AUTHOR CONTRIBUTIONS
G.B., C.M.L., I.P. and E.V. performed the data analysis. G.B., D.C. and P.M. wrote the manuscript. M.L.P., D.H.R.B., B.P., D.I.B. and P.F.S. provided additional replication data and comments.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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McMahon *et al.* reply:

Breen *et al.* report that their re-analysis of our published data[1] supports association of rs2251219 with bipolar disorder (BP) at the $P < 10^{-8}$ level. However, in the independent samples they examined, this SNP did not show much evidence of association with major depressive disorder (MDD).

Neither result is surprising. Although we are confident in the analyses we performed using the data we had available, MDD is likely to be even more heterogeneous than BP[2], making a negative association result in individual samples very difficult to interpret. In our paper[1], we already stated that the association signal on 3p21.1 is more robust in BP than in MDD. If the genetic effect size is actually different in BP and MDD, as we suggested, then the power to replicate in each of the two disorders alone must be calculated separately. For their power calculation, Breen *et al.* use the upper confidence interval we reported for our combined analysis. This is almost certainly too high for MDD and would lead to an overestimation of the power to replicate in their sample. Therefore it is likely that their study is not adequately powered to support their strong conclusion.

Much larger sample sizes will ultimately be needed to reliably detect most loci having modest effects on risk[3]. This is one reason why it makes sense to group similar disorders as we did, especially when they so often run together in families. Additional kinds of data, such as gene expression and functional variants, should also be considered before reaching final conclusions[4,5]. We do agree with Breen *et al.* that large consortium efforts may ultimately offer a clearer picture, not because they are 'more structured' than our analysis, but simply because large consortia can muster even larger sample sizes.

It is becoming clear that SNP associations arising from large meta-analyses will often cross traditional diagnostic boundaries. Genes do not encode diseases, even when those diseases are much better validated than the clinical syndromes with which we work in psychiatry. The next big challenge for psychiatric genetics lies in the identification of higher risk alleles that may possess some diagnostic specificity. This will not be achieved in genome-wide association studies of common alleles but rather will require innovative approaches[6].

We thank Breen *et al.* for pointing out the strong evidence of association with bipolar disorder that emerges from our study and for pulling together the major depression data they present, which certainly have some value. They should press on until they have the necessary statistical power to draw truly convincing conclusions about replication or non-replication. Anything less misjudges the complexity of the problem.

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