Schizophrenia remains an enigmatic illness. Despite the enormous amount of research that has been devoted to disentangling its mysteries, it is still best described by the clinically evident disruptions in mental functioning and behavior that define the condition. Although hereditary factors are significant in the illnecessities' etiology, no major genes have been identified. Furthermore, it is fairly certain that nongenetic environmental events also contribute to risk for the disease. In the majority of cases, multiple genes and additional environmental insults likely interact to cause schizophrenia. Nonetheless, the pathophysiologic mechanisms through which genes and environmental exposures render an individual susceptible to schizophrenia are unknown.

This month’s issue of CNS Spectrums focuses on several aspects of schizophrenia vulnerability. The first two articles consider relatively unexplored etiologic pathways to schizophrenia, specifically advancing paternal age and stressful life events. The final three articles deal with aspects of neural functioning that may illuminate the neurobiologic underpinnings of schizophrenia vulnerability.

The issue begins with a review article by Malaspina and colleagues. The authors present the evidence and putative mechanisms whereby advanced paternal age is associated with schizophrenia risk in offspring. This recently described risk factor in schizophrenia has been found to account for a quarter of the disorder's cases in a large prospective birth cohort. Since advancing paternal age is the major source of de novo mutations in the human population, the association of disease risk with paternal age suggests the involvement of de novo mutations in schizophrenia vulnerability genes.

Next, Corcoran and colleagues present evidence supporting the role of stress in schizophrenia expression in individuals vulnerable to the disorder. The authors review both the basic neurobiological underpinnings of the stress cascade and the current debate over whether neurodegenerative changes may exist in schizophrenia concurrent with neurodevelopmental abnormalities.

The third paper in this month’s issue is contributed by Coleman and colleagues. It is an original research report on olfactory abnormalities in schizophrenia. Deficits in odor identification are among the most robust and stable abnormalities present in the illness and may represent a trait marker. The nature of these deficits and the relationship between odor and social functioning make smell identification an intriguing aspect of schizophrenia psychopathology. The data presented confirm the presence of gender differences in odor identification capacity but show no effect on diagnostic subtype or numerous demographic measures of smell identification.

In their original research feature this month, Malaspina and colleagues examine heart rate variability in a unique sample of schizophrenia patients studied during treatment with haloperidol and while free of medication. High-frequency heart rate variability is a good indicator of cardiac vagal (parasympathetic) modulation, and diminished high-frequency heart rate variability has been associated with increased sudden death following myocardial infarction. The study demonstrated that low vagal tone may be present in schizophrenia patients in the absence of antipsychotics and that haloperidol did not show any effect on the measure. Future research should examine whether low heart rate variability is related to the high death rate from cardiac events among schizophrenia patients.

Finally, Mujica-Parodi and colleagues integrate the affective and cognitive symptoms of schizophrenia in an innovative model that emphasizes emotional arousal and its effect on the filtering of information. An important finding in their data that has great import for other studies on the phenomenology and psychophysiology of schizophrenia is that different positive symptom constellations may interact with arousal to variably yield either improvements or deficits in logical reasoning during stress. This is consistent with schizophrenia being considered a heterogeneous illness.

While schizophrenia may be caused by both genetic factors and environmental exposures, a simple examination of clinical symptoms may not elucidate these etiological pathways. The articles in this month’s issue of CNS Spectrums suggest that cognitive and neurobiological markers may be more proximal indicators of brain dysfunction and hence shed light on the pathophysiology of this illness. Elucidating vulnerability markers in schizophrenia has wide-ranging implications for early identification and prevention (ie, advanced paternal age and odor identification) as well as for treatment (ie, psychosocial and pharmacologic approaches to minimize arousal and effects of stress).