$ nicotinic receptor binding (97) and impaired sensory gating (95). Figure 5 illustrates the differences in sensory gating seen between C3H and DBA/2 mice.

Two other mouse models, congenic and heterozygotic knockouts, support the role of the $\alpha 7$ nicotinic receptor in sensory gating. Congenic mice are mice in which, through selective breeding, a small region of one chromosome is moved onto the genetic background of another strain. When the chromosomal region containing the $\alpha 7$ nicotinic receptor gene from a DBA/2 mouse is bred onto a C3H background, the animal gates like a DBA/2 mouse, not a C3H mouse (Adams, Yoncheck, & Stitzel, 2006). This supports the role of this region of chromosome on gating ability. Heterozygotic knockout mice were developed on a C3H background; one of the $\alpha 7$ nicotinic receptor genes is a “normal gene;” the other has been removed. The heterozygotic knockout has $\alpha 7$ nicotinic receptors less than 50% of the levels of the wildtype animal (Adams, Yoncheck, Zheng, Collins, & Stevens, 2008). While C3H mice generally show good sensory gating (that is a low test/conditioning ratio), the heterozygotic knockouts have poor sensory gating, supporting the specific role of the $\alpha 7$ nicotinic receptor gene.

Animal models: the role of development

Given that schizophrenia-associated attentional deficits are seen years to decades prior to onset of the diagnostic symptomology, it is important to assess whether the $\alpha 7$ nicotinic receptor plays a role not only in adult circuit functioning, but also in the developmental processes which create that circuit. To explore the effects of this receptor on early development, DBA/2 and C3H mouse brains were analyzed prenatally (Adams, 2003). A differential level and distribution of the $\alpha 7$ receptor was identifiable as early as the first day receptors could be seen

and continued throughout prenatal and early postnatal development. Figure 6 summarizes the prenatal results: α -bungarotoxin binding, reflecting $\alpha 7$ nicotinic receptor densities, is first identifiable on embryonic day 13 (E13) in C3H mice, but not until E16 in the DBA/2 mouse. For C3H mice, binding begins in the dorsal portion of the hippocampal anlage, while for the DBA/2 mouse binding is first identified in area CA3. C3H mice show an increase in binding in hippocampal areas CA1 and CA3 between E18 and postnatal day 5, while DBA/2 mice show no such increase.

In summary, across prenatal development, C3H mice express $\alpha 7$ nicotinic receptors sooner, at higher levels, and in different locations than DBA/2 mice. In particular, C3H mice exhibit a rapid, large, and transient increase in receptors late in gestation that is not reproduced in the DBA mouse. The increased availability of perinatal receptors available in the C3H mouse does not occur in congenic mice (DBA $\alpha 7$ nicotinic receptor on a C3H background); the lack of the $\alpha 7$ receptor increase is associated later in development with impaired adult sensory gating. The close relationship between perinatal $\alpha 7$ nicotinic receptor density and physiological outcome suggests that adequate stimulation of the $\alpha 7$ nicotinic receptor is necessary for optimal development of these local inhibitory circuits.

Animal models: ligand availability

The strong relationship between early $\alpha 7$ nicotinic receptor density and later sensory gating suggests normal development of inhibitory neurocircuits requires adequate stimulation of the $\alpha 7$ nicotinic receptor. This suggests that both receptor density *and* ligand availability may play critical roles.

For rodent models, hippocampal choline acetyltransferase is absent until late prenatal or early postnatal development (Makuch et al., 2001; Descarries, Aznavour, & Hamel, 2008; Perry, Piggott, Court, Johnson, & Perry, 1993). Thus, while sufficient stimulation of the receptor appears to be necessary for normal local inhibitory circuit development, the early developmental ligand for this receptor is not acetylcholine. At physiological concentrations, choline is a selective $\alpha 7$ agonist (Uteshev, Meyer, & Papke, 2003), and it appears that choline acts as the primary ligand during the prenatal period.

Choline is actively transported through the placenta and then into the brain, leading to fetal brain choline concentrations several times maternal serum levels (Zeisel, 2006). Females synthesize choline *de novo*; however *de novo* synthesis is insufficient to meet fetal demands (Garner, Mar, & Zeisel, 1995; Zeisel, 2000; Zeisel, Mar, Zhou, & da Costa, 1995); maternal dietary intake is also required. Thus, by manipulating maternal dietary choline, it is possible to manipulate choline availability and to assess the role of choline in development of P50 sensory gating. Two such manipulations have been completed.

In the first, an animal model with good P50 sensory gating, Sprague-Dawley rats were fed choline-deficient diets during embryonic days 12-18, a critical developmental period (Meck, Williams, Cermak, & Blusztajn, 2008). The offspring of that pregnancy were then fed a normal-choline diet until adulthood. When tested as young adults, a history of deficient perinatal dietary choline is associated with impaired P50 sensory gating (Figure 7)(Stevens, Adams, Mellot, Robbins, & Kisley, 2008b).

While the choline deprivation model is helpful in exploring the concept of choline involvement in hippocampal development, the ubiquitous presence of choline makes it highly unlikely that humans will be gestated on a diet with a deficit limited to choline. In contrast, the DBA/2 mouse model, as a model of a genetically vulnerable organism, may be more translatable to the human condition. The DBA/2 mouse has a strain-specific restriction fragment length polymorphism in the $\alpha 7$ receptor gene locus (Stitzel, Farnham, & Collins, 1996) associated with decreased

density of $\alpha 7$ nicotinic receptor binding (Adams, Stitzel, Collins, & Freedman, 2001; Stitzel et al., 1996) and impaired sensory gating (Stevens et al., 1996). Pregnant DBA/2 mice were given daily dietary supplements of choline from onset of pregnancy through weaning; then sensory gating was measured in the pups after they reached early adulthood. Choline supplementation during the perinatal period increased α -bungarotoxin binding in the adult brain (Figure 8) and normalized adult sensory gating (Figure 9), consistent with the hypothesis that choline supplementation normalizes hippocampal development by stimulation of the $\alpha 7$ nicotinic receptor (Stevens et al., 2008a).

A developmental model suggests a primary prevention strategy

Based on the human adult and animal models, we propose a model suggesting that the development of schizophrenia-associated attentional dysfunction occurs as a result of an interaction, during very early brain development, between $\alpha 7$ nicotinic receptor density and choline availability. Receptor density and choline availability are both likely multi-determined, but both have genetic contributions. Genetic variation in the $\alpha 7$ nicotinic receptor gene (CHRNA7), neuregulin (which is influential in $\alpha 7$ receptor activity), and phosphatidylethanolamine-N-methyltransferase (PEMT; a synthetic enzyme for *de novo* synthesis of choline) would all be predicted to impact the developmental process. Notably, while the genetics of schizophrenia remain incompletely determined, all three of these genes have been associated with risk for schizophrenia (CHRNA7: (Freedman et al., 2001; Leonard et al., 1998; Liu et al., 2001; Riley et al., 2000; Xu et al., 2001; Tsuang et al., 2001; Gejman, Sanders, Badner, Cao, & Zhang, 2001); neuregulin: (Mathew et al., 2007; Addington et al., 2007; Walss-Bass et al., 2006; Munafo, Thiselton, Clark, & Flint, 2006; Norton et al., 2006; Hall, Gogos, & Karayiorgou, 2004; Li et al., 2004; Yang et al., 2003; Williams et al., 2003); PEMT (Liu et al., 2007)). CHRNA7 polymorphisms have also been associated with P50 sensory gating performance in a non-psychotic population (Leonard et al., 2002).

The enzyme phosphatidylethanolamine-N-methyltransferase (PEMT) allows for human *de novo* synthesis of choline. In the healthy premenopausal adult female, this *de novo* synthesis is normally sufficient to meet daily needs (Fischer et al., 2007). However, pregnancy is a time of heavy choline demand, primarily because of the strong fetal need for choline-containing-phospholipids as a necessary component of new cell development. Pregnant women are unable to synthesize all of the required choline and therefore dietary sources are needed; variation in dietary intake can lead to relative choline deficiency in some pregnant women (Gossell-Williams, Fletcher, McFarlane-Anderson, Jacob, & Zeisel, 2005). The combination of lowered $\alpha 7$ nicotinic receptor density and lower choline availability may alter inhibitory neurocircuit development and increase risk for later schizophrenia-associated attentional deficits (Figure 10).

There has been a hesitation to translate genetic findings into primary prevention strategies with concerns predominantly focused on the risks of pharmacological intervention in vulnerable but not yet affected brains. The ultimate risk of primary prevention is the introduction of negative consequences in individuals who may never develop the illness of interest. One of the fortuitous components of the current developmental hypothesis is the role of choline, a commonly occurring nutritional component included in the class of substances the U.S. Federal Drug Administration defines as “generally regarded as safe.” It may be possible to supplement pregnant women with choline-containing compounds during pregnancy at doses sufficient to prevent acute deficiency with minimal risk of negative consequences.

The translation of a model into a testable primary prevention strategy

The development of any primary prevention strategy is difficult; low frequency of illness and long duration between intervention and outcome are particularly problematic methodological

issues. For example, given the low frequency of schizophrenia in the general population, even optimistic projections of effect size and attrition rates suggests a controlled perinatal choline supplementation trial might require enrollment in the tens of thousands of pregnant women with 30+ year follow-up of their offspring. In other illnesses and with other prevention strategies, primary prevention trials have enrolled tens of thousands (e.g. see (Bartolucci & Howard, 2006)), and decades-long follow-up of perinatal intervention is possible (e.g. (Olds et al., 1998; Olds, 2006)). However, prior to devoting the resources necessary such a trial, several intermediate steps need to be completed.

First and foremost is safety. Choline is included in products categorized by the U.S. Food and Drug Administration as “generally regarded as safe;” and supplementation doses that fall within the normal range of daily intake likely have low risk. However, particularly given the vulnerability of the population to be exposed (including fetuses), careful attention to safety is warranted.

Second, the biological effect of choline supplementation should be established. P50 sensory gating appears strong influenced by $\alpha 7$ nicotinic receptor stimulation. If perinatal choline has a positive impact on infant P50 sensory gating, this would support the biological impact of the intervention and may clarify which doses during which critical windows are most likely to be effective.

Third, assess more proximal intermediate outcomes. The prevalence of schizophrenia is around 1% in the general population and onset generally is not until late adolescence or early adulthood. However attentional dysfunction not only is present by early school-age years, it is more penetrant than the disease itself. The type of attentional dysfunction associated with schizophrenia is relatively common in the general population. While the etiology of attentional function is likely as complex as the full schizophrenia phenotype with differences in perinatal $\alpha 7$ nicotinic receptor stimulation explaining only a small part of the variance, the fact that dysfunction is more prevalent and is measureable at much young ages raises the possibility that the impact of perinatal intervention may be measurable with smaller sample sizes and with much shorter follow-up than possible when waiting for disease onset. Relating infant P50 sensory gating to childhood attentional function, both in general and in the presence of perinatal choline supplementation, are important next steps in model development.

Summary

One of the fundamental promises of molecular studies has been the identification of drug targets amenable to intervention. For example, in adults with schizophrenia, the hypothesized relationship between genetic polymorphisms, $\alpha 7$ nicotinic receptor density, electrophysiologically measured sensory gating, and attentional dysfunction has led to clinical trials, with early success, of nicotinic agonists (Olincy et al., 2006; Lee, Lee, Lee, & Kim, 2007; Schubert, Young, & Hicks, 2006). However, for the development of primary prevention strategies, the value to identifying etiologic agents may not be in their direct application to primary prevention strategy. Instead, a less direct process may be more appropriate, first using genetic findings to advance developmental models only then followed by primary prevention development. For example, the association between CHRNA7 and schizophrenia has been useful in creating animal exemplars, which in turn have allowed for advancement of neurocircuitry paradigms, and testing of potential primary interventions. In this case, the association between CHRNA7 and schizophrenia led to a developmental model where local inhibitory neurocircuits maturation requires adequate stimulation of the $\alpha 7$ nicotinic receptor at appropriate times during early development. Once the model was developed, it was possible to recognize that CHRNA polymorphisms are only one of many factors which could effects this ligand-receptor interaction. Other genetic influenced possibilities include neuregulin levels

(neuregulin influences $\alpha 7$ receptor activity), and phosphatidylethanolamine-N-methyltransferase activity (which would influence in vivo synthesis of choline). Environmental factors that may influence this process include dietary variation in choline intake and maternal stress (which may lead to sequestration of free choline away from fetal access). Independent of the cause of the disruption, the model hypothesizes that a maternal increase in dietary choline would compensate. Thus, while the relation between any etiologic factor and developmental effects may be low, choline supplementation during early development may have a measurable impact.

Similar to decreasing the risk of spina bifida by encouraging all pregnant women to take folate or decreasing the risk for dental caries by population-wide fluoride supplementation, schizophrenia may best be treated by preventive strategies years or even decades prior to the onset of diagnostic symptomology. As is true across multiple medical diseases, a focus on primary prevention aimed at countering risk factors has the potential to dramatically reduce morbidity and mortality for severe psychiatric illness.

The model does not rule out that alternative interactions elsewhere in the circuit might lead to similar neurocognitive difficulties, and it is likely that brain maldevelopment in other locations or other at other times during development also contributes to schizophrenic psychopathology. It is also probable that additional work on the model will enhance the value of some components while reducing or invalidating the value of others. The model is presented here as an example of the process by which interdisciplinary efforts to coordinate genetic, animal, and human studies can lead to the identification of testable hypotheses related to novel primary prevention strategies.

Key points

- Neurodevelopmental illnesses are complex diseases where illness is the end result of an often decades-long interaction between genetic and environmental factors. The perinatal period may be a stage where even small interventions may alter the developmental course.
- No single etiologic factor, be it genetic or environmental, will account for much of the risk in developing the disorder. However, identification of even small contributors to illness may be applicable to animal modeling, lead to neurodevelopmental models, which then may suggest primary prevention strategies.
- The study of cholinergic mechanisms, their role in early brain development, and the relationship of this early brain development to risk for schizophrenia-associated cognitive deficits may be a model for developing mental illness primary prevention strategies.
- Prenatal activation of $\alpha 7$ nicotinic receptors by maternal dietary choline supplementation deserves further exploration as a primary prevention strategy for the cognitive deficits of schizophrenia.

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Figure 1.

Analysis of a developmental illness can occur at several levels and at several ages. deficits at each level correlate with each other. Schizophrenia (represented in black) occurs in adults, adolescents, and rarely in children and is associated with attentional, physiological, and neural circuit dysfunction. These schizophrenia-associated deficits are more penetrant than the full disease, both preceding onset of diagnostic symptomatology by a decade or more and occurring at high rates in non-psychotic first-degree relatives. Symptomatically, the attentional deficits often meet criteria for attention deficit-hyperactivity disorder (ADHD), can be identified by psychological testing, and themselves correlate with similar physiological impairments (represented in grey). Attention and working memory deficits are present by 6 years of age (the earliest anyone has looked) and may be identifiable even earlier; schizophrenia-associated deficits in physiological correlates of attentional function are identifiable by early infancy. Local inhibitory circuits are critical to physiological test performance and failures in those circuits are present in both individuals with schizophrenia and a high percentage of their 1st degree relatives at all age ranges, including infants. Perinatal development (represented in light gray) may be a critical window for intervention aimed at long-term permanent physiological, cognitive, symptomatic, and functional improvement.

$\alpha 7$ nAChR expression

Figure 2.

The $\alpha 7$ nicotinic receptor and local inhibitory circuits at different stages of development. (A) Early in brain development, GABA is an excitatory neurotransmitter and the $\alpha 7$ nicotinic receptor is found in multiple locations (generalized) across a local inhibitory neurocircuit. Stimulation of the $\alpha 7$ nicotinic receptor activates the interneuron-pyramidal cell circuit, enhancing and stabilizing the connection. Decreased $\alpha 7$ nicotinic receptor stimulation, whether because of lower receptor density or decreased agonist, is associated with long-term impaired circuit function. Acetylcholinergic innervation, at least in the rodent hippocampus, has not yet developed; the endogenous ligand for these receptors is not acetylcholine, but instead appears to be choline. (B) In the mature brain, GABA is primarily an inhibitory neurotransmitter and $\alpha 7$ receptors are restricted to specific synaptic locations. In the mature brain, acetylcholine is the primary agonist at the $\alpha 7$ nicotinic receptor. As shown, the interneuron acts to limit the spread of excitatory activity enhancing spectral specificity. Similarly (not shown), the interneuron provides negative feedback onto the originating pyramidal cell, providing temporal specificity.

Figure 3.

(reprinted with permission from Kisley et al, Figure 1 (Kisley et al., 2003b)): P50 sensory gating in (A) a normal adult and (B) an adult with schizophrenia. Evoked potentials are recorded after 2 identical stimuli presented 500 milliseconds apart. The first stimulus is termed the conditioning stimulus; the second is termed the test stimulus. The amplitude of the P50 wave is measured between the trough and the peak (as identified by hash marks on the figure). Tracing A represents normal gating, as seen in greater than 74-90% of control subjects, where the amplitude of the second P50 is reduced compared to the first P50 amplitude. Tracing B represents abnormal gating, as seen in 55-90% of schizophrenic subjects and 40-50% of their relatives: the amplitude of the second P50 is almost identical to the amplitude of the first P50 (the ratio is 0.99). In other words, most individuals with schizophrenia, and 40-50% of their first-degree relatives, have trouble inhibiting the P50 response to the second stimulus. Positivity is plotted upwards.

Figure 4.

(reprinted with permission from Stevens et al, Figure 1 (Stevens et al., 1996)): Grand-average (a) and individual examples (b,c) of responses by infants during REM sleep by conditioning (left) and test (right) clicks. Clicks occur at 0 ms. Component P1 (termed P50 to correspond to studies in adults) and preceding negativity indicated by tick-marks. Grand-average waveform was not explicitly analyzed, but is shown here to demonstrate general response suppression of the group as a whole. Infant B (49.29 weeks conceptual age) exhibits a relative lack of response ($T/C=1.05$) compared to infant C (53.86 weeks, $T/C = 0.24$). Positivity plotted upwards.

Figure 5.

(copied with permission from Adams et al, Figure 1 (Adams, 2003)): Auditory evoked potentials in response to two identical clicks presented 500 milliseconds apart. Arrows represent the presentation of the stimuli; amplitudes of the N40 wave are measured between the two vertical marks. The ratio is the amplitude of the N40 response to the second sound divided by the amplitude of the N40 response to the first sound. The C3H mouse responds in a fashion similar to that seen in normal humans, where the amplitude of the N40 response to the second sound is greatly diminished relative to the response to the first sound. DBA mice show a response similar to that seen in adults with schizophrenia, where the amplitude of the N40 wave is similar in response to both sounds.

Figure 6.

(A) Binding for α -bungarotoxin (α -BTX) is initially observed in the dorsal portion of the hippocampal anlage of C3H mice on embryonic day 13 (E13). Binding is both diffuse (arrowheads) and clumped (arrows) in appearance. No α -BTX binding is observed in the neuroepithelium (NE). (B) Binding of α -BTX is not detectable in the developing hippocampus of DBA/2 mice on E13. (C) Binding of α -BTX is increased in density and is present in both hippocampal areas CA1 and CA3 of the C3H mouse strain on E16, but not in the immature dentate gyrus (D). The pattern of hippocampal α -BTX is again comprised of a mixture of diffuse (arrowheads) and clumped (arrows) silver grains. (D) Binding of α -BTX is initially detected in the hippocampal formation of DBA/2 mice on E16. The level of binding is higher in area

CA3 than in area CA1, while no binding is observed in the dentate gyrus. Scattered clumps of silver grains (arrows) are seen within a more diffuse background (arrowheads). Overall, the level of α -BTX binding in DBA/2 mouse hippocampus on E16 is much lower than that observed in C3H mouse hippocampus at the same age. (E) Binding of α -BTX is increased in density in hippocampal areas CA1 and CA3 and is initially detected in the dentate gyrus (D) on E17 in C3H mice (arrowheads). (F) The level of α -BTX binding is also increased in hippocampal areas CA1 and CA3 in DBA/2 mice on E17, but is not detectable in the dentate gyrus. (G) A marked increase in the density of α -BTX binding is seen in hippocampal area CA1 of C3H mice on E18, especially at the border between stratum pyramidale and stratum radiatum of area CA1 (arrows). α -BTX binding density is also increased in hippocampal area CA3 and in the dentate gyrus of C3H mice at this state of development. (H) Binding of α -BTX is initially observed (arrowheads) in the dentate gyrus (D) of DBA/2 mice on E18. An increase in the density of α -BTX binding is also seen in both hippocampal areas CA1 and CA3 of DBA/2 mice at this age, although binding levels are still greater in area CA3 than in area CA1. Calibration bar = 120 μ m.

Figure 7.
(copied with permission from Stevens et al, Figure 2 (Stevens et al., 2008b)): The test to conditioning N40 ratio for young adult rats gestated on normal (con), deficient (def), or supplemented (sup) diets during gestation. $N= 14$ (con) 13 (def) and 7 (sup). $**p<0.01$

Figure 8.

(copied with permission from Stevens et al, Figure 3 (Stevens et al., 2008a)). Gestational supplementation with choline produced an overall increase in α -bungarotoxin ($\alpha 7$) binding in the hippocampus of DBA/2 mice. Regionally, both the dentate gyrus and area CA1 showed statistically significant increases for supplemented mice over those gestated on normal choline levels. $n=12$ for normal choline, $n=11$ for supplemented, data are mean $\pm$ SEM, * $p<0.05$, ** $p<0.01$.

Figure 9.

The DBA/2 mouse has been utilized extensively as a model for one aspect of schizophrenia-associated brain functioning. Both individuals with schizophrenia and DBA/2 mice have a polymorphism in *CHRNA7*, a gene associated with decreased $\alpha 7$ nicotinic receptor expression; both individuals with schizophrenia and DBA/2 mice have abnormalities in the ability to inhibit evoked responses to repetitive stimuli (often measured as the ratio of the response to a second stimulus divided by the first stimulus, with lower numbers meaning greater inhibition); and both humans with schizophrenia and DBA/2 mice demonstrate improved inhibition with cholinergic agonists. In this figure, the ratio of the second evoked potential to the first (termed the test to conditioning or T/C ratio) for young adult DBA/2 mice gestated on choline supplemented diets is improved (“normalized”) as compared to normal choline diets. Choline supplemented diets during gestation may normalize one schizophrenia-associated brain

dysfunction. Data are mean $\pm$ SEM, n = 14 (normal choline), n = 13 (supplemented choline).
*p<.01

Figure 10.
A developmental hypothesis for development of schizophrenia-associated deficits.

Table 1

Replication studies of the P50 sensory gating in schizophrenia, 2000- March 2008. All papers compare individuals with schizophrenia to a normal comparison group. Only the latest report per group from 2000 or later is shown.

Citation	Comparison Group P50 Ratio (N)	Schizophrenia P50 Ratio (N)
Cadenhead 2000 (Cadenhead, Light, Geyer, & Braff, 2000)	0.36 (N=23)	0.72 (N=26)
Patterson 2000 (Patterson et al., 2000)	0.36 (N=10)	1.18 (N=10)
Clementz 2001 (Clementz & Blumental, 2001)	0.52 (N=20)	0.62 (N=20)
Thoma 2003 (Thoma et al., 2003)	0.34 (N=15)	0.56 (N=20)
Arnfred 2003 (Arnfred, Chen, Glenthøj, & Hemmingsen, 2003)	0.40 (N=12)	0.32 (N=12)
Houy 2004 (Houy et al., 2004)	78% < 0.5 (N=85)	88% > 0.5 (N=111)
Becker 2004 (Becker et al., 2004)	0.44 (N=25)	0.82 (N=25)
Boutros 2004 (Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004)	0.41 (N=23)	0.54 (N=23)
Hsieh 2004 (Hsieh et al., 2004)	0.37 (N=10)	0.70 (N=10)
Wegrzyn 2004 (Wegrzyn & Wciorka, 2004)	0.25 (N=46)	1.45 (N=23)
Ringel 2004 (Ringel, Heidrich, Jacob, & Fallgater, 2004)	0.44 (N=12)	0.79 (N=79)
Louchart-de la Chapelle 2005 (Louchart-de la Chapelle et al., 2005)	0.38 (N=113)	0.82 (N=144)
Price 2006 (Price et al., 2006)	0.47 (N=44)	0.63 (N=60)
de Wilde 2007 (de Wilde, Bour, Dingemans, Koelman, & Linszen, 2007a)	0.43 (N=28)	0.65 (N=53)
Hong 2007 (Hong et al., 2007)	0.56 (N=17)	0.70 (N=59)