SUPPLEMENTARY NOTES

1. We do not know why induction of Bdnf exons III and IV (~50%) cannot account fully for the much larger increase (~2.5 fold) seen in total Bdnf mRNA levels (see Fig. 2). It is unlikely that this difference is due to variability in primer efficiencies, since all primers were standardized in initial experiments to have similar efficiencies. Rather, it is conceivable that the difference could be due to the relatively large variance in the expression of each exon observed among individual animals within the various experimental groups, with outlier animals perhaps masking larger induction of exons III and IV. The discrepancy could also suggest the existence of an additional, not previously described exon that is also transcriptionally up-regulated by chronic imipramine, however, there is no evidence for such additional exons despite exhaustive study of the mouse Bdnf gene.

2. It is clinical folklore in psychiatry that antidepressant medications do not produce mood-elevating effects in normal subjects. However, this point has not been extensively studied, in part because of the troubling side effects of the medications, particularly the tricyclic antidepressants, and the difficulty of getting normal controls to take them. Nevertheless, several studies have examined the action of chronic antidepressants in relatively small numbers of normal humans. Two early well-controlled studies demonstrated no effect of chronic imipramine on mood or related ratings of well-being in normal subjects\textsuperscript{51,52}. This was replicated in a third study\textsuperscript{53}. A fourth study showed no effect of chronic nortriptyline (a related tricyclic antidepressant) on anxiety measures in patients with panic disorder\textsuperscript{54}. Similarly, several well-controlled studies have more recently
found no effect of the SSRI’s, fluoxetine or paroxetine, on mood and well-being after chronic administration⁵⁵-⁵⁸. On the other hand, one study reported that chronic paroxetine administration reduced measures of negative affect in normal controls, although it again had no effect on positive affect⁶⁹. Hence, while some caution must be exercised in accepting the clinical lore that antidepressants are not mood-elevating in normal subjects, there is some objective evidence to support this view.