a predisposition to different forms of pathology, including schizophrenia (Rotenberg 1979; 1982; 1995; Schore 2003).

Cutting (1992) proposed that schizophrenic patients with a preponderance of negative symptoms display right-hemisphere dysfunction. In schizophrenic patients, the right hemisphere is no more dominant in the functions it usually controls in normal subjects: perception of facial emotions (Borod et al. 1993), visuospatial task performance (Gabrovska-Johnson et al. 2003), attention (Kucharska-Pietura et al. 2002), and ability to grasp global forms (Ferman et al. 1999).

The basic initial symptoms of schizophrenia not responsible to the modern neuroleptics (peculiarity of nonverbal behavior; deficiency of self-image; difficulty in grasping information to form a polydimensional picture of the complex situation and picture of the world; affective blunting; lack of empathy) can be explained by the inability to create and process the polysemantic context (Rotenberg 1994).

On the other hand, patients with dominating positive symptoms are characterized by the increased physiological and metabolic activity of the dysfunctional left hemisphere (Flor-Henry 1976; 1983; Friedman et al. 2001; Galderisi et al. 1999; Gur 1978; Gur & Chin 1999; Romney et al. 2000).

I have made an attempt to explain the relationship between the right and left hemisphere dysfunctions in schizophrenia (Rotenberg 1994). Integration with the world by means of the polysemantic way of thinking is the most important feature of a subject's mental health. Without such integration, the subject finds himself in front of a very complicated reality full of inner contradictions, and can use as an option an attempt to resolve difficult task by creating a simplified "left-hemispheric" model of reality. It does not fit. And then, in subjects predisposed to schizophrenic disorders, the left hemisphere creates an artificial explanatory system, in the form of delusions, paranoid ideas, and verbal hallucinations.

According to this proposition, functional right hemisphere deficiency is not unique to schizophrenia. Depression is characterized by disrupted functional connections between anterior cingulate cortex and right orbitofrontal and prefrontal cortex regions (Pizzagalli et al. 2003) – very similar to what Burns suggest for the mechanism of schizophrenia. This means that the next problem we have to solve is what brain (and genetic) mechanisms predispose a subject who suffers from right hemisphere insufficiency to the development of the concrete forms of mental disorders. In the case of schizophrenia, what is it, for example, about the dopaminergic system that leads to a greater release of dopamine? (Zipursky & Kapur 1998).

Natural selection and schizophrenia

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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.

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 their association with adaptive social genes" (target article, sect. 9.2, para. 6) and that they represent part of a "costly trade-off" related to "evolving complex cognitive and social abilities" in humans (sect. 10, para. 4). Burns' "costly trade-off" argument follows similar perspectives set forth by Book (1953), Gottesman and Shields (1982) and Crow (1990b) 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 & 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 & Watts 1971; Erlenmeyer-Kimling & Paradowski 1966; Huxley et al. 1964), nor do 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 & 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 & 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" (sect. 2.1, last para.). 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 (Allen & Laycock 1997; Hezel & Wylie 1992). 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 & Harding 1990, Sullivan & Allen 1999). The need to account for intersex variability in evolutionary models of schizophrenia has been acknowledged by Crow (1993b; 1996b), 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

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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 & 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 & 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.

Are the DTI results positive evidence for George Bernard Shaw's view?

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Abstract: We discuss how Burns' conception may be further extended to integrate research on eye movement abnormalities, but then point to a contradiction between Burns' conception of schizophrenia as the genetic price for human social life and the diffusion tensor imaging (DTI) data, which constitute his central piece of evidence.

Burns' target article fascinates by its integrative approach, conceiving schizophrenia as biologically determined pathology of those abilities that underlie social relations and behavior. This latter aspect, though certainly important from a clinical point of view, has often been neglected in studies that were conducted under the information-processing paradigm and that measured physiological variables (e.g., our own; Verleger & Cohen 1978), not sufficiently reflecting on the difference between schizophrenia and neurological diseases.

The target article thus offers a framework for integrating various fields of research. One aspect, unmentioned by Burns, is the ongoing research on eye-movement abnormalities in schizophrenic patients. Indeed, "disconnections" within frontoparietotemporal networks, as postulated by Burns, may also underlie the disturbances of eye movements leading to failures in initiating and maintaining smooth pursuit, higher error rates in antisaccade tasks, and disrupted exploratory eye movements. All of these can be observed in schizophrenic patients as well as their relatives (e.g., Crawford et al. 1998; Lencer et al. 2000; Kojima et al. 2001). For smooth pursuit eye movements (SPEM) a genetic linkage to a polymorphism on the short arm of chromosome 6 has recently been shown and replicated (Arolt et al. 1996; Holzman 2001). There is evidence that the SPEM-deficit is associated with negative symptoms in schizophrenic patients (Ross et al. 1996), as well as with traits for "sensitivity" and "suspiciousness" in relatives (Lencer et al. 2003) and in individuals with schizotypal personality (O'Driscoll et al. 1998). Note that this latter syndrome is mainly characterized by formal thought disorders, a syndrome that also could be explained by the disconnectivity hypothesis. The important point in relating this research to Burns' conception is that these disturbances of schizophrenic patients in moving their eyes may underlie their false perception of the environment, resulting in their misinterpreting social situations. In view of the notorious variability of schizophrenic patients in any study, it might prove useful to use these SPEM disturbances as a phenotypic marker which, being easily quantifiable and probably genetically determined, may be used to define more specific subgroups of patients to investigate more closely the hypothesis that specific psychopathological symptoms or neuropsychological signs are caused by disconnections within specified neuronal networks (see also Lee et al. 2001), using the DTI technique.

However, with regard to those neuroanatomical DTI results that form the central piece of evidence in the well-assembled mosaic presented by the target article, there appears to be a major problem: These results do not seem to fit well Burns' general framework, conceiving schizophrenia as the genetic price to be paid for human social life, as highlighted by his introductory citation of George Bernard Shaw saying that progress is thanks to unreasonable people who attempt to adapt the world to themselves. Elaborating on this notion, Burns argues as follows: Cognitive abilities in primates consist of modules only loosely interconnected. Human development is largely related to how those modules formed a network, mutually transforming each other and leading to a hypermorphosis of especially the frontal brain due to increasing fiber tracts connecting frontal cortex with parietal and with temporal cortex. The principal psychological correlate of this networking process is to attribute causality and sense to external events and to refine cognitive skills, but this process may also give rise to creative genius. Therefore, according to Burns, the hallmark of schizophrenia, precisely as suggested by Shaw's bon mot, is the overuse of this attribution, leading to delusional ideas and other main symptoms.

How can this conception be tested by neuroanatomical data? According to Burns, there is evidence from his recently published DTI data that these interconnecting fibers were less clearly marked in schizophrenic patients, forming evidence for weaker cortical connections (Burns et al. 2003). But is this DTI result a proof for Burns' argument? Would the target article have been less convincing if DTI had rendered the opposite finding – that is, if fibers had been more developed in schizophrenic patients? Clearly not! On the contrary, such a finding would have been of advantage for the general thesis: If schizophrenia is conceived of as over-networking, as a disease of the creative, synthetic, imaginative mind, then fiber tracts should indeed be more marked in these patients, not less. Reduced DTI signals were also found in studying the interhemispheric connections of schizophrenic patients' visual cortex (Agartz et al. 2001) which finding underlines the question about how specific the DTI results reported by Burns et al. (2003) in fact are. But as these results now stand, they might lead to the conclusion that George Bernard Shaw was wrong.

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