Description of Additional Supplementary Files

File Name: Supplementary Data 1
Description: Differential miRNA expression in the dorsolateral prefrontal cortex (dlPFC) of subjects with major depressive disorder who died by suicide (MDD-S) and matched controls (discovery cohort; 17 MDD-S-control pairs: 10 male and 7 female). Sheets DE_all, DE_males and DE_females contain the results for both sexes combined (17 vs. 17), males (10 vs. 10) and females (7 vs. 7), respectively; differential expression was assessed with DESeq2 using a design including MDD-S-control pair and diagnosis. Sheet RRHO_common contains the 1,702 miRNAs detected in both sexes, ranked for the rank-rank hypergeometric overlap (RRHO2) analysis (Fig. 2h). Positive $\log_2$FC indicates higher expression in MDD-S than in controls. Column descriptions: miRNA ID = miRBase v22.1 name; miRBase accession = miRBase accession number; Max group mean = highest of the two group means of normalized counts; $\log_2$FC = $\log_2$ fold change, MDD-S vs. control; p-value = uncorrected two-sided p-value; P.adj = Benjamini-Hochberg-adjusted p-value within each comparison; RRHO metric = $-\log_{10}$(p-value) × sign($\log_2$FC), calculated from the sex-specific analyses.

File Name: Supplementary Data 2
Description: Experimentally validated targets of the differentially expressed miRNAs (DEmiRs) confirmed by RT-qPCR and their functional enrichment, in males and females. Sheets Targets_males and Targets_females contain all miRNA-target interactions retrieved from miRTarBase v11.0 for the confirmed DEmiRs of each sex, with the original miRTarBase fields. Sheets Enrichment_males and Enrichment_females contain the KEGG pathways and Gene Ontology (GO) Biological Process and Molecular Function terms enriched among these targets (WebGestalt over-representation analysis against the human protein-coding genome); all terms with P.adj < 0.05 are listed, and those shown in Figs. 3 and 4 are a subset. Column descriptions: Target Site = location of the binding site, when reported; Support Type = strength of evidence as defined in miRTarBase; References (PMID) = PubMed identifiers of the supporting studies; Database = KEGG, GO_BP or GO_MF; GeneSet = pathway or term identifier; Description =pathway or term name; Overlap = number of target genes in the pathway or term; Enrichment Ratio = observed/expected number of target genes; p-value = uncorrected p-value; P.adj = Benjamini-Hochberg-adjusted p-value; GeneID = target genes in the pathway or term.

File Name: Supplementary Data 3
Description: Differential mRNA expression in the dlPFC of MDD-S subjects and matched controls, and ranked gene lists used for RRHO2 analyses. Sheets DE_males and DE_females contain the results for all detected genes in males (10 vs. 10) and females (7 vs. 7), respectively; differential expression was assessed with two-sided two-sample t-tests on counts per million (CPM), and differentially expressed genes (DEGs) were defined as protein-coding genes with p-value < 0.05. Sheet RRHO_mRNA contains the protein-coding genes detected in both sexes, ranked for the RRHO2 analysis of our data using paired t-tests (Fig. 5h). Sheet RRHO_Labonte contains the genes ranked for the RRHO2 analysis of an independent dlPFC dataset (Labonté et al., GEO: GSE102556; males, 13 MDD-S vs. 13 controls; females, 13 MDD-S vs. 9 controls; DESeq2; Supplementary Fig. 10). Positive $\log_2$FC indicates higher expression in MDD-S than in

controls. Column descriptions: Control Mean and MDD-S Mean = mean CPM in each group; $\log_2$FC = $\log_2$ fold change, MDD-S vs. control; p-value = uncorrected two-sided p-value; P.adj = Benjamini-Hochberg-adjusted p-value within each sex; RRHO metric = -$\log_{10}$(p-value) × sign of the change.

File Name: Supplementary Data 4
Description: Functional enrichment of DEGs shared by both sexes (Enrichment_shared), found only in males (Enrichment_male_only) or found only in females (Enrichment_female_only), and GO Biological Process terms enriched in both male-only and female-only DEGs (Common_GO_BP; Fig. 6g). Enrichment of KEGG pathways and GO Biological Process and Molecular Function terms was assessed with WebGestalt over-representation analysis against the human protein-coding genome; for each database, the 60 pathways or terms with the lowest p-values are listed. Column descriptions: Database = KEGG, GO_BP or GO_MF; GeneSet = pathway or term identifier; Description = pathway or term name; Sex = sex in which the term was enriched; Overlap = number of DEGs in the pathway or term; Enrichment ratio = observed/expected number of DEGs; p-value = uncorrected p-value; P.adj = Benjamini-Hochberg-adjusted p-value; Genes = DEGs in the pathway or term.

File Name: Supplementary Data 5
Description: Sex-by-diagnosis interaction analysis of protein-coding gene expression in the dlPFC (discovery cohort; 10 male and 7 female MDD-S-control pairs; 10,540 genes, 10,529 detected in both sexes). Sheet Gene_results contain, for each gene, the per-sex $\log_2$FC and p-value (as in Supplementary Data 3), the category of change, the sex-specificity level and the interaction statistics from a limma model ($\log_2$(CPM + 1) ~ MDD-S-control pair + diagnosis + diagnosis × sex). Sex-specificity levels are cumulative and apply to genes significant in one sex only: 1, p-value < 0.05 in one sex only; 2, plus interaction p-value < 0.05; 3, plus p-value ≥ 0.2 in the other sex; 4, plus p-value ≥ 0.5 in the other sex and |$\log_2$FC| in the other sex < 25% of that in the sex with the effect. Sheet Permutation_null compares the observed number of genes per category and level with 2,000 permutations of sex labels across MDD-S-control pairs. Sheets Internal_replication and Internal_replication_by_gene report the replication of between-sex differences in held-out pairs across 200 random splits of the pairs of each sex into discovery and held-out halves (null: 500 permutations of sex labels × 5 splits); Level indicates the minimum sex-specificity level of the genes considered. Column descriptions: Interaction $\log_2$FC (females - males) - effect of MDD-S in females minus effect in males ($\log_2$(CPM + 1) scale); Interaction t = moderated t statistic; p-value = uncorrected two-sided p-value; P.adj = Benjamini-Hochberg-adjusted p-value; Empirical p-value = one-sided permutation p-value, calculated as (1 + number of permutations with a count ≥ observed)/(number of permutations + 1), or with counts ≤ observed for the opposite direction.

File Name: Supplementary Data 6
Description: miRNA-mRNA regulatory networks and cell-type mapping of their target genes. Sheets Network_males and Network_females contain the DEmiR-target pairs retrieved from miRTarBase v11.0 in which the miRNA and its target changed in opposite directions (Figs. 7a,b and 8a,b); miRNA $\log_2$FC was measured by RT-qPCR (males, MDD-S vs. control; females, MDD subjects who died by suicide or natural causes (MDD-

S/N) vs. control), and target log_2FC and p-value by RNA-seq (MDD-S vs. control). Sheet snRNA_targets contains the differential expression of the network target genes in each cell cluster of the dlPFC single-nucleus RNA-seq dataset of Maitra et al. (GEO: GSE213982), comparing MDD subjects with controls within each sex (Seurat, two-sided Wilcoxon rank-sum test; Fig. 9). Positive log_2FC indicates higher expression in MDD-S (networks) or MDD (snRNA_targets) than in controls. Column descriptions: Direction = direction of change of the miRNA and its target; Lineage and Cluster = cell lineage and cluster, following the annotation of the original study; Fraction of nuclei, MDD and Fraction of nuclei, control = fraction of nuclei expressing the gene in each group; p-value = uncorrected p-value; P.adj = Bonferroni-adjusted p-value across the 36,588 features of the dataset.