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Different Paths to Core Pathology: The Equifinal Model of the Schizophrenia Syndrome

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Schizophrenia is a clinically heterogeneous disorder that is perhaps more accurately characterized as "the schizophrenia syndrome." This clinical heterogeneity is reflected in the heterogeneous neurobiological presentations associated with the illness. Moreover, even highly specific neural aberrations that are associated with distinct symptoms of schizophrenia are linked to a wide range of risk factors. As such, any individual with schizophrenia likely has a particular set of risk factors that interact and converge to cross the disease threshold, forming a particular etiology that ultimately generates a core pathophysiology. This core pathophysiology may then produce 1 or more symptoms of schizophrenia, leading to common symptoms across individuals in spite of disparate etiologies. As such, the schizophrenia syndrome can be considered as an *equifinal* entity: a state of dysfunction that can arise from different upstream etiologies. Moreover, schizophrenia etiologies are multifactorial and can involve the interactive effects of a broad range of genetic, environmental, and developmental risk factors. Through a consideration of how disparate etiologies, caused by different sets of risk factors, converge on the same net dysfunction, this paper aims to model the equifinal nature of schizophrenia symptoms. To demonstrate the equifinal model, we discuss how maternal infection and adolescent cannabis use, 2 recognized schizophrenia risk factors, may interact with other genetic, environmental, and/or developmental risk factors to cause the conserved clinical presentation of impaired working memory.

Key words: basket cell/maternal infection/cannabis/etiology/working memory/prefrontal cortex/parvalbumin/cholecystokinin

Introduction

Schizophrenia is a neurodevelopmental syndrome associated with functional impairments extending across social, emotional, perceptive, and cognitive domains.[1,2] The complex clinical presentation of schizophrenia is accompanied by an equally complex etiology and pathology, thought to involve genetic susceptibility that provides a vulnerable substrate upon which environmental insults can act.[3,4] Many identified gene × environment interactions emerge during particular developmental periods. Thus, the etiologies that produce symptoms of schizophrenia may be thought of as the convergence of gene × environment × development (G × E × D) risk factors, which may need to be present in particular combinations to produce clinically relevant pathology. Such combinations of risk factors are likely necessary to initiate the pathogenic cascade that ultimately produces clinical symptoms.[5] As there are likely many sets of G × E × D risk factors capable of ultimately producing an individual clinical symptom of schizophrenia, any given symptom of schizophrenia can represent an *equifinal* outcome: one that can emerge from different upstream etiologies (figure 1). One research strategy to mitigate this etiological complexity is to focus studies on symptoms that are associated with defined neuronal circuitry pathways, as even different etiologies will likely arrive at a common pathological entity.[6] Impaired cognitive ability, namely working memory, is a candidate symptom to study through this type of approach.

Working memory, the ability to transiently hold information in mind to guide future thoughts or behaviors,[7] is a fundamental cognitive function consistently impaired across individuals with schizophrenia.[6,8] Indeed, working memory deficits are present before the emergence of positive symptoms,[9] are pervasive and persistent,[8,10] and may underlie deficits seen in other cognitive domains in schizophrenia.[11] Further, cognitive ability, including working memory, is the best predictor of important functional outcomes, such as employment, reintegration into society, and relapse.[12,13] Working memory ability depends

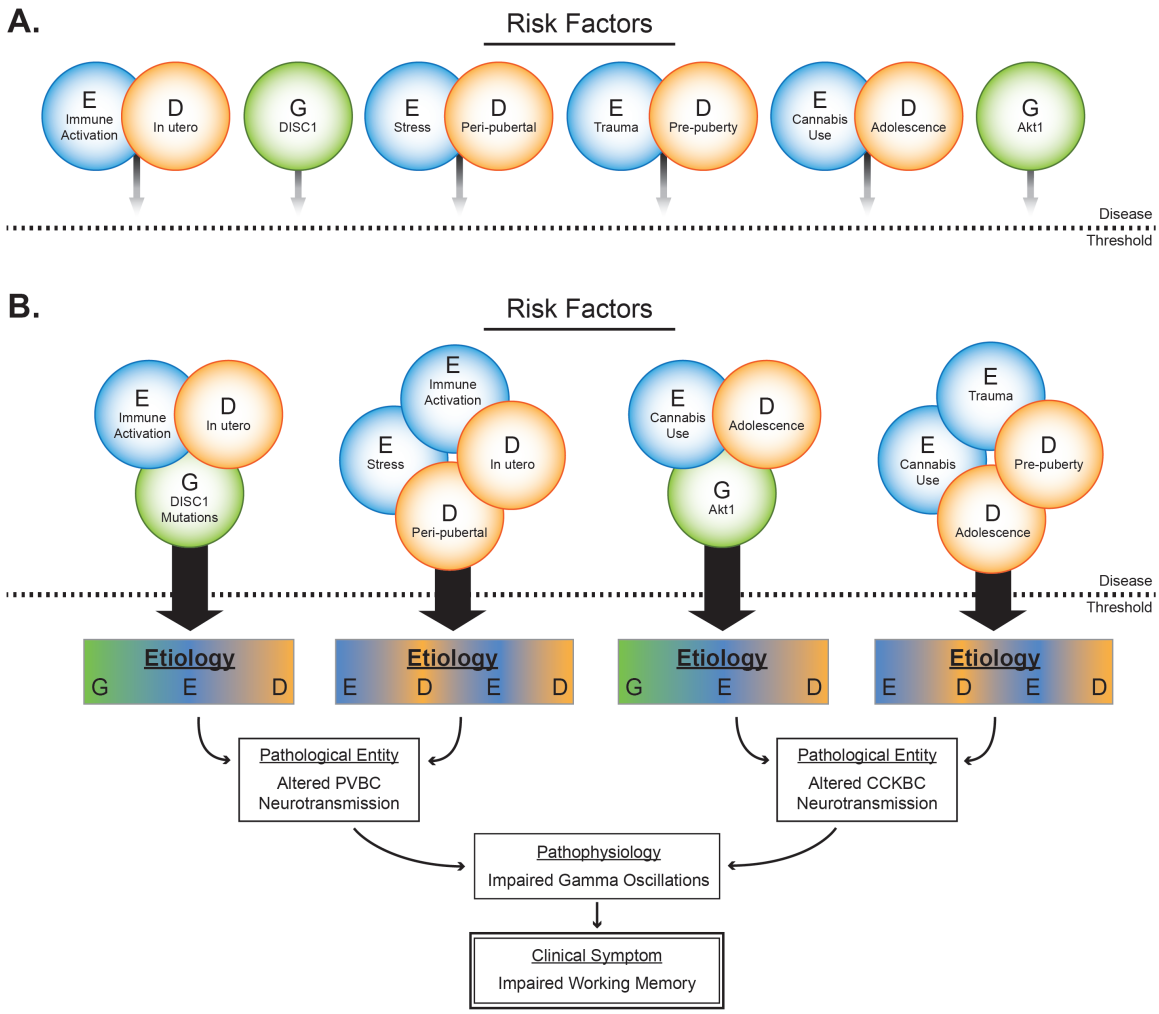

Fig. 1. Model of the equifinal nature of impaired working memory in schizophrenia. **(A)** Genetic (G), environmental (E), and developmental (D) risk factors are not potent enough to cross the disease threshold. **(B)** In specific combinations, these risk factors can cross the disease threshold to produce a multifactorial etiology. These distinct etiologies can then initiate pathogenesis to produce a pathological entity, which leads to the core pathophysiology that underlies the clinical symptom. Distinct etiologies can lead to the same pathological entity, and distinct pathological entities can lead to a common pathophysiology. This framework identifies how different, multifactorial etiologies can ultimately lead to a common clinical symptom.

upon proper activation of circuitry in the prefrontal cortex (PFC).[14,15] One process thought to be essential for working memory ability is synchronized neuronal activity in the gamma frequency (30–80 Hz).[16–19] Accordingly, individuals diagnosed with schizophrenia show altered PFC activation, including lower power of gamma oscillations, during tasks that recruit working memory.[18,20] Thus, alterations in PFC circuitry may contribute to the cognitive impairment seen in individuals with schizophrenia.

Gamma oscillations depend upon the coordinated inhibition of pyramidal cells by perisomatic-targeting GABAergic basket cells that express the calcium-binding protein parvalbumin (PV).[18,21] PV basket cells are thought to be critical for the precise, rapid pace of gamma oscillations, and direct stimulation of PV basket cells can generate gamma oscillations.[22,23] Gamma oscillatory activity can be modulated by a second population of GABAergic basket cells that express the neuropeptide cholecystokinin (CCK).[24] CCK basket cells are thought to be critical for fine-tuning gamma oscillations and PV basket cell activity,[21,24] and they also express the cannabinoid 1 receptor (CB1R).[25] In addition to distinct molecular and electrophysiological profiles, these 2 basket cell populations also have distinct developmental trajectories from birth to adulthood.[26] Interestingly, molecular alterations that may impair the ability of PV and CCK basket cells to regulate gamma oscillations have been identified in studies of postmortem human PFC tissue of individuals with the schizophrenia syndrome.[27] In PV basket cell axonal boutons, protein levels of PV and the cardinal GABA-synthesizing enzyme, GAD67, are lower.[28,29] In CCK basket cells, mRNA levels of CCK and the CB1R are lower.[30]

The distinct molecular and developmental profiles of PV and CCK basket cells render them sensitive to

different risk factors. However, as each population can influence gamma oscillations, disparate factors acting on either cell type may produce a core pathophysiology of dysfunctional gamma oscillations (figure 1). This paper considers the equifinal nature of working memory deficits in the schizophrenia syndrome by discussing how different multifactorial etiologies, through different neurobiological mechanisms and active at different developmental periods, could give rise to the core pathophysiology of impaired gamma oscillations and the common clinical symptom of impaired working memory.

Maternal Infection-Associated Risk Factors and PV Basket Cell Dysfunction

One ExD risk factor associated with increased risk of schizophrenia is maternal infection.[31–33] For example, 1 review of epidemiological studies calculates that approximately 30% fewer individuals would develop schizophrenia if the 3 most common maternal infections were completely prevented.[34] However, maternal infection alone is not sufficient to cause schizophrenia. For example, while up to 50% of the general population is infected during influenza pandemics,[35] the relative risk of schizophrenia increases 1- to 3-fold after such an outbreak.[34,36] As such, most offspring exposed to maternal infection will not go on to develop schizophrenia. Thus, the vulnerability induced by maternal infection must interact with other genetic, environmental, and/or developmental factors to cross the disease threshold.[37–40]

Experimental animal models of maternal immune activation have provided insights into these multifactor relationships. For example, mice exposed to immune activation in utero show schizophrenia syndrome-relevant behavioral abnormalities in adulthood, such as impaired sensorimotor gating[41–43] and cognitive ability,[41,43–47] including working memory.[48,49] Maternal immune activation models also show molecular changes that are identified in the PFC of individuals with schizophrenia,[50] including lower expression of PV,[43] GAD67,[51] and GAD67 in PV axonal boutons.[52]

As diverse infectious agents can cause similar molecular and behavioral alterations, some shared mechanism of immune activation likely underlies this effect. One likely candidate is the maternal and/or fetal immune response. Maternal infection significantly increases the levels of immune-associated agents in the fetal brain, namely proinflammatory cytokines.[53,54] Proinflammatory cytokines increase the production of reactive oxygen and reactive nitrogen species, which can lead to a state of oxidative stress. While a short period of oxidative stress can be tolerated in the stable adult cortex, the developing fetal brain may be particularly vulnerable given its lower antioxidant capacity, high rate of oxygen metabolism, and significant population of immature cells.[55,56] PV basket cells appear to be particularly sensitive to the damaging effects of proinflammatory cytokine release and oxidative stress given their protracted development and the especially high energetic demands their electrophysiological and circuit properties afford.[57–59]

Importantly, maternal infection alone is unlikely to initiate a pathogenic cascade significant enough to cross the disease threshold. However, once PV basket cells are impaired by prenatal immune activation, additional insults acting upon these vulnerable cells may more readily tip the system over the disease threshold. Indeed, recent animal studies investigating the effects of combinatorial E × D risk factors support just such an interpretation. Studies that induce maternal immune activation followed by peripubertal stress show an additive effect on both behavioral and molecular measures. This combination produces more robust deficits in cognition and sensorimotor gating[60] and GAD67 mRNA and protein levels[61] than either challenge alone. Moreover, mice exposed to maternal immune activation show greater proinflammatory cytokine release during peripubertal stress.[60] Together, these results suggest that maternal immune activation is a risk factor that renders the developing cortex, and especially PV basket cells, more vulnerable to the proinflammatory cytokine release initiated by peripubertal stress. The lower PV and GAD67 expression caused by these upstream insults is predicted to impair gamma oscillations,[62] and subsequently working memory ability.[27]

Experimental animal studies have also investigated G × E × D interactions in the context of maternal immune activation. Mutations in the DISC1 gene have been linked to schizophrenia and other severe mental illnesses,[63] and DISC1 mutations in mice can cause reductions in PV and GAD67[64–67], as well as deficits in gamma oscillations[68] and working memory ability.[69] Combining maternal immune activation with a DISC1 genetic mutation (G × E × D risk factors) produces greater deficits in PV in the PFC[70] and measures of cognitive ability and sensorimotor gating[70–73] than the gene mutation alone. Thus, DISC1 mutations appear to render animals, and putatively humans, more susceptible to in utero immune activation. Accordingly, an epidemiological study demonstrated that in utero exposure to infection combined with genetic liability (ie, a family history of schizophrenia) conferred a significantly increased risk for developing schizophrenia.[38] As such, other genetic and environmental risk factors present in an individual may determine the impact of maternal infection on cognitive function, with clinically relevant pathology emerging only when specific risk factors co-occur.

Adolescent Cannabis Use-Associated Risk Factors and CCK Basket Cell Dysfunction

Sustained cannabis use during early adolescence has repeatedly been shown to increase risk for developing

schizophrenia.[74] It may also potentiate schizophrenia onset: in a large meta-analysis, cannabis users developed psychotic symptoms an average of 3 years earlier than individuals who developed psychotic symptoms but did not use cannabis.[75] Further, the link between heavy cannabis use during adolescence and schizophrenia is not readily explained as "self-medication," as cannabis use almost always precedes emergence of psychotic symptoms in these individuals.[74]

Cannabis use during adolescence is associated with persistent impairments in cognitive ability, including working memory, which can extend for years after abstinence.[74,76–80] For example, studies in rats found that when Δ9-tetrahydrocannabinol (THC), the principal psychoactive chemical in cannabis,[81] is chronically administered during adolescence, it can produce spatial working memory deficits in adulthood.[82] Given this lasting relationship, cannabis may exert its effects by altering the circuitry involved in regulating gamma oscillations and working memory processes. Studies in both humans and animal models support this interpretation: the power of evoked gamma oscillations is significantly reduced in chronic cannabis users,[83] in human subjects acutely administered THC,[84] and in adult mice that were administered THC during the pubertal period.[85]

CCK basket cells may be especially affected by the presence of THC in the brain. THC exerts its actions by activating the CB1R,[86] a $G_{i/o}$-protein coupled receptor.[87] CB1Rs are highly expressed in the PFC,[88] and in primate PFC, CB1Rs are almost exclusively expressed on CCK basket cells.[25] The unique sensitivity of prefrontal CCK basket cells to exogenous cannabinoids suggests that they may be a key anatomical substrate mediating the long-term effect of cannabis on both gamma oscillations and working memory performance. Indeed, during the intense pyramidal cell firing characteristic of gamma oscillations, endogenous cannabinoids (known as endocannabinoids) are retrogradely released from these pyramidal cells and bind to the CB1Rs located on CCK basket cells.[89] Activation of CB1Rs suppresses GABA release from CCK basket cells,[89–91] leading to reduced inhibition of pyramidal cells[92,93] in a process termed depolarization-induced suppression of inhibition. Chronic activation of CB1Rs via exogenous cannabinoids during prefrontal cortical development may disrupt this usually carefully regulated system and cause persistent impairments in the ability of CCK basket cells to properly regulate gamma oscillations.[94]

However, despite a significant interaction with both schizophrenia onset[74] and working memory impairment,[95] and the existence of a plausible biological mechanism for its effects, adolescent cannabis use appears to be neither necessary nor sufficient to cause schizophrenia onset. Indeed, only a minority of adolescents who smoke cannabis develop any kind of psychosis, and not all individuals who develop schizophrenia smoke cannabis during adolescence.[74] Thus, as in the case of maternal immune activation, adolescent cannabis use may represent an E × D interactive risk factor, promoting schizophrenia symptomology only in individuals specifically vulnerable due to the presence of other risk factors. Indeed, studies suggest that genetic variation may play a significant role in determining an individual's susceptibility to the damaging effects of adolescent THC exposure. For example, carriers of the *AKT1* rs2494732 C/C single nucleotide polymorphism who also used cannabis were at a 2 times greater risk of developing a psychotic disorder, compared with T/T carriers.[96,97] Moreover, the influence of the C/C genotype scaled with frequency of use: C/C allele carriers who used cannabis daily had a 7-fold greater risk of developing a psychotic disorder than T/T allele carriers with equivalent cannabis use.[97] Further, heavy cannabis users with the C/C genotype perform worse on cognitive tasks, even after a year of cannabis abstinence.[98] As such, the *AKT1* rs2494732 C/C genotype may render individuals especially sensitive to the effects of chronic CB1R stimulation during adolescence.

Finally, like maternal immune activation, sustained adolescent cannabis use may interact with other E × D risk factors to compound schizophrenia risk. Childhood trauma is an E × D risk factor[99] shown to act in conjunction with adolescent cannabis use to compound risk for schizophrenia onset.[100] For example, a national comorbidity study demonstrated that individuals who experienced childhood sexual trauma and used cannabis before 16 years of age were nearly 12 times more likely to develop a psychotic disorder than individuals who only experienced 1 risk factor.[101] As such, adolescent cannabis use may represents a single contributory E × D "hit" that may produce the net outcome of schizophrenia only in conjunction with other genetic, environmental, and/or developmental risk factors.

Conclusions

Maternal immune activation and adolescent cannabis use represent just 2 examples, selected from a pool of schizophrenia syndrome risk factors, which can interact with other genetic, environmental, and developmental risk factors to create a schizophrenia etiology[102–104] (figure 1). Throughout their lifetimes, individuals are invariably exposed to a wide range of schizophrenia-related risk factors. The studies discussed in this article suggest that these risk factors must occur in particular combinations to cross the disease threshold. It is important to recognize that while these examples outline a useful model of the disease progression, the precise neurobiological underpinnings of disease are invariably more complex. Indeed, impaired PFC gamma oscillations are neither the only mechanism through which the risk factors discussed in this article may confer symptomatology nor the only neurobiological substrate of impaired working memory.

However, a consideration of how particular symptoms can emerge from different etiologies[105,106] may be valuable for producing effective and potent treatments for individuals with a mental illness, and preventative measures for individuals at risk for a mental illness.[5] The efficacy of such a personalized approach has already been demonstrated in medical conditions ranging from breast cancer[107] to cystic fibrosis,[108] and identification of individual etiological routes may inform psychiatric treatment as well.[109,110] For example, drugs that target CCK basket cell functioning may be uniquely effective in individuals with schizophrenia who have a particular genotype and had heavy use of cannabis during adolescence. Such a technique is highly individualized, with treatments targeting individuals who have experienced specific risk factors, and preventative measures targeting individuals with a high likelihood of experiencing specific risk factors. Indeed, with such an approach, the equifinality of schizophrenia symptoms, and the multifactorial nature of schizophrenia etiologies, may become a useful facet of treatment and prevention, rather than an obstacle in its path.

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