Natural Selection and Schizophrenia
Behavioral and Brain Sciences, volume 27, number 6, December 2004.

Roger J. Sullivan and John S. Allen
Department of Anthropology, California State University, Sacramento, Sacramento, CA 95819-6106; Department of Neurology, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242.
sullivar@csus.edu
www.csus.edu/indiv/s/sullivanr

Open Peer Commentary of Burns, J. K. An Evolutionary Theory of Schizophrenia: Cortical Connectivity, Metarepresentation, and the Social Brain.

Abstract
Evolutionary theories of schizophrenia must account for the maintenance of putative alleles in past and present populations despite reduced fitness among the affected. Such models must also account for extant intersex and population-level variability in the expression of schizophrenia. We argue that genetic balanced-polymorphism hypotheses remain the most robust in terms of modeling and testing these processes in populations.

Commentary
Although we applaud Burns' comprehensive review of several literatures exploring the biology and natural history of schizophrenia, we have several problems with his developmental "costly trade-off" scenario of the evolution of schizophrenia. Our main criticism is that the model does not adequately address why alleles expressing as social dysfunction in schizophrenia have not been removed by natural selection. Burns' very brief rationale is that such genes "may have survived in the genome because of association with adaptive social genes" (pp. 63) and that they represent part of a "costly trade-off" related to "evolving complex cognitive and social abilities" in humans (pp. 64). Burns' "costly trade-off" argument follows similar perspectives set forth by Book (1953), Gottesman and Shields (1982) and Crow (1990) that we will gloss for the sake of brevity as "genetic load" arguments. Costly trade-off and genetic load models do not appear to be very amenable to testing or falsification, and it is thus unclear how they advance our understanding of schizophrenia. While not assuming that evolution operates without constraints, or results in optimality, we find it particularly problematic to argue that social functioning has been highly conserved in social primates, but that genes with a profoundly asocial expression have escaped the action of natural selection.

Taking natural selection seriously requires specifying how schizophrenic alleles are maintained in populations at frequencies higher than mutation rates would allow, given that individuals who are overtly schizophrenic suffer substantially reduced fitness (Allen and Sarich 1988). We believe that the most robust model accounting for the action of natural selection on such alleles remains some manifestation of balanced polymorphism as originally proposed by Huxley et al. (1964). However, there is little evidence supporting the notion advanced by Huxley and others that the polymorphism is maintained by a "physiological advantage" (Carter and Watts 1971, Erlenmeyer-Kimling and Paradowski 1966, Huxley et al. 1964), nor does the genetic data support

a simple heterozygous advantage model to maintain that polymorphism. We support the notion that schizophrenic alleles are maintained via selection of behaviors in the relatives of individuals with schizophrenia that confer higher than average reproductive success (Allen and Sarich 1988). As Burns points out, research results supporting the balanced polymorphism hypothesis are mixed. Such ambiguity is predictable given that an absolute selective advantage in the relatives of individuals with overt schizophrenia of ~5% would be adequate for the maintenance of the polymorphism and yet be difficult to demonstrate (Allen and Sarich 1988; Kidd 1975). The main issue is not to confuse ambiguity in results supporting the balanced polymorphism hypothesis with its viability as a testable genetic model.

A related problem is how Burns' description of a universal schizophrenic genotype can account for population and intersex variability in the expression of schizophrenia. The often reported generalization of a 1% global prevalence of schizophrenia should be thought of as a global average, not the uniform distribution implied in Burns' "constant prevalence of schizophrenia" (pp. 6). Micronesia, where we have been conducting cross-cultural research of the expression of schizophrenia for several years (Sullivan et al. 2000), is a good example with point prevalence ranging from a low in eastern Micronesia of ~0.04% to a high of ~2.0% in the islands of western Micronesia (Hezel and Wylie 1992, Allen and Laycock 1997). In regard to sex-differences in the expression of schizophrenia, the Lifetime Morbid Risk of"strictly defined" schizophrenia in the Micronesian nation of Palau is 2.8% for males and 1.2% for females – a greater than 2:1 male to female risk ratio (Myles-Worsley et al. 1999). Not only is the expression of schizophrenia widely recognized to vary profoundly between males and females, but much of this variation occurs in the crucial domain of social functioning, with females tending to retain significantly more social functioning than males (Childers and Harding 1990, Sullivan and Allen 1999). The need to account for inter-sex variability in evolutionary models of schizophrenia has been acknowledged by Crow (1993; 1996), who has proposed that sex-differences in the expression of schizophrenia may reflect differences in male and female reproductive strategies during the course of human evolution.

The Palauan context is also a good example of reduced reproductive fitness among people with schizophrenia, particularly males. Fertility in a cohort of 49 males (mean age 38.5 years, SD 7.0) and 21 females (mean age 40.8 years, SD 10.1) with chronic schizophrenia was 0.5 (1.1) and 2.3 (1.7) offspring on average for the males and females respectively (unpublished data), compared to a total Palauan fertility of 2.8 at the time of the 1993 census (Levin et al. 1993).

We believe that an evolutionary account of schizophrenia must necessarily uncouple the selection events that led to the conservation of traits for social functioning in the environments of the past, and the environments of the present which may interact with behavioral phenotypes in ways that are entirely novel in evolutionary terms. For example, based on the assumption that the selective environment of schizophrenic alleles comprised small, face-to-face social groups, we have hypothesized 1) that negative selection against schizophrenic genes in small-scale societies with unavoidable social-competence demands was more profound than in the comparative anonymity of modern urban environments (Allen 1997); and 2) that social dysfunction among people with schizophrenia today will be maximized in face-to-face contexts (Sullivan and Allen 1999).

In summary, an evolutionary model of pathology must specify plausible selection pressures affecting the putative alleles in both the past and present contexts and must be able to account for population variability in the expression of the pathology in the present (Sullivan and Hagen 2002). Burns' developmental model is weak in addressing either of these criteria. Genetic balanced-polymorphism models of schizophrenia remain robust in that they can accommodate population-level variation in the expression of schizophrenia and the maintenance of alleles in extant populations despite reduced fertility in overt schizophrenics. In contrast, Burns' "costly trade-off" model does not adequately address these processes and will be difficult to test or falsify.

References

Allen, J. S. (1997). Are traditional societies schizophrenogenic? Schizophrenia Bulletin, 23(3), 357-364.

Allen, J. S., & Laycock, J. L. (1997). Major mental illness in the island Pacific: A review. Pacific Health Dialogue, 4, 105-118.

Allen, J. S., & Sarich, V. M. (1988). Schizophrenia in an evolutionary perspective. Perspectives in Biology and Medicine, 32, 132-153.

Book, J. A. (1953). Schizophrenia as a gene mutation. Acta Genetica et Statistica Medica, 4, 133-199.

Carter, M., & Watts, C. A. H. (1971). Possible biological advantages among schizophrenics' relatives. British Journal of Psychiatry, 118, 453-460.

Childers, S. E., & Harding, C. M. (1990). Gender, premorbid social functioning, and long-term outcome in DSM-III schizophrenia. Schizophrenia Bulletin, 16(2), 309-318.

Crow, T. J. (1990). The continuum of psychosis and its genetic origins: The Sixty-fifth Maudsley Lecture. British Journal of Psychiatry, 156, 798-797.

Crow, T. J. (1993). Sexual selection, Machiavellian intelligence, and the origins of psychosis. Lancet, 342, 594-598.

Crow, T. J. (1996). Sexual selection as the mechanism of evolution of Machiavellian intelligence: a Darwinian theory of psychosis. Journal of Psychopharmacology, 10(1), 77-87.

Erlenmeyer-Kimling, L., & Paradowski, W. (1966). Selection and schizophrenia. Am. Nat., 100, 651-665.

Gottesman, I. I., & Shields, J. (1982). Schizophrenia: The Epigenetic Puzzle. Cambridge: Cambridge University Press.

Hezel, F. X., & Wylie, M. A. (1992). Schizophrenia and chronic mental illness in Micronesia:

An epidemiological survey. ISLA: A Journal of Micronesian Studies, 1(2), 329-354.

Huxley, J., Mayr, E., Osmond, H., & Hoffer, A. (1964). Schizophrenia as a genetic morphism. Nature, 204, 220-221.

Kidd, K. (1975). On the magnitude of selective forces maintaining schizophrenia in the population. In R. Fieve, D. Rosenthal, & H. Brill (Eds.), Genetic Research in Psychiatry. Baltimore: The Johns Hopkins University Press.

Levin, M. J., Gorenflo, L. J., & Hosie, H. F. (1993). Republic of Palau 1990 Census Monograph: Population and Housing Characteristics . Koror: Office of Planning and Statistics.

Myles-Worsley, M., Coon, H., Tiobech, J., Collier, J., Dale, P., Wender, P., Reimherr, F., Polloi, A., & Byerley, W. (1999). A genetic epidemiological study of schizophrenia in Palau, Micronesia: Prevalence and familiarity. American Journal of Medical Genetics, 88(1), 4-10.

Sullivan, R. J., & Allen, J. S. (1999). Social deficits associated with schizophrenia defined in terms of interpersonal Machiavellianism. Acta Psychiatrica Scandinavica, 99, 148-154.

Sullivan, R. J., Allen, J. S., Otto, C., Tiobech, S., & Nero, K. (2000). The effects of chewing betel nut (Areca catechu) on the symptoms of people with schizophrenia in Palau, Micronesia. British Journal of Psychiatry, 177, 174-178.

Sullivan, R. J., & Hagen, E. H. (2002). Psychotropic substance-seeking: evolutionary pathology or adaptation? Addiction, 97(4), 389-400.

Schizophrenia:a cognitive science viewpoint. NMDA Receptor hypofunction in schizophrenia: from mouse to man. Evolution and schizophrenia. Latent inhibition and learnedirrelevance paradigms: a convenientway to assess information processingdeficits in schizophrenia. The association of verbal learning deficits with unawareness of mental disorder: implications for psychological treatments in schizophrenia.Â Chapter I. Body Image Deviation in Chronic Schizophrenia: New Research Reiko Koide and Akira Tamaoka. Chapter II. Schizophrenia: A Cognitive Science Viewpoint Guy Sandner. Chapter III.