Endophenotypes in Schizophrenia for the Perinatal Period: Criteria for Validation

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Endophenotypes are disease-associated phenotypes that are thought to reflect the neurobiological or other mechanisms that underlie the more overt symptoms of a psychiatric illness. Endophenotypes have been critical in understanding the genetics, neurobiology, and treatment of schizophrenia. Because psychiatric illnesses have multiple causes, including both genetic and nongenetic risk factors, an endophenotype linked to one of the mechanisms may be expressed more frequently than the disease itself. However, in schizophrenia research, endophenotypes have almost exclusively been studied in older adolescents or adults who have entered or passed through the age of risk for the disorder. Yet, schizophrenia is a neurodevelopmental disorder where prenatal development starts a cascade of brain changes across the lifespan. Endophenotypes have only minimally been utilized to explore the perinatal development of vulnerability. One major impediment to the development of perinatally-useful endophenotypes has been the established validity criteria. For example, the criterion that the endophenotype be more frequently present in those with disease than those without is difficult to demonstrate when there can be a decades-long period between endophenotype measurement and the age of greatest risk for onset of the disorder. This article proposes changes to the endophenotype validity criteria appropriate to perinatal research and reviews how application of these modified criteria helped identify a perinatally-usable phenotype of risk for schizophrenia, P50 sensory gating, which was then used to propose a novel perinatal primary prevention intervention.

Key words: infant/endophenotype/schizophrenia/sensory gating/biological markers

Introduction

Most modern neurodevelopmental models of schizophrenia suggest 2 critical windows of development: prenatal and adolescent. Abnormalities in prenatal brain development lead to schizophrenia vulnerability and, in some individuals with already vulnerable brains, further abnormalities in adolescent brain development result in conversion from vulnerability to psychotic illness. Identification and intervention in vulnerable adolescents, for the express purpose of preventing conversion to psychosis, has received significant attention over the last decade.[1–44] Conversely, despite the high potential for benefit, there has been less attention paid to the perinatal period of rapid brain development. The contribution of prenatal brain development to onset of schizophrenia has been consistently recognized for over a quarter of a century,[45,46] and prenatal brain changes remain central to even the most recent versions of the neurodevelopmental hypothesis for schizophrenia.[47] While later developmental and environmental influences may moderate the impact, alterations in perinatal brain development set the stage of a lifetime of vulnerability. Prenatal abnormalities in brain development increases lifelong risk for significant cognitive and functional impairment, even if the later outcome of schizophrenia itself does not occur.[39,48–53] The malleability of the brain during this early developmental period makes it an ideal time to intervene, with intervention lasting only a few months having potential life-long ramifications.

While there is general agreement on the concept and potential value of perinatal prevention, it has been difficult to identify and test intervention strategies. One approach is to intervene in prenatal correlates of schizophrenia risk such as parental psychosis, maternal tobacco smoking, maternal depression, prenatal infection, severe psychosocial stress (such as war or death of a loved one), famine, delivery complications, and premature birth. Reduction in any of these would have broad public health benefits and are generally included as public health goals. However, the relative risk for any individual environmental factor is low, costs to intervene are

high, and many of these issues have proven recalcitrant to intervention. When one considers the often decades-long delay between any prenatal intervention and onset of diagnosable symptoms, some experts suggest that it may be difficult to demonstrate an effect of intervention unless efforts are focused on the highest risk individuals.[54] Using parental diagnosis of schizophrenia as the high-risk marker, even with low long-term attrition, sample size analysis suggests that, after completion of a randomized prenatal trial, over 30 000 individuals would have to be followed for 30+ years. While large simple randomized long-term follow-up trials are being utilized in a variety of medical disorders[55–61] including schizophrenia,[62,63] the cost and logistical problems associated with such trials are significant. In general, when there is a delay between intervention and onset of symptoms, justification of large simple trials includes first completing shorter-term studies demonstrating an impact of the intervention on a marker of risk.[64] Endophenotypes may be of particular value because, to the degree with which they reflect the underlying genetic and neurobiological substrates, they may suggest methods for intervention.[65–67]

Endophenotypes are a subtype of biomarkers that are presumed to be in the pathway between genetic vulnerability and disease onset.[68] The potential value of endophenotypes for identifying and testing novel treatments for schizophrenia has been extensively discussed and a number of endophenotypes are under investigation in adolescents and adults with or at risk for schizophrenia.[69–75] Development of endophenotypes for schizophrenia that are usable in the perinatal period has been less successful with only 2 nongenetic biomarkers having received significant attention: structural neuroimaging[76–78] and an evoked potential reflective of cerebral inhibition, P50 sensory gating. One of the main criteria for validating a biomarker is its association with disease; the long duration between the perinatal period and onset of schizophrenia makes testing the validity of perinatal endophenotypes problematic and has been a major impediment to the development of additional endophenotypes.

Since the endophenotype concept was initially proposed for use in schizophrenia research, the understanding of psychiatric illness has advanced. Major conceptual shifts include the move towards continuous rather than categorical evaluation of symptoms[79–83] and the awareness that, in some circumstances, psychiatric illness may be better thought of as domains where impairment in any given domain may be common across a number of psychiatric disorders,[84,85] Incorporating these into the concept of endophenotype would somewhat offset the problem of long delay between the perinatal period and schizophrenia onset. We thus propose a new set of criteria for evaluating perinatal endophenotypes (table 1) and review how our use of these criteria with P50 sensory gating led to initial testing of a novel perinatal primary prevention intervention.

We present this information with the goal of stimulating further efforts directed at the perinatal period.

The Endophenotype Should be Present and Reliable by the End of the Vulnerability Window

When developing a phenotype for infants, one common approach is to see if adult-based endophenotypes can be adapted. Infants, particularly young infants, are affectively volatile, physically limited, and highly state-dependent (hunger and sleep needs actively and unpredictably drive behavior). It is not uncommon for behavioral studies of infants to have data collection failure rates in excess of 25%. Psychophysiological measures, particularly passive tasks, are thus of particular interest. P50 sensory gating, prepulse inhibition, and mismatch negativity are passive psychophysiological measures and putative adult schizophrenia endophenotypes.[86,87] Prepulse inhibition may not fully develop until adolescence and mismatch negativity quantification is confounded in infants by mismatch positivity.[88] While some labs have found low reliability,[89] meta-analysis supports the relationship between P50 sensory gating and schizophrenia[90] and the method for measuring P50 sensory gating in infants has been established.[91] Thus, this report utilizes P50 sensory gating as a model for how to approach the development of an infant endophenotype.

In adults, when presented with repetitive stimuli, the evoked potential quickly reduces in amplitude and is thought to reflect an individual's ability to filter out irrelevant information (sensory gating).[92] The two largest multisite schizophrenia biomarker studies have identified schizophrenia-associated reduced suppression (impaired sensory gating) for early components at 50[93] and 100 ms.[94] We focus here on the positively directed wave 50 ms after the stimulus. Although a number of quantitative representations of suppression are possible, we utilize the P50 sensory gating ratio: the amplitude of response to the second sound divided by the amplitude of the response to the first sound.

In adapting this endophenotype to infant populations, two changes are evident. First, latency of the evoked response components is slightly longer in young children; the P50 terminology is maintained for consistency with the adult literature. Second, while the degree of P50 suppression is stable over time in most adults,[95] suppression in many children is not reliable (the same child has P50 good suppression at some time points and poor suppression at others).[96] In adults, elevated adrenergic tone transiently impairs sensory gating,[97] raising the possibility that the stress of visiting an unfamiliar laboratory and/or the novel stimulus of electro-encephalogram wires being placed on and hanging from the head may explain the lack of reliability in children. Noting that P50 sensory gating is similar between awake and rapid eye movement (REM) sleep states[98,99] and that adrenergic tone is minimized during REM, infants were assessed during REM sleep. When assessed during REM, P50 sensory gating is fully developed[91] and reliable[100] by a few months of age.

Table 1. Proposed Extension of Criteria for an Endophenotype to be (a) Applicable for the Perinatal Period and (b) Useful for the Development of Novel Primary Prevention Strategies

Standard Criteria Used in Adults[a]	Proposed Perinatal Criteria
(1) The endophenotype should be a trait that can be measured reliably, and ideally is more strongly associated with the disease of interest than with other psychiatric conditions.	(1) The endophenotype should be present and reliable by the end of the vulnerability window.
(2) The endophenotype is primarily state-independent (manifests in an individual whether or not the illness is active) but may require a challenge to elicit the indicator.	(2) After the critical window closes (after early infancy), the endophenotype is primarily age-independent.
(3) The endophenotype is heritable.	(3) The endophenotype reflects identifiable neurobiological processes.
(4) The endophenotype found in affected family members and is found in nonaffected family members at a higher rate than in the general population.	(4) The endophenotype is found in infants with an affected parent at a higher rate than in the general population.
(5) The endophenotype is more prevalent among the ill relatives of ill probands compared with the well relatives of the ill probands (ie, within families, endophenotype, and illness co-segregate).	(5) The endophenotype is associated with known prenatal correlates of risk.
(6) The endophenotype is associated with illness in the population.	(6) The endophenotype predicts elevated risk for schizophrenia-associated core cognitive and/or behavioral deficits
	(7) The endophenotype is modifiable during the perinatal window

Note: [a]adapted from Lenzenweger.[144]

After the Critical Window Closes (After Early Infancy), the Endophenotype Is Primarily Age-independent

One of the original goals of developing endophenotypes was their potential use in genetic linkage (and later genetic association) studies. To be useful in that regard, the endophenotype should be state-independent, present before onset and throughout the course of illness, during both acute episodes and remission. Since fetuses and young infants do not cycle through stages of psychosis, this criterion is less relevant for this age range. Instead, the more relevant problem for this age range is rapid and dramatic brain development. Thus, we propose an alternative criterion, specifically that once the critical period closes (usually sometime in infancy), the endophenotype should be stable as the child ages, ie, age-independent. We identified good stability for P50 sensory gating, at least between infant and 4 years of age (figure 1).[101]

The Endophenotype Reflects Identifiable Neurobiological Processes

Over the last 3+ decades, tremendous effort and resources have been committed to the identification of schizophrenia endophenotypes. The original purpose of endophenotypes was the idea that some schizophrenia-related phenotypes would be more penetrant reflections of genetic vulnerability than the disease itself and would thus facilitate gene identification.[102] Identified genes could then be used as targets for novel pharmacological interventions.

However, there is an increasing evidence that endophenotypes are as genetically and environmentally complex as the clinical phenotypes they represent. Several authors have suggested that the potential value of endophenotypes may be in their ability to reflect underlying neurobiology.[103–105] Identification of neurobiology has the same end goal as identification of genes: to identify and test novel pharmacological interventions. Thus, the endophenotypic criterion of heritability should be replaced with the criterion that the endophenotype reflects known neurobiological processes.

P50 sensory gating was one of the first schizophrenia-associate endophenotypes to be linked with a chromosomal region and candidate gene, CHRNA7.[106] Replications supporting association between those CHRNA7 promoter polymorphisms which decrease $\alpha 7$ nicotinic cholinergic receptor (α7nAChR) expression and impaired P50 sensory gating have been reported.[107–111] Parallel work led to a neurobiological model of P50 sensory gating deficits related to deficits in these nicotinic receptors. In humans, P50 sensory gating has been localized to the hippocampus, thalamus, and prefrontal cortex.[112] We have extended the model to include its development component (figure 2).[113]

This developmental model is consistent with the known effects of many prenatal risk factors. Factors which decrease α7nAChR expression (genetic polymorphisms in CHRNA7 and NRG1), desensitize the receptor (maternal tobacco smoking), or decrease availability of agonist (a micronutrient-poor diet) would all be expected to impair cerebral inhibition development and increase risk for schizophrenia. In addition, elevated stress leads to sequestration in the mother's liver of some micronutrients including choline, which is the primary prenatal agonist for this receptor.[113] Such hepatic sequestrations in pregnant women would decrease availability to the fetal brain. Maternal
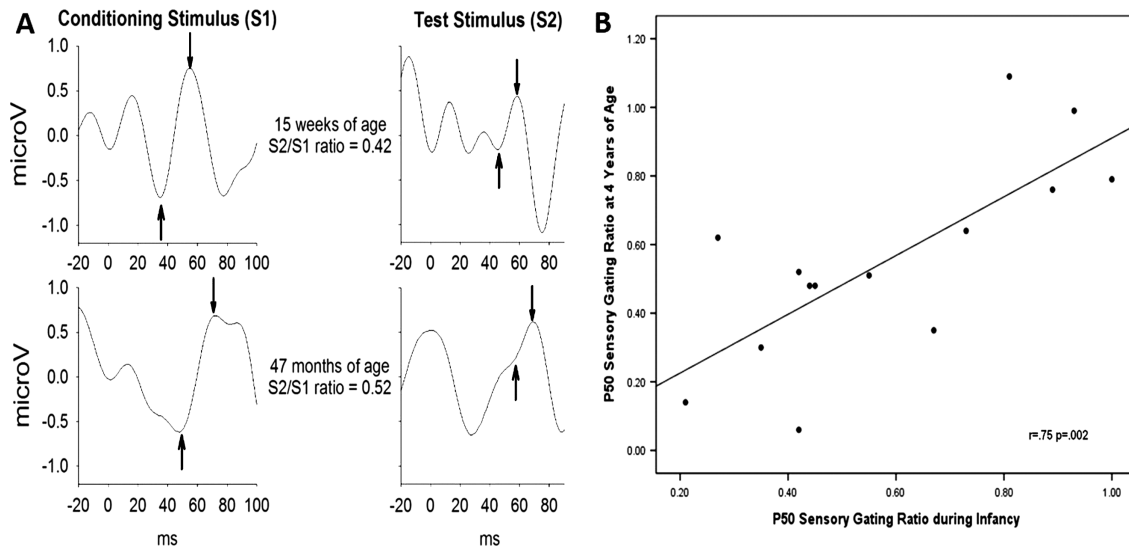
Fig. 1. (A) Averaged auditory event related potentials from the same infant at 15 weeks of age (top row) and 47 months of age (bottom row). Stimulus onset occurred at 0. P50 evoked response amplitude is measured between the arrows. (B) Relationship of P50 sensory gating ratio in Infancy with P50 sensory gating ratio at 4 years of age ($r = .73$, $P = .003$). Adapted from figures 1 and 3, Hunter et al.[145]
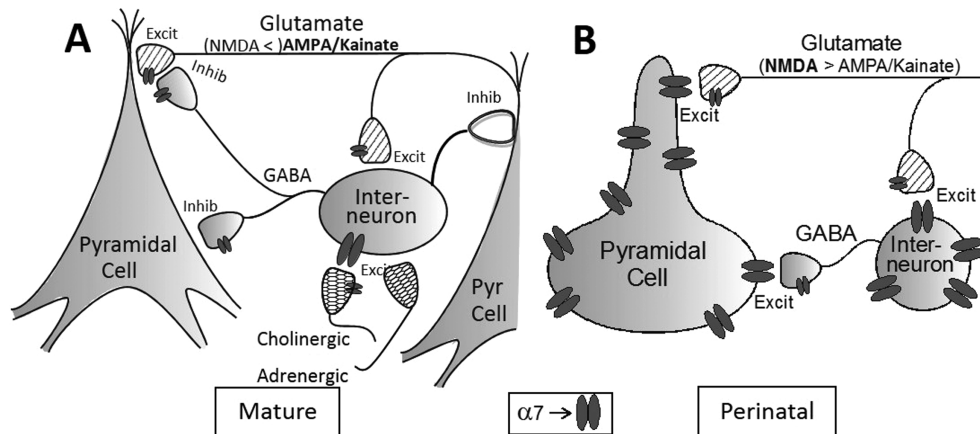

Fig. 2. A developmentally-sensitive neurobiological model of P50 sensory gating involving Glutaminergic/GABAergic cerebral inhibition. (A) The cerebral inhibition circuit as seen in the mature brain. Gamma amino butyric acid (GABA) is primarily an inhibitory neurotransmitter and α7 nicotinic cholinergic receptors (α7nAChRs) are restricted to specific synaptic locations. In the mature brain, acetylcholine is the primary agonist at the α7nAChR. Stimulation of the α7nAChR activates the interneuron, limiting the spread of excitatory activity. (B) The Glutaminergic/GABAergic cerebral inhibition circuit as seen in the prenatal brain. Early in brain development, GABA is an excitatory neurotransmitter and the α7nAChR is found in multiple locations across the local inhibitory neurocircuit. Stimulation of the α7nAChR activates the interneuron-pyramidal cell circuit, enhancing and stabilizing the connection. Acetylcholinergic innervation, at least in the rodent hippocampus, has not yet developed; the endogenous prenatal ligand for these receptors is choline. Decreased α7nAChR stimulation, whether because of lower receptor density or decreased agonist availability, is associated with long-term impaired circuit function. Adapted from figure 2, Ross et al.[113]

anxiety, a proxy for maternal stress, is associated with impaired offspring development of P50 sensory gating.[114]

The Endophenotype Is Found in Infants With an Affected Parent at a Higher Rate Than in the General Population and the Endophenotype Is Associated With Known Prenatal Correlates of Risk

Endophenotypes are representations of genetic risk more penetrant than the disease itself. This central concept is currently reflected in 2 validity criteria. The first criterion is increased endophenotype presentation in those who are unaffected (ie, don't have schizophrenia) but who share similar genetic profiles, eg, unaffected relatives, as compared to individuals who have less similar genetic profiles (eg, individuals without a family history of schizophrenia). Infants do not express schizophrenia, so they can only be considered as unaffected relatives. Since infants are unlikely to have siblings old enough to have entered the age-range of risk for onset of schizophrenia, the only affected first-degree relative they are likely to have is an affected parent. Thus, the endophenotype criteria for elevated endophenotypic presentation in unaffected relatives is modified to be elevated endophenotypic presentation in infant offspring of affected parents. An additional adjustment is the

definition of an affected parent. Meta-analysis and adoption studies identify an increased risk for schizophrenia in offspring of a parent with schizophrenia and in offspring of a parent with bipolar disorder with no significant difference in risk between these 2 parental diagnoses.[115,116] Previous work has suggested P50 sensory gating may be more closely aligned with psychosis than with a particular disorder[117]; thus, the criteria is modified to define an affected parent as a parent with a psychotic illness.

The second family-related criterion is that endophenotype expression should be more prevalent in affected relatives of ill probands than unaffected relatives of ill probands. Since infants are not affected, this criterion is less relevant for infant populations. Instead, we propose a modification that elevated rates of endophenotype expression should be related to known prenatal exposures that epidemiological studies have shown to increase later risk psychosis.

Using these two modified family-based criteria, we examined, in healthy infants, the relationship between infant P50 sensory gating and both parental diagnosis of psychosis and two prenatal exposures known to increase later risk for schizophrenia: maternal prenatal depression and maternal tobacco smoking.[118,119] Parental psychosis and both prenatal exposures—maternal depression and tobacco—were found to be associated with impaired development of infant P50 sensory gating (figure 3).
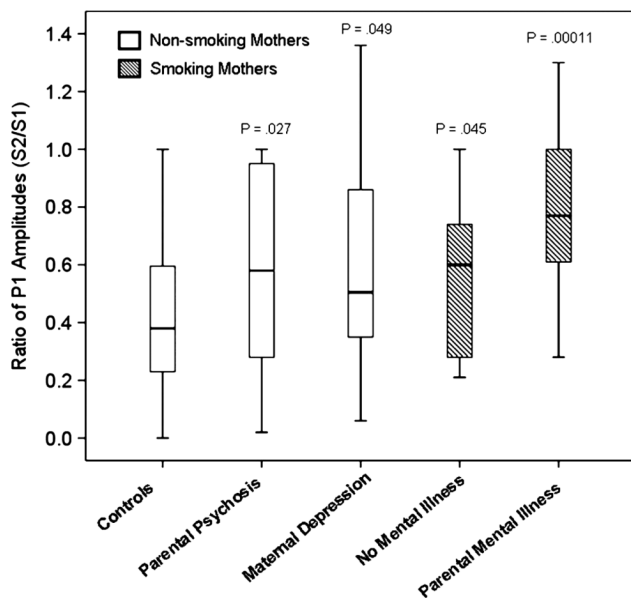

Fig. 3. Inhibitory Gating of the P50 Auditory Evoked Response in the Paired Stimulus Paradigm. Increased ratios (S2/S1) in infants with psychotic parents or depressed mothers compared with controls are indicative of diminished cerebral inhibition. Increased ratios were also seen infants whose mothers smoked during pregnancy, regardless of whether the parents had mental illnesses. *P* values represent each group's comparison with controls. Copied with permission (figure 2, Hunter et al[146]).

The Endophenotype Predicts Elevated Risk for Schizophrenia-Associated Core Cognitive and/or Behavioral Deficits

The criterion that has perhaps created the most difficulty for infant schizophrenia endophenotype development is the requirement of association to disease. The delay between infant endophenotype assessment and the potential onset of psychosis is, at a minimum, years, and extends up to 4 decades before all individuals age out of the developmental period of highest risk. However, more recent conceptualizations of schizophrenia consider schizophrenia as a complex illness with multiple domains of impairment,[120–126] many of which may overlap with other psychiatric disorders.[84,85] While the optimal way to parse these various domains remains under debate, many of the nonpsychotic domains may develop at a younger age. As an initial exploration of this area, we chose to examine two nonpsychotic but clinically relevant domains, attentional impairment[127,128] and anxiety.[129,130] Both domains can present as early as preschool age. The relationship between infant sensory gating and preschool symptomology was explored in 48 children (24 with robust infant P50 sensory gating and 24 with impaired P50 sensory gating). Impairments in infant sensory gating are associated, over 3 years later, with elevated parent-reported attentional and anxiety symptoms.[131] Given the neurobiological and symptomatic overlap between schizophrenia-vulnerability and a number of neuropsychiatric disorders, it is not surprising that P50 sensory gating is abnormal in attention deficit-hyperactivity disorder,[132] lower IQ autism,[133] schizophrenia,[134] bipolar disorder,[135] panic disorder,[136] and posttraumatic stress disorder.[137–140] Validation of P50 sensory gating as a schizophrenia endophenotype does not preclude its value in studying other developmental psychiatric disorders.

## The Endophenotype Is Modifiable During the Perinatal Window

The long-term goal for infant endophenotype development should be use of the endophenotype to identify and test primary prevention strategies. Thus, we propose an additional criterion, that the endophenotype should be modifiable during the perinatal window. Once this window has closed at or soon after birth, there is little evidence for undoing in childhood or adulthood any abnormalities of early fetal brain development. Based on the neurobiological model described in figure 2, we hypothesized that increased agonist would increase α7nAChR activity and improve early development. Such increased activity might compensate for the decrease in alpha7 nicotinic receptor expression associated with genetic risk for schizophrenia. The expression of CHRNA7 mRNA and alpha7 nicotinic receptors is higher in the fetal period than after birth.[141] Therefore, fetal development would appear to be

the relevant window of development to address pathophysiological risk related to these receptors. Despite high prenatal α7nAChR expression, acetylcholine neurons have not yet formed synapses with their postsynaptic targets on inhibitory interneurons. Instead, prenatal stimulation of α7nAChR appears to be via choline, a selective α7nAChR agonist. Choline is present at substantive levels in both the amniotic fluid and in the fetus itself, including in the fetal brain. Fetal brain levels of choline can be increased by maternal dietary supplementation.[142]

We thus hypothesized that perinatal choline supplementation would increase activation of alpha7 nicotinic receptors and normalize any developmental defect associated with deficiencies in the receptors, including
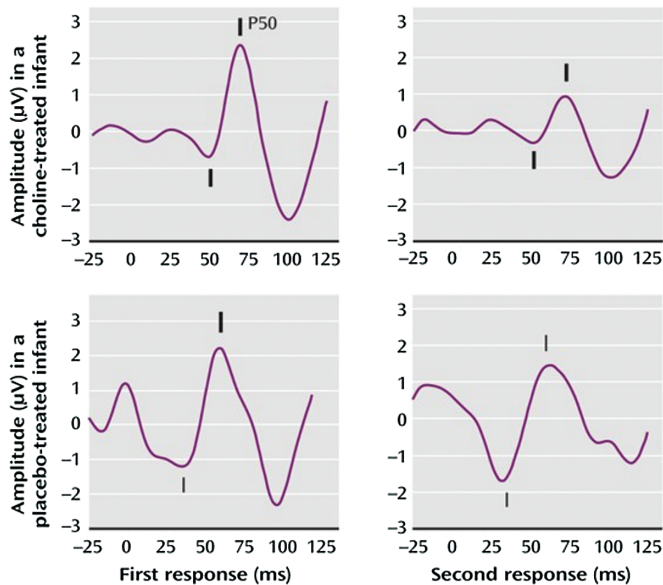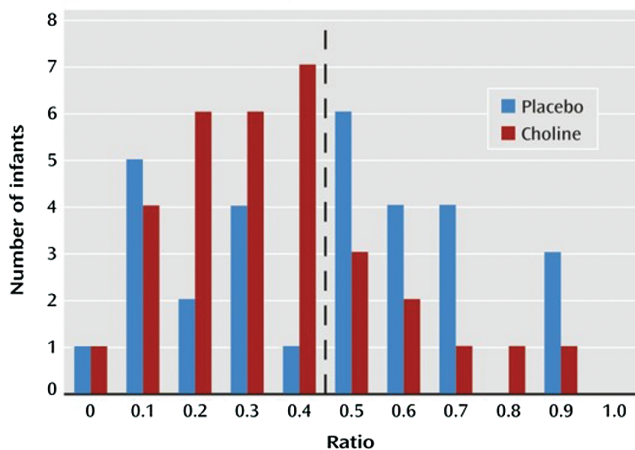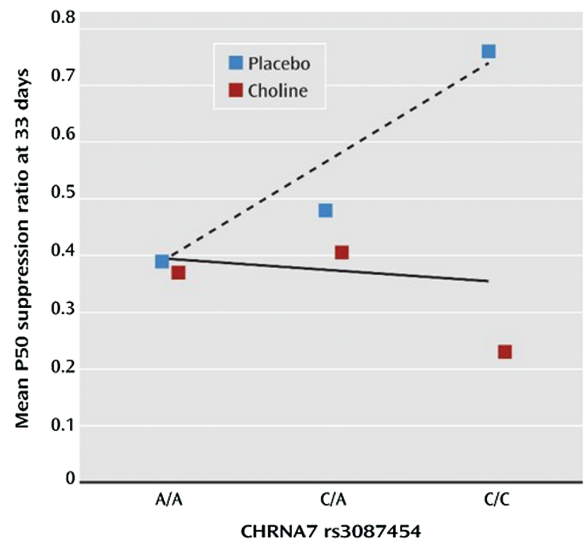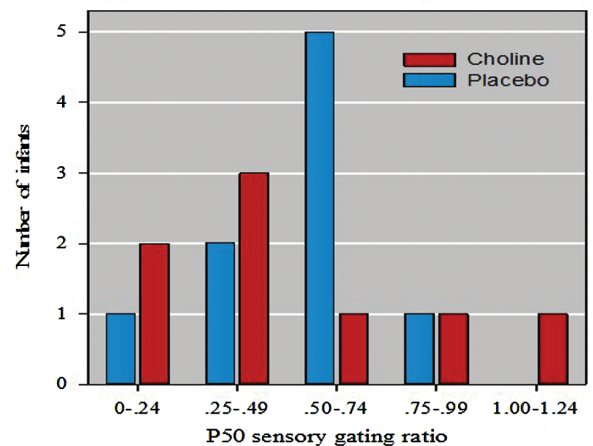

Fig. 4. Outcomes of perinatal trial in infant who had received choline or placebo in utero and after birth. (A) Recordings of P50 averaged evoked potentials in 2 infants. The gestation-adjusted age is 30 days for the infant treated with choline and 29 days for the infant treated with placebo. For each infant, the 2 auditory stimuli were delivered 0.5 seconds apart. The diminished amplitude of the second response relative to the first demonstrates cerebral inhibition, quantified as the P50 ratio, which was 0.38 in the choline-treated infant and 0.92 in the placebo-treated infant. Positive potential is upward; amplitudes were measured from the preceding negative potential, both indicated by tick marks. (B) Histogram of the P50 ratio at a mean adjusted age of 33 days. The dashed line demarcates the normal level of P50 inhibition, with a ratio <0.5. More choline than placebo-treated infants were in this normal range ($\chi^2 = 6.90$, $df = 1$, $P = .009$). (C) CHRNA7 SNP rs3087454 has been associated with risk for schizophrenia and impacts α7 nicotinic cholinergic receptor expression. In the placebo-treated infants, a significant correlation of P50 ratio with rs3087454 was observed ($r_s = 0.38$, $df = 30$, $P = .032$, dashed line). There was no significant correlation for the choline-treated infants (solid line). In human infants, perinatal choline supplementation mitigates the effect of genetic risk on early cerebral inhibition development. (D) Histogram of the P50 ratio in a separate group of infants whose mothers had psychosis. Seventeen subjects provided insufficient power for statistical analysis; however, the distribution of scores is similar to that seen in infants from healthy parents. A higher percentage of infants with psychotic parents who received choline had P50 sensory gating rations <0.50 (62.5% vs 33.3%). Adapted from figures 1 and 2, Ross et al.[143]

deficits in P50 sensory gating. We completed a preliminary randomized control trial in 76 healthy pregnant women. Infants whose mothers had received prenatal choline supplementation demonstrated improved infant P50 sensory gating, compared to those whose mothers received placebo. Notably, there was an interaction between choline supplementation and CHRNA7 genotype supporting the proposed mechanism of α7nAChR agonism.[143] A separate randomized trial, focused on pregnant women with psychosis, is underpowered for statistical significance; however, outcomes are consistent with those found in healthy pregnant women (figure 4). Maternal choline supplementation thus appears to modify P50 sensory gating by overcoming the pathophysiological effect of infant CHRNA7 genotypes that are associated with increased risk for later development of schizophrenia (figure 4).

Conclusions

Schizophrenia is a neurodevelopmental disorder whose pathogenesis begins in the perinatal period. The endophenotype strategy has been of high scientific value for studies in adults, advancing understanding of the disease and facilitating development and testing of novel intervention strategies. However, the lack of endophenotypes useful in young infants has contributed to the lack of focused primary prevention strategies. The proposed validity criteria are intended to facilitate discovery and use of developmentally-sensitive endophenotypes. While a number of issues remain to be tackled to fully validate the endophenotype, this approach has already resulted in the identification of a possible neurobiologically-informed primary prevention intervention. Broader adoption of these modified criteria may facilitate the identification and validation of other perinatally-usable endophenotypes and lead to effective primary prevention.

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