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 systems² 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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Gene-Brain Structure Relationships: Arbitrary Assumptions of Heterogeneity Generate Unfalsifiable Claims

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 scans²⁻⁴ with sample sizes of more than 300 sibling pairs now reported, only 1² shows any peak of linkage on chromosome 8p, and in the meta-analysis of Lewis et al⁵ 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 enlargement⁷ well documented in the later literature to which Gurling et al refer, but related to schizophrenia as a whole and not to any clinical subgroup.⁸⁻¹⁰ Thus, the claim for heterogeneity of morphological change among subgroups of patients with schizophrenia is hazardous.

We are concerned that without a more critical¹¹ and hypothesis-based approach the literature will rapidly be weighed down with claims for association of diverse genetic polymorphisms with variations in brain structure 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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In reply

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 on the X chromosome. The widely accepted view is that there is heterogeneity of linkage or locus heterogeneity in schizophrenia. For example, chromosome 22 deletions are associated with velo-cardio-facial syndrome and schizophrenia.¹ Other cytogenetic abnormalities associated with schizophrenia are on chromosomes 1, 2, and 11.^{2,3} Furthermore, linkage and association studies of schizophrenia have now produced statistically significant and replicable results that can only be explained by the existence of locus heterogeneity, with different loci increasing susceptibility to schizophrenia in subgroups of families.⁴ Furthermore, the presence of replicated positive linkages to schizophrenia on specific chromosomal regions has successfully predicted where the genes associated with schizophrenia have later been fine-mapped using familial and case-control allelic association studies.

Crow and DeLisi have selected 3 linkage studies for comment, but they have ignored 5 other positive 8p21-22 linkage studies of schizophrenia. Two of the 3 linkage studies that they cited indeed showed no evidence for linkage on 8p21-22; but these studies used the sib pair method, which is notoriously weak at detecting linkage, especially if chromosome 8p21-22 cases compose only 5% to 10% of all cases and families. The fact that there are now 5 published linkage studies of 8p22-21, each with logarithm of odds (LOD) scores higher than 3.00, means that 8p21-22 is one of the most well-confirmed regions linked to schizophrenia.⁵⁻⁹ Two other studies have provided further support for 8p21-22 link-

age to schizophrenia, with LOD scores of between 2.00 and 3.00.^{10,11} The meta-analyses by Lewis et al⁴ supported linkage between schizophrenia and 8p21-22 markers, but Crow and DeLisi are wrong when they claim that Lewis et al⁴ placed the 8p21-22 schizophrenic susceptibility in a bin centromeric to the actual position of the PCM1 locus. The cytogenetic localization of the 8p bin used by Lewis et al was 8p22-21, and this bin does actually contain PCM1. The 8p21-22 bin was ranked sixth of the 13 most well-replicated loci.

Crow and DeLisi also erroneously claim that variation in PCM1 has not been shown to be associated with schizophrenia in our study. We found that the database PCM1 single nucleotide polymorphism (SNP) rs370429, which was associated with schizophrenia with a significance of .01,¹² consists of A to G nucleotide substitution, which causes the nonconservative amino acid isoleucine to change to a threonine. This amino acid is a causal candidate for genetic susceptibility to schizophrenia. Another SNP, rs13276297, that we reported to be associated with schizophrenia (P=.02) causes a C/T variation in intron 6. Such intronic variants are now known to sometimes increase disease susceptibility.

With respect to the imaging aspect of our work on PCM1, contrary to the claims of Crow and DeLisi, our findings of temporal pole and orbitofrontal cortex (OFC) volumetric deficits are highly compatible with the previous findings on voxel-based morphometry in schizophrenia as reported by Honea.¹³ The criticism that temporal lobe and OFC involvements are not in the "right" areas is largely irrelevant. The comments of Crow and DeLisi are also wrong with respect to functional deficits in schizophrenia. The fact that previous imaging studies have produced inconsistent results is entirely to be expected for a disease with well-established genetic heterogeneity. In both PCM1- and non-PCM1-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 PCM1-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" temporal lobe region. It seems that people with schizophrenia in the PCM1-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 al¹ demonstrated a rapid antidepressant effect from ketamine hydrochloride, an antago-nist at the N-methyl-D-aspartate (NMDA) iono-phore. The proof-of-principle study needs to be ad-dressed in the context of drug development and a risk and benefit assessment. Interestingly, they also re-ported memantine, another NMDA antagonist, does not improve depressive symptoms.² High doses of D-cycloserine, a weak antagonist on the glycine coagonist site, also failed to improve depression.³ 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 com-petitive site, like D-cycloserine, are ineffective.

Repeated administration of ketamine or other non-competitive NMDA antagonists induce unacceptable clini-cal adverse effects. Accordingly, many NMDA receptor antagonists have failed advanced clinical trials for neu-roprotection. Exceptionally, memantine, which does not accumulate in the NMDA channel to interfere with nor-mal synaptic transmission, had been demonstrated to have modest neuroprotective effects.⁴ When long-term ad-ministration of a high-affinity NMDA channel blocker is necessary for the treatment of depression, the dilemma would be that strong NMDA antagonists come with un-bearable anticognitive and psychedelic 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 psychoto-mimetic properties. These blockers are countertherapeu-tic since depression is often associated with cognitive impairment⁵ and psychotic features and a single admin-istration of ketamine hydrochloride at 0.5 mg/kg gener-