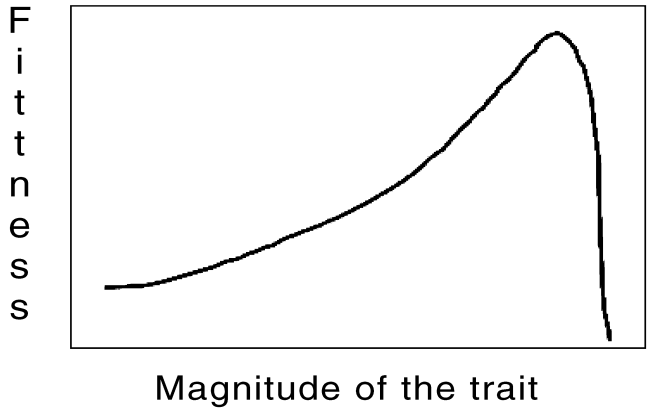

Figure 1 (Nesse). A cliff-edged fitness function: As the trait increases, fitness increases increasingly rapidly, then crashes.

This perspective makes it unnecessary to seek specific adaptive benefits for schizophrenia or schizotypy, even while it suggests that both conditions may nonetheless offer clues about beneficial characteristics that may select for mental characteristics related to the disorders. It suggests looking for traits and mechanisms that give such a substantial advantage that selection would have quickly pushed the mean to an extreme where the system fails in some individuals. Such cliff-edge fitness functions are especially likely when selection has recently been strong for a particular trait, as it has for horses' legs or uric acid levels in humans, and as it presumably has been for social cognition. After another few thousand generations, modifier genes may well reduce the risk. Since we don't want to wait, intense pursuit of the questions addressed by this target article will be most worthwhile.

Schizophrenia: The elusive disease

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Abstract: All mammals have social brains, and there is presently no evidence that humans have relatively more genetically dictated social brain circuitry than other species. The postulation that schizophrenia arises from disruption of brains systems uniquely devoted to social traits is obviated not only by the large number of anatomical and biochemical brain differences, but also by nonsocial symptoms of schizophrenic disorders.

Ever since Kraepelin and coworkers started to examine demented brains anatomically a century ago (Panksepp 2004), the neuroscientific study of schizophrenia, as the quip goes, has been the graveyard of neuroanatomists. With so many brain changes, but few of *general* etiological significance, no discrete neural theory of schizophrenia has survived the test of time. Enter Burns, with his vision of the unique cortical interconnectivities of the human "social brain." Anyone interested in schizophrenia should read this article. It is erudite, novel, and weaves abundant information into a fascinating hypothesis. However, the central idea – that schizophrenia reflects genetically promoted derangement of the higher humanoid "social brain" connectivities – remains dubious.

Cognitive/evolutionary psychological views commonly ignore too many of the foundational social circuits of the cross-mammalian limbic brain, including systems for sexuality, maternal care, separation distress, social bonding, and play (Panksepp 1998). The genetic analysis of the limbic "lower social brain" shared by all mammals (Panksepp et al. 2002) will be considerably easier than clarification of neocortical aspects unique to humans. But Burns believes schizophrenic genotypes and phenotypes are restricted to our own species. Early comparative literature was replete with descriptions of psychotic animals (Lindsay 1879), and productive modern models for specific symptoms exist abundantly (e.g., Gainetdinov et al. 2001; Kilts 2001). Also, let us not forget that among domestic animals there surely has been enforced culling of those that seemed to exhibit troublesome symptoms of insanity.

With similar core deficits, simpler brains may not be as functionally impaired as humans'. For example, rearrangement of cortical layering in animals with heterozygous *reelin* deficits – a genetic model of schizophrenia (Costa et al. 2002) – may impair mice less than men. Because of our ultracomplex corticocognitive apparatus, many schizophrenic symptoms may reflect the costs of complexity rather than genetically dictated *social* features.

Burns' proposal hinges on dubious genetic and neuronal assumptions, as do most "modular" views of evolutionary psychology. Much of heteromodal cortex in humans is capable of nonspecialized information processing which becomes specialized only epigenetically. How would Burns defuse the following major concern? That the higher social brain of humans, which readily elaborates theories of mind and complex sociocognitive strategies, reflects epigenetic programming within general-purpose computational spaces, guided by limbic socioemotional functions rather than by genetic sociocortical connections unique to humans (Panksepp & Panksepp 2000)?

We also wish guidance on linkages with established neurochemical vectors of schizophrenia – dopamine hyperactivity and glutamate/GABA hypoactivity perspectives. These chemistries are not uniquely devoted to elaboration of social processes. Dopamine-generated appetitive seeking urges (Panksepp & Moskal 2004) and glutamatergic general information processing (Riedel et al. 2003) provide abundant opportunities to modulate social thoughts and emotions independently of any genetic prescriptions. Dopamine facilitation of core symptoms of schizophrenia (e.g., paranoid delusions, also modeled in animals; Lipska & Weinberger 2000) makes sense from the ability of hyperdopaminergic states to promote causal inferences from correlative relationships (Panksepp 1998, Ch. 8). Social wiring problems are *not* a prerequisite for such symptoms. Likewise, glutamatergic mediation of all memory and cognitive processes in all mammals, makes "higher social brain" assumptions unparsimonious. Although modern brain imaging is well positioned to evaluate the abundant *correlative* changes in schizophrenic brains (Kubicki et al. 2003; Winterer et al. 2003), animal models allow causal analysis. Can Burns' many inferential possibilities be winnowed for specific sociocausal influences?

Burns' analysis ignores much data from molecular genetics. In which of the 15 already demonstrated susceptibility loci (see Pesold et al. 2004) would he search for "social genes"? Would Burns share new molecular biology predictions concerning hominid-specific "evolved complex cortical interconnectivities"? Don't general deficits, such as those related to myelin, cytoarchitectural, and synaptic activity regulation (Pesold et al. 2004) cast doubt on his disrupted socioanatomical pathway hypothesis and potentially also explain lower fecundity and increased early mortality associated with schizophrenia?

It seems more likely that schizophrenia is *not* actively maintained in the genome, but that certain genes predispose or make one vulnerable to epigenetic and environmental factors that promote schizophrenic phenotypes (Kato et al. 2002). DNA methylation can alter gene expression during development and alter cellular function, with major impact on behavior and cognition. Genetic anticipation, chromatin rearrangements, viral integration into the genome, and epigenetic modulation of neurochemical systems may all play a role in schizophrenia (Jones & Cannon 1998; Petronis et al. 1999).

Considering what we already know about schizophrenia, we think Burns' alternative has much to explain before it can be

deemed a major title contender. Although psychiatric genetics is in a state of crisis (DeLisi 2000), with little reproducible data (except for childhood disorders; Peterson & Panksepp 2004), molecular biology in conjunction with functional neuroscience will nevertheless eventually tell us what actually is contained in the neural ground-plan of the genome. Evolutionary theorists need to be quite clear on how they might facilitate the molecular and neuropsychological search.

Since evolutionary speculation is such fun, let us also consider how real-life social processes may affect the genetic survivability of schizophrenia with no costly genetic trade-off with the evolution of complex social cognition. Schizophrenic genotypes may subsist in human populations if high background incidence, coupled with comparatively low penetrance, offer some benefits – for example, the capacity to enthrall others around the endless social "campfires" of our ancestral past and entertainment-obsessed modernity. Humans enjoy stimulating story-telling, ranging from slapstick to mystical. Our fascination with human quirks may have created cultural spandrels for the survival and propagation of individuals who survived less well without such cultural supports. Consider the classic "stress-diathesis" model: Schizophrenic phenotypes may diminish as supportive cultural practices allow afflicted individuals to keep their symptoms in check or socially useful. Also, with the insistent sexuality of mature males, genetic dispositions for schizophrenia could be sustained if borderline women, partly through helplessness, are more likely recipients of male lust than non-schizophrenic ones.

We hope Burns' fascinating proposal will have a better shelf life than past neuroantomical hypotheses, but at present, the distance between fact and theory remains vast. We need concrete hypotheses to enable this intriguing theory to be tested robustly, and potentially falsified.

The ontogeny and asymmetry of the highest brain skills and the pathogenesis of schizophrenia

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Abstract: The most developed and the latest-to-mature mental skills represented in the creation of mono- versus polysemantic contexts are related respectively to the left and right frontal lobe. A polysemantic way of thinking is responsible for the subject's successful integration in the polydimensional world. The functional insufficiency of this right-hemispheric way of thinking displays a predisposition toward the development of mental disorders, including schizophrenia.

I agree with the main messages of the target article, that schizophrenia is a disorder of the social brain, that the development of this disease is related to the disturbed frontoparietal and frontotemporal connectivity, and that some peculiar features of human ontogenesis predispose subjects to these disturbances of connectivity. However, one important point is missed, related to the ontogeny and function of the orbitofrontal asymmetry.

The disturbance of this area does not cause definite and well-traceable single signs, like apraxia, spatial hemineglect, and so on. In contrast to these relatively local disorders, right anterior insult has interfered with the ability to explore an image in an organized fashion and with the more global functions like empathy, theory of mind, sense of self (Craik et al. 1999; Devinsky 2000; Keenan et al. 2001; Schore 2003; Shamay-Tsoory et al. 2003).

I suggest that in the most general form, the difference between two strategies of thinking related to the frontal functions of the left- and right hemispheres is reduced to opposite modes of organizing the contextual connection between elements of information (Rotenberg 1979; 1982; 1985; 1993; 2004; Rotenberg & Arshavsky 1979). Left-hemisphere frontal pole so organizes any sign material (whether symbolic or iconic) as to create a strictly ordered and unambiguously understood monosemantic context. The formation of this context requires an active choice from the many real and potential connections between the multiform objects and phenomena of a few definite connections that would facilitate an ordered analysis, building a pragmatically convenient but simplified and restricted model of reality based on probability forecasting and cause-and-effect relations.

In contrast, the function of the symmetrical structure of the right hemisphere is a simultaneous capture of an infinite number of connections and the formation of an integral, but ambiguous, polysemantic context. In such a context, the whole is determined by the interconnections between its elements that interact with each other on many semantic planes simultaneously, like images in dreams. Understanding of metaphors and sense of humor are dependent on the right hemisphere (Wapner et al. 1981; Winner & Gardner 1977).

These two types of context complete each other and have sense only in comparison with one another. For the right hemisphere disconnected from the left one, the world is holistic but not polysemantic. However, these types of context are not equal, because the polysemantic view on the world, although being opposite to the monosemantic one, actually includes the latter as a component, while the converse is not true. Polysemantic thinking is the highest human mental function, responsible for creativity and integration of past, present, and future experience (Wheeler et al. 1997). Great apes lack even the initial precursors of polysemantic thinking.

The advantage of the right frontal brain corresponds to the more prominent arborization of the neural net (Saugstad 1998) and to the activation of a much broader net of associations in comparison to the left hemisphere (Beeman et al. 1994; Chiarello 1998; Coney & Evans 1999).

Brain maturation starts with faster overall growth of the right hemisphere in the first years after birth, interrupted by the left hemisphere maturation gradient, followed by another shift to a leading role of the right hemisphere in early adolescence. The frontal lobes and particularly the right frontal lobe structures and connections are the last regions to mature (Thatcher et al. 1987; Saugstad 1998).

In the frame of the theory of contexts, this schedule of maturation has a following explanation: The main functions of the right hemisphere that precede the development of the polysemantic way of thinking (the ability to grasp the reality as a whole; the emotional attachment to the mother [Schore 2003]; the regulation of the withdrawal behavior in the inappropriate conditions [Davidson 1992]; the integration of affect, behavior and autonomic activity [Schore 2003]) are the basic functions of survival (Saugstad 1998), and for this reason they are the first to appear. In the next crucial stage of the development, a process of differentiation of the elements of reality appears: a distinguishing of self from the environment, the ability to analyze cause-and-effect relationships, the orientation in the time vector, and finally the creation of the conscious model of the reality and of self-concept. This process of differentiation requires the expertise of the left hemisphere and its ability to form a monosemantic context.

However, to be comfortably integrated in the polydimensional world and to cope with all contradictions, a subject has to overcome, on a new level, the restrictions of the monosemantic model that is included in the more broad polysemantic picture.

Females are characterized by earlier brain maturation (i.e., achieving the final point of maturation sooner) than males. In general, the longer the process of maturation, the higher the level of brain structure development achieved. This may be a reason why males more often display outstanding creativity (Saugstad 1998). However, the increased duration of maturation in males makes the right hemisphere more sensitive and vulnerable to any alterative influences and may cause its functional insufficiency that displays