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Relating the effects of prenatal stress in rodents to the pathogenesis of schizophrenia

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The study by Escobar et al in this issue (1) shows that exposure of the pregnant rat dam at day 19 of gestation to a bacterial endotoxin, a manipulation used to model maternal immune activation (MIA), leads to abnormal postnatal development of synaptic long-term depression (LTD) in the CA3-CA1 hippocampal circuit in the offspring. The form of LTD they examined is induced by low frequency stimulation of the glutamatergic efferents from CA3 which synapse extensively onto the dendrites of the CA1 projection neurons. The study shows that in neonatal brains from control and MIA-exposed offspring, LTD in the CA3-CA1 circuit induced by a train of low-frequency stimuli is prominent and depends on NMDA receptors and downstream messengers. This LTD normally decreases across postnatal development; however, MIA-exposed offspring show a more rapid developmental reduction, losing this form of plasticity altogether by the late juvenile period. The authors also find a parallel developmental loss of NMDA (relative to AMPA) currents in CA1 neurons of MIA offspring, but do not address whether this is causally related to the developmental loss of LTD. They add a more preliminary finding, that MIA offspring also show abnormal ontogeny, particularly evident in the late juvenile period, of a different form of synaptic plasticity regulated in part by metabotropic glutamate receptors. Taken together, the findings support the hypothesis that MIA leads to changes in mechanisms regulating synaptic plasticity in the CA3-CA1 circuits that may, in turn, be hypothesized to have a profound and persistent impact on the ability of CA1 neurons to integrate input signals from other hippocampal subregions, the subiculum, the entorhinal and parahippocampal cortex, and the limbic basal forebrain (c.f. 1) (2).

Many believe that the Escobar et al. and similar studies have important implications for the pathogenesis and expression of schizophrenia. Unpacking the assumptions underlying this belief, however, reveals critical gaps in knowledge that remain to be filled in order to build a theory linking prenatal maternal stress exposure to neural circuit dysfunction in schizophrenia. Below, we illustrate some of the domains of knowledge and the gaps among them.

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The perhaps most necessary of these domains is the evidence linking ‘prenatal stressors’ to the risk for schizophrenia in the offspring. Epidemiologic studies have shown that adverse maternal exposures during gestation, including various nutritional deficiencies, infections, and toxins are associated with increased risk for neurodevelopmental disorders in children, and some specifically to disorders, such as schizophrenia, generally diagnosed after puberty (e.g. Reference 2 in Escobar et al.) (3). Although it is not yet clear which of these findings will stand the test of time, the accumulating evidence suggests that at least some of them will. These ‘prenatal stressors’ are sometimes considered as a group that may operate via common mechanisms. There is some support for this in both the animal and epidemiologic literature. Although maternal infection is the exposure most closely modeled by MIA (3, 4), oxidative stress, a mechanism postulated as contributing to the effects of MIA, can be induced by a wide range of prenatal stressors (5). Indeed, Escobar et al show and cite evidence from rodent studies in support of multiple prenatal stressors impacting NMDA receptor function, possibly altering regulation of free radical release.

Nonetheless, there remain significant gaps in our understanding of the similarities and differences among these putative prenatal stressors, more specifically how they differ in terms of the sensitive period of gestation, the maternal, placental and fetal responses induced, or the impact on the expression of schizophrenia-relevant phenotypes. As an example, epidemiologic and animal model studies provide complementary, but incomplete, evidence that the effects of prenatal stressors on the expression of schizophrenia-related abnormalities depend on the gestational timing of the exposure, and that this may differ among stressors. In the epidemiologic literature, a schizophrenia-relevant sensitive period is best illustrated for the association between maternal starvation in early gestation and schizophrenia (4). This is consistent with the sensitivity of the early embryo to epigenetic effects, and with the potential for *de novo* mutations in the early embryo to disrupt neurodevelopment (4). Exposure to maternal starvation in later gestation has been associated with affective disorders but not with schizophrenia (4). These epidemiological data are complemented by evidence from rodent models that the gestational timing of MIA and other maternal stressors determines the sequelae of brain-behavior abnormalities in the offspring (e.g. 6, 7, 8). For MIA, mid-to-late gestational exposure produces neuropathological and behavioral abnormalities relevant to schizophrenia (8). On the other hand, early gestational exposure to immobilization stress or corticosteroid treatment may produce psychomotor and social behavioral abnormalities in offspring relevant to negative symptoms in schizophrenia (6, 7). Before we conclude that there are discrepancies with regard to “schizophrenia-relevant” gestational periods across species and exposures, more work is needed to compare the relevant stressors and maternal stress responses across species, to identify homologous phases of neurodevelopment in the neural systems most affected in schizophrenia, and to characterize the effects of cell metabolic challenges at these phases. The reality of multiple sensitive periods impacting the risk for schizophrenia requires us to be more precise as we translate findings from one level of analysis to the next.

Two more links in our chain of evidence pertain to regulation of synaptic function by the NMDA receptor or its downstream effectors, and to the possibly a heightened sensitivity of the hippocampus to changes in these mechanisms. Systemically administered NMDA antagonists such as phencyclidine and ketamine produce psychosis in humans, as well as schizophrenia-relevant brain metabolic and cognitive deficits in humans and animal models (9). In support of this, post-mortem studies show decreases in the number of NMDA and other glutamatergic receptors in the hippocampus, with variation across subregions (10)(and fewer studies other cortical regions). In rodent prenatal stressor models, reduced synaptic plasticity mediated by NMDA receptors in the hippocampus has been reliably reported (c.f. 1), but there is less sampling of other brain regions. Appearing at first inconsistent with a reduction in NMDA receptor function are the brain imaging data from healthy humans

administered NMDA antagonists and schizophrenia patients showing an *increase* in apparent basal metabolic activity in limbic and paralimbic cortical regions, prominent in patients in CA1 and subiculum (11, 12). This is accompanied by a *decrease* in the capacity for activation in response to cognitive demands (9, 11). Reduced activity of interneurons may help explain this (9). However, overall, there is insufficient data on functional changes in NMDA receptors or related cellular processes in schizophrenia, and a similar paucity of animal studies examining the intervening variables that may causally link changes in synaptic plasticity (or related intracellular processes) to imaging and cognitive phenotypes homologous to those measurable in schizophrenia. The capacity for plasticity in hippocampal circuits may also be related to increased vulnerability of specific hippocampal subregions to the cellular stress events induced by the maternal stress or immune responses (1). This may, in turn, relate to the histopathology and reduced *in vivo* volume of the hippocampus in schizophrenia (9). Still it is unclear whether the hippocampus is special or just one among many cortical circuits in which developmental abnormalities in NMDA-dependent synaptic plasticity impair the ability of neurons to properly integrate inputs and transmit a normal signal to the next node. Perhaps there is truth in both. To answer this, clinical and animal disease-model studies must systematically examine regional differences in neuropathology, neural activity and connectivity. In parallel, basic studies are needed to better characterize the regional heterogeneity in neurodevelopment and synaptic plasticity regulation that might underlie these differences.

In the above-illustrated and other domains of evidence, we find some support for the idea that a maternal stress response, perhaps requiring an immune component, may induce a cascade of biochemical events that ultimately ‘stresses’ developing neurons, and perturbs development of synaptic plasticity in hippocampal and perhaps other circuits. But we also find considerable gaps in the knowledge needed to elaborate a well-grounded theory. To fill these gaps we propose a more directed inter-disciplinary effort involving parallel and interrelated research. This research must examine whether the exposures and their timing in rodents model the human exposures. Moreover, the translational schizophrenia research in psychiatry needs to draw more from, and influence, developmental neurobiological research in order to understand the neurodevelopmental events underlying mediating the increased risk for psychiatric disease conferred by prenatal stressors. We need to increase our use of outcome measures used in clinical and epidemiologic studies in the animal models. This will allow us to more directly test whether the synapse- and circuit-level abnormalities produced by various prenatal exposures can drive imaging, neurophysiological or cognitive phenotypes measurable in schizophrenia. And finally, epidemiologic studies could be more explicitly designed to test the predictions generated by animal studies. Such research will put our optimism about translational research to the test. We are confident, however, that it will lead to a deeper understanding of the development and vulnerabilities of neural systems that mediate the symptoms of schizophrenia, and accelerate the discovery of new strategies for prevention and treatment.

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REFERENCES

1. Escobar M, Crouzin N, Cavalier M, Quentin J, Roussel J, FLante' F, et al. Early, time-dependent disturbances of hippocampal synaptic transmission and plasticity after in utero immune challenge. *Biological Psychiatry*. 2011 this issue.

2. Witter MP, Wouterlood FG, Naber PA, Van Haeften T. Anatomical organization of the parahippocampal-hippocampal network. *Annals of the New York Academy of Sciences*. 2000; 911:1–24. [PubMed: 10911864]
3. Brown AS, Derkits EJ. Prenatal Infection and Schizophrenia: A Review of Epidemiologic and Translational Studies. *Am J Psychiatry*. 2010; 167:261–280. [PubMed: 20123911]
4. Lumey LH, Stein AD, Susser E. Prenatal famine and adult health. *Annual Review of Public Health*. 2011; 32:237–262.
5. Wells PG, McCallum GP, Chen CS, Henderson JT, Lee CJJ, Perstin J, et al. Oxidative stress in developmental origins of disease: teratogenesis, neurodevelopmental deficits, and cancer. *Toxicol Sci*. 2009; 108:4–18. [PubMed: 19126598]
6. Kleinhaus K, Steinfeld S, Balaban J, Goodman L, Craft TS, Malaspina D, et al. Effects of excessive glucocorticoid receptor stimulation during early gestation on psychomotor and social behavior in the rat. *Developmental Psychobiology*. 2010; 52:121–132. [PubMed: 20091810]
7. Seckl JR. Glucocorticoids, developmental 'programming' and the risk of affective dysfunction. *Progress in Brain Research*. 2008; 167:17–34. [PubMed: 18037004]
8. Meyer U, Nyffeler M, Engler A, Urwyler A, Schedlowski M, Knuesel I, et al. The Time of Prenatal Immune Challenge Determines the Specificity of Inflammation-Mediated Brain and Behavioral Pathology. *The Journal of Neuroscience*. 2006; 26:4752–4762. [PubMed: 16672647]
9. Krystal J, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R. NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. *Psychopharmacology*. 2003; 169:215–233. [PubMed: 12955285]
10. Harrison PJ, Law AJ, Eastwood SL. Glutamate Receptors and Transporters in the Hippocampus in Schizophrenia. *Annals of the New York Academy of Sciences*. 2003; 1003:94–101. [PubMed: 14684437]
11. Heckers S. Neuroimaging studies of the hippocampus in schizophrenia. *Hippocampus*. 2001; 11:520–528. [PubMed: 11732705]
12. Schobel SA, Lewandowski NM, Corcoran CM, Moore H, Brown T, Malaspina D, et al. Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. *Archives of General Psychiatry*. 2009; 66:938–946. [PubMed: 19736350]