particularly vulnerable for unipolar and bipolar minor and major depressive episodes and why hyperthymic temperament unrelated to central serotonin but possibly related to the dopamine/norepinephrine systems is protective against them.

Our view, that the mediating variable between environment and clinical depression might be affective temperaments other than hyperthymic, is a viable hypothesis that needs further study.

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We agree with Gurling et al1 that the central question in psychosis is the relationship between genetic susceptibility and brain change but have concerns about their claim to have established that “The PCM1 gene is implicated in susceptibility to schizophrenia and is associated with orbitofrontal gray matter volumetric deficits.” Uncertainty in the identification of any gene relevant to psychosis on the one hand and the nonspecificity of morphological change in the brain on the other maximize the scope for multiple testing. In each case, Gurling et al have assumed heterogeneity on the basis of a post hoc criterion and have thereby increased the risk of attaching significance to a random association that will be difficult to disprove even with very large samples.

Concerning the linkage to chromosome 8p, of 3 genome scans2-3 with sample sizes of more than 300 sibling pairs now reported, only1 shows any peak of significance on chromosome 8p, and in the meta-analysis of Lewis et al4 of more than 10 genomewide linkage studies on schizophrenia, the eighth highest-ranking finding appears to be on chromosome 8p but well centromeric of the PCM1 gene that Gurling et al propose as a candidate. If PCM1 was indeed the cause of 5% to 10% of cases of schizophrenia as Gurling et al claim, linkage should be apparent in these large studies and the meta-analysis. Further evidence implicit in the Gurling et al claim—the presence of a mutation in affected individuals or accelerated change of the gene in hominin evolution—is notable by its absence. Thus, there is no basis for the identification by Gurling et al of “PCM1-associated schizophrenia” as a distinct category. Put simply, variation in PCM1 has not been shown to be associated with schizophrenia.

With respect to brain morphology, there is also considerable variation between studies. In a meta-analysis of voxel-based morphometry studies, Honea et al6 found that the most consistent deficits were in the left medial temporal lobe and superior temporal gyrus. Neither of these areas corresponds to those regions (temporal pole and orbitofrontal cortex) that Gurling et al claim differentiate their chromosome 8 “positive” and chromosome 8 “negative” cases. The best-established structural finding in chronic schizophrenia is a degree of ventricular enlargement well documented in the recent literature to which Gurling et al refer, but related to schizophrenia as a whole and not to any clinical subgroup.10 Thus, the claim for heterogeneity of morphological change among subgroups of patients with schizophrenia is hazardous.

We are concerned that without a more critical2 and hypothesis-based approach the literature will rapidly be weighed down with claims for association of diverse genetic polymorphisms with brain structures that are impossible to evaluate because they are based on arbitrary assumptions of heterogeneity and genetic and morphological findings that have not been shown to be replicable across samples.

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We do not agree with the criticisms that Crow and DeLisi make of our research. The claim that we have been arbitrarily assuming locus heterogeneity in schizophrenia on a post hoc basis is at odds with what has already been published in numerous cytogenetic, linkage, and allelic association studies. Crow and DeLisi remain isolated in their views about the genetics of schizophrenia, and they cling to the belief that schizophrenia is linked only to a single locus entirely to be expected for a disease with well-established genetic heterogeneity. In both PC1-M- and non-PC1-M-associated groups of individuals with schizophrenia, there was a pattern of gray matter loss compared with controls that was highly consistent with most studies of schizophrenia. Nevertheless, within these regions, there were marked differences between the 2 groups in gray matter density within D2-rich dopamine projection regions of the temporal pole and OFC. Notably, the OFC involvement of the PC1-M-associated group would predict, from a neuropsychological perspective, more perseverative, behavioral, and social impairments with less insight and would therefore be likely to cause a more “difficult to treat” subtype of schizophrenia than subtypes of schizophrenia with volumetric deficits in the “perceptual” temporallobe region. It seems that people with schizophrenia in the PC1-M-associated subgroup are likely to display a particular subset of both specific volumetric and cognitive deficits. Therefore, it is likely that different genetic risk factors may be associated with different structural effects in the brain.

While we appreciate that there may be risks involved with multiple testing, we took great care to correct all imaging significance values for multiple tests. All tests of genetic association were performed by computing empirical Monte Carlo tests of significance, which took into account multiple alleles and multiple marker loci so that further correction was not required. Caution should be exercised with these complex types of analyses, but the combined study of genetic and anatomical heterogeneity...
together should provide a powerful approach for understanding schizophrenia.

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Searching for Rational Anti-N-methyl-d-aspartate Treatment for Depression

Zarate et al demonstrated a rapid antidepressant effect from ketamine hydrochloride, an antagonist at the N-methyl-d-aspartate (NMDA) ionophore. The proof-of-principle study needs to be addressed in the context of drug development and a risk and benefit assessment. Interestingly, they also reported memantine, another NMDA antagonist, does not improve depressive symptoms. High doses of D-cycloserine, a weak antagonist on the glycine coagonist competitive site, also failed to improve depression. Taken together, high-affinity, strong open-channel blockers with a slow off-rate, like ketamine, possess antidepressant effects whereas low-affinity, weak open-channel blockers with a fast off-rate, like memantine, or antagonists on the competitive site, like D-cycloserine, are ineffective. Repeated administration of ketamine or other non-competitive NMDA antagonists induce unacceptable clinical adverse effects. Accordingly, many NMDA receptor antagonists have failed advanced clinical trials for neuroprotection. Exceptionally, memantine, which does not accumulate in the NMDA channel to interfere with normal synaptic transmission, had been demonstrated to have modest neuroprotective effects. When long-term administration of a high-affinity NMDA channel blocker is necessary for the treatment of depression, the dilemma would be that strong NMDA antagonists come with unbearable anticognitive and psychotelic effects and weak NMDA antagonists are not therapeutic. N-methyl-d-aspartate neurotransmission is essential for learning and memory. The main adverse effects of NMDA channel blockers are anticognitive and psychotelic properties. These blockers are countertherapeutic since depression is often associated with cognitive impairment and psychotic features and a single administration of ketamine hydrochloride at 0.5 mg/kg generally...