**Supplementary Figure 1**. Cocaine-induced locomotor changes. **a**, Male and female Sprague-Dawley rats were treated with 20mg/kg for 1 hour and locomotor behavior was measured for 30 minutes. Cocaine-treated animals travelled signficantly more than saline-treated animals. Left, acute cocaine-induced locomotor changes in male rats (n=4/group, unpaired Student's t-test: $t(6)=6.974$, ***$p<0.0005$). Right, acute cocaine-induced locomotor changes in female rats (n=4/group, unpaired Student's t-test: $t(6)=4.769$, **$p<0.005$) Data from Savell*, Tuscher*, Zipperly*, Duke*, Phillips* et al. 2020, _Science Advances_. **b**, Male and female Sprague-Dawley rats were treated with 20mg/kg once daily for 7 consecutive days. Locomotor behavior was measured for 30 minutes. Cocaine-treated animals travelled signficantly more than saline-treated animals on each testing day. Left, repeated cocaine-induced locomotor changes in male rats across 7 days (n=4/group, two-way ANOVA for main effect of treatment $F_{(1,42)}$ = 41.40, ****$p<0.0001$). Right, repeated cocaine-induced locomotor changes in female rats across 7 days (n=4/groups, two-way ANOVA for main effect of treatment, $F_{(1,42)}$ = 156.8, ****$p<0.0001$).
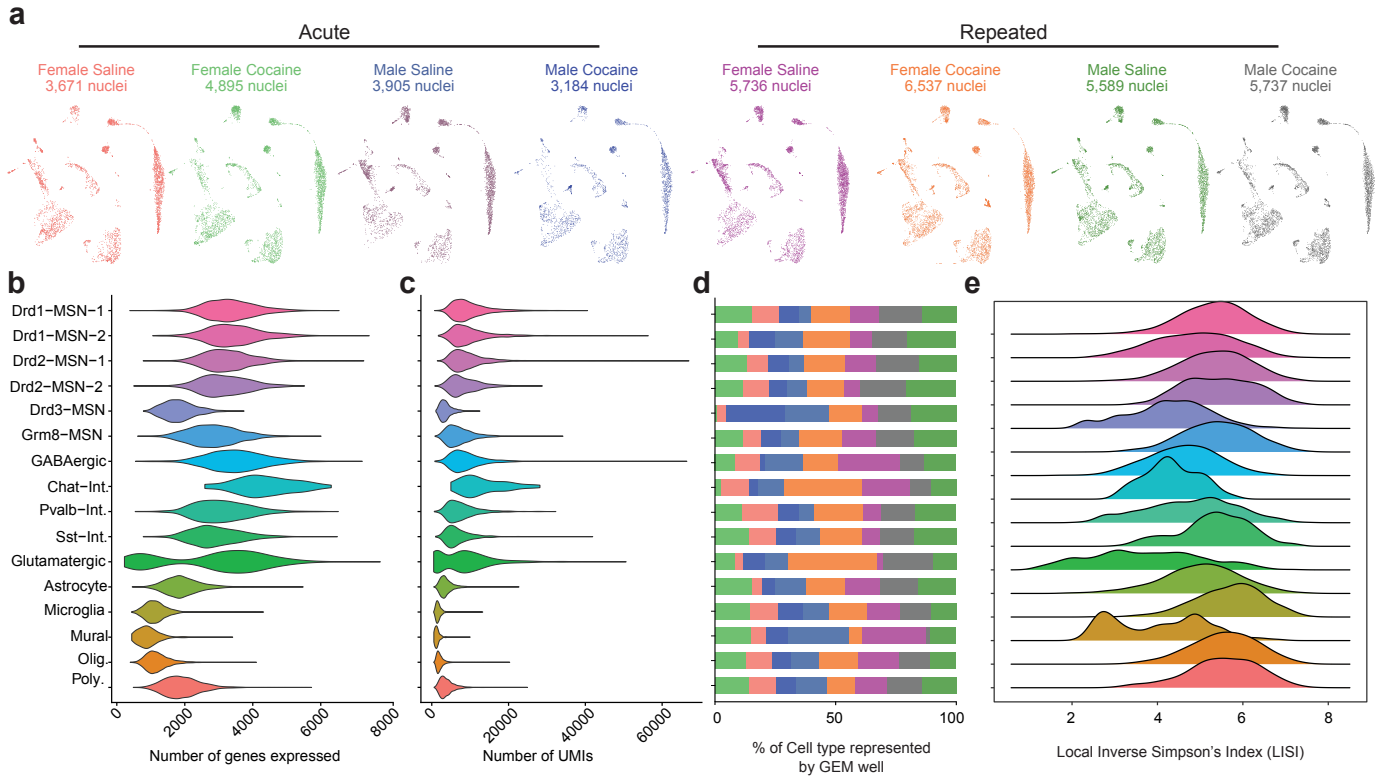
Supplementary Figure 2. Clustering and integration quality control. **a**, UMAPs grouped by sex and treatment group for the acute and repeated datset.**b**, Violin plot showing the number of genes expressed in each cell type. **c**, Violin plot showing the number of unique molecular identifiers (UMIs) within each cell type. **d**, Bargraph showing the percentage of each cell type represented by each of the 8 individual GEM wells used for integration. **e**, Ridge plot for Local Inverse Simpson's Index (LISI) for each cell type. LISI is a measure of integration sucess with higher values indicating a well-mixed cluster.
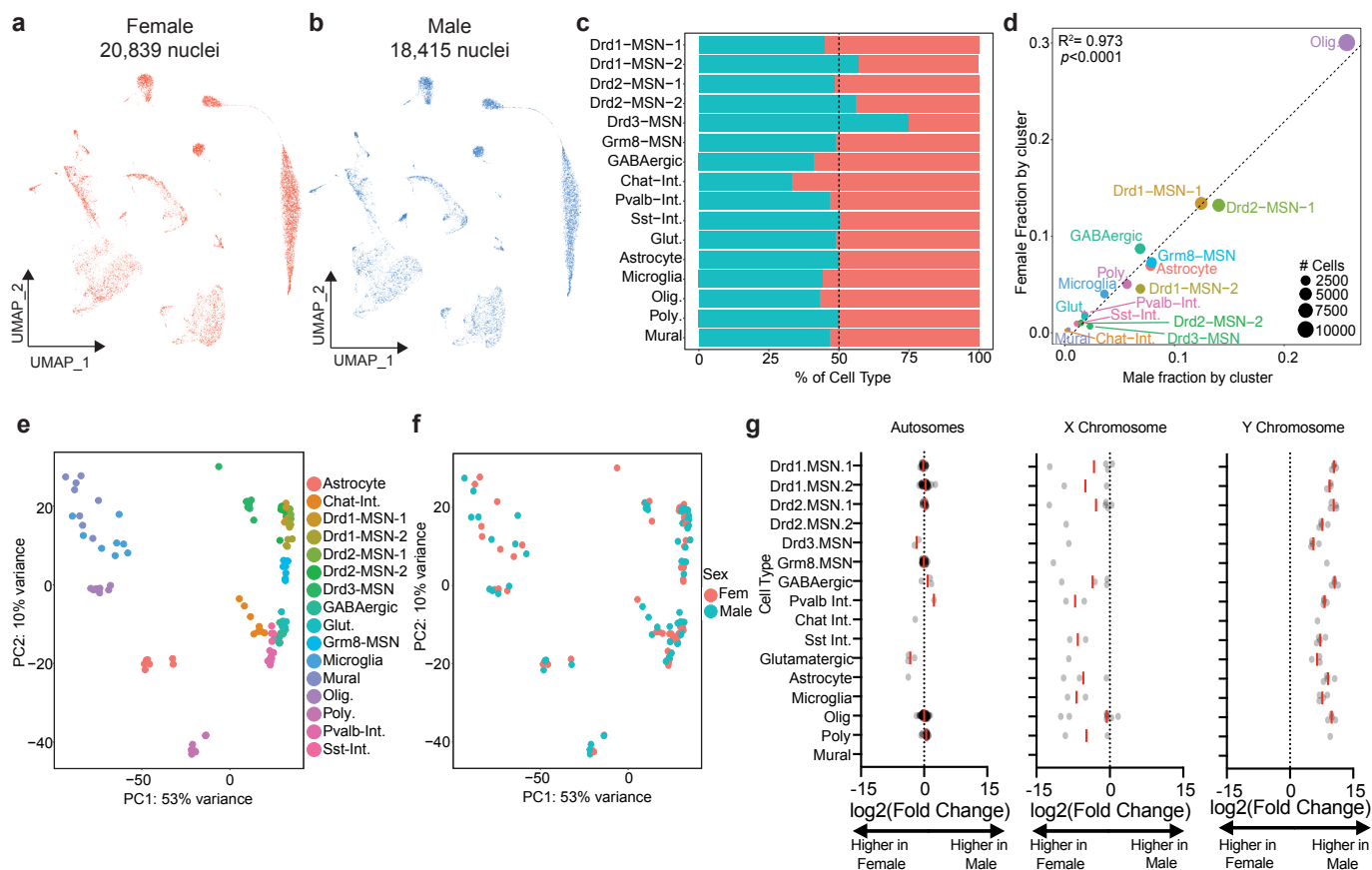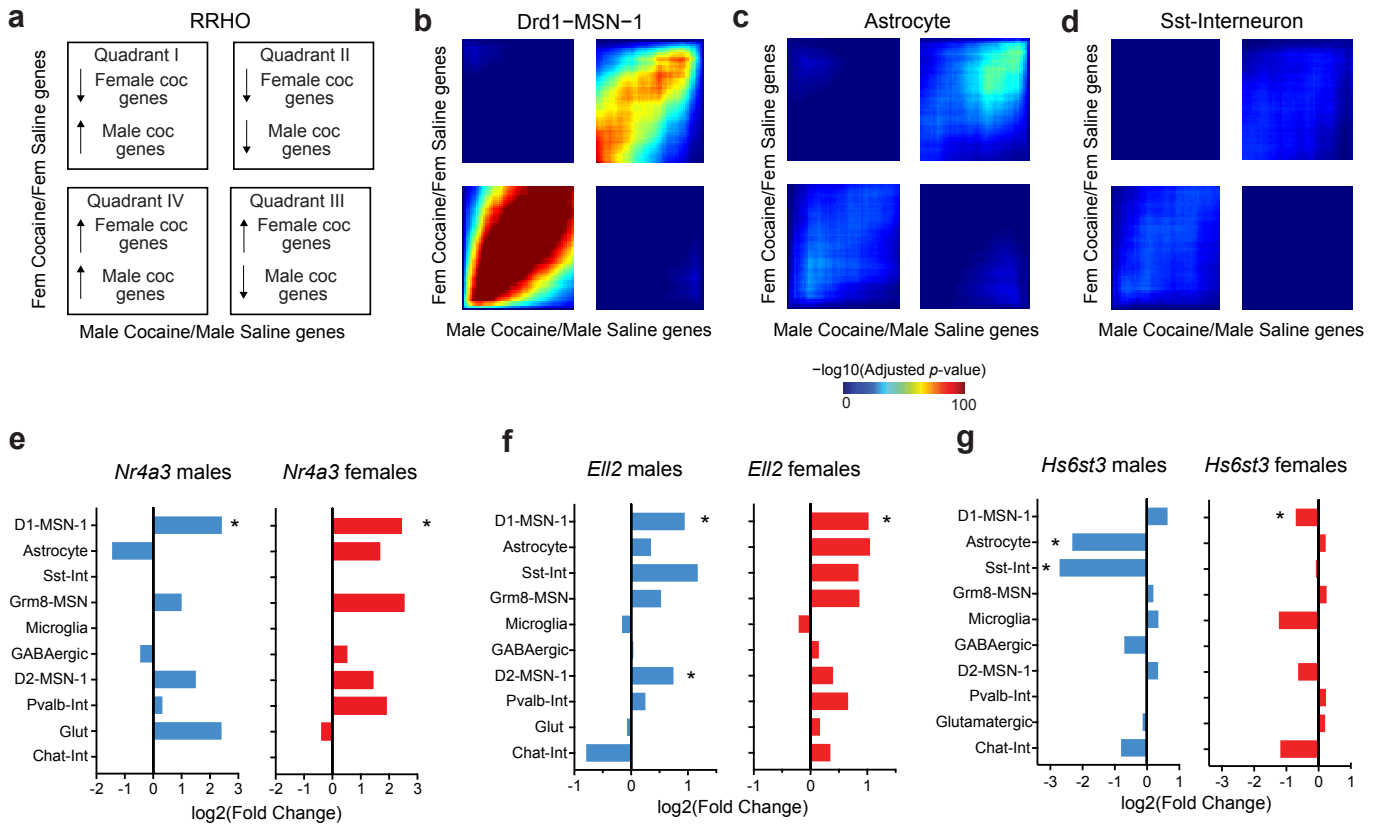
Supplementary Figure 3. Comparison of baseline transcriptional profiles of male and female cells. **a-b**, UMAPs split by sex. **c**, Percentage of each cell type represented by each sex. **d**, Correlation of the fraction of male and female cells represented by each cluster. Size of the point is representative of the number of cells within the cluster. **e-f**, PCA plots demonstrating that variance within the dataset is largely driven by transcriptional profiles of the cell types and not sex. Each cell type will have 8 individual points that represent 8 GEM wells. **g**, DEGs calculated using a DESeq2-based pseudobulk analysis with dataset and stim used as covariates. Each point on the graph represents a single DEG. The red line represents the average log2(Fold Change) of all DEGs for that cluster.
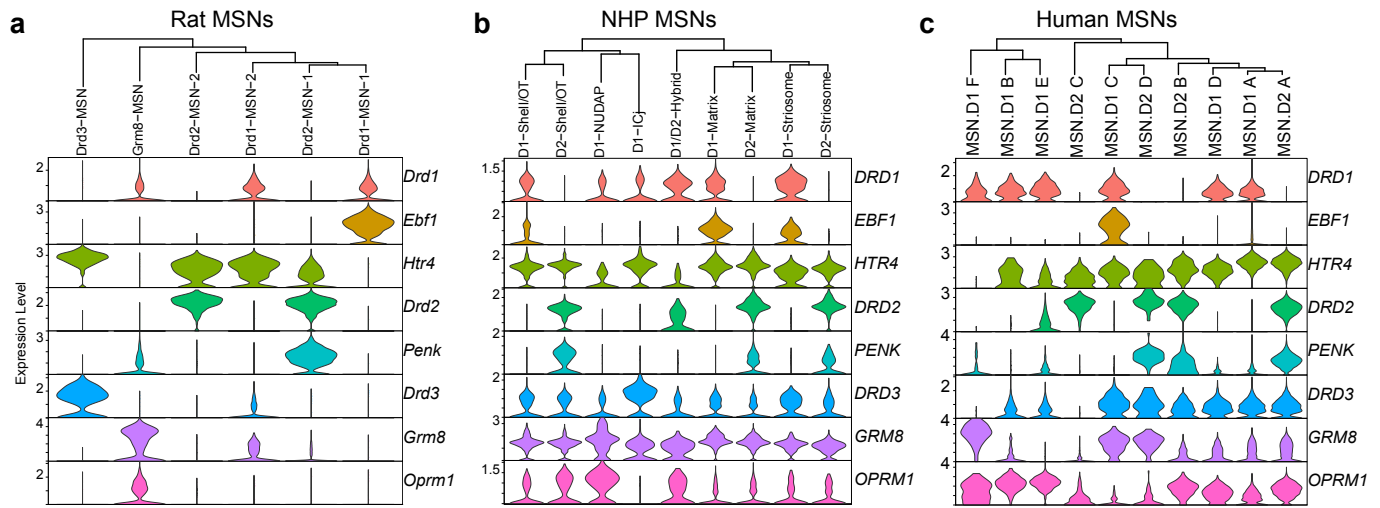
Supplementary Figure 4. Expression of MSN marker genes across species. **a-c,** Violin plots demonstrating expression of MSN specific markers in rat, NHP, and human MSN clusters.
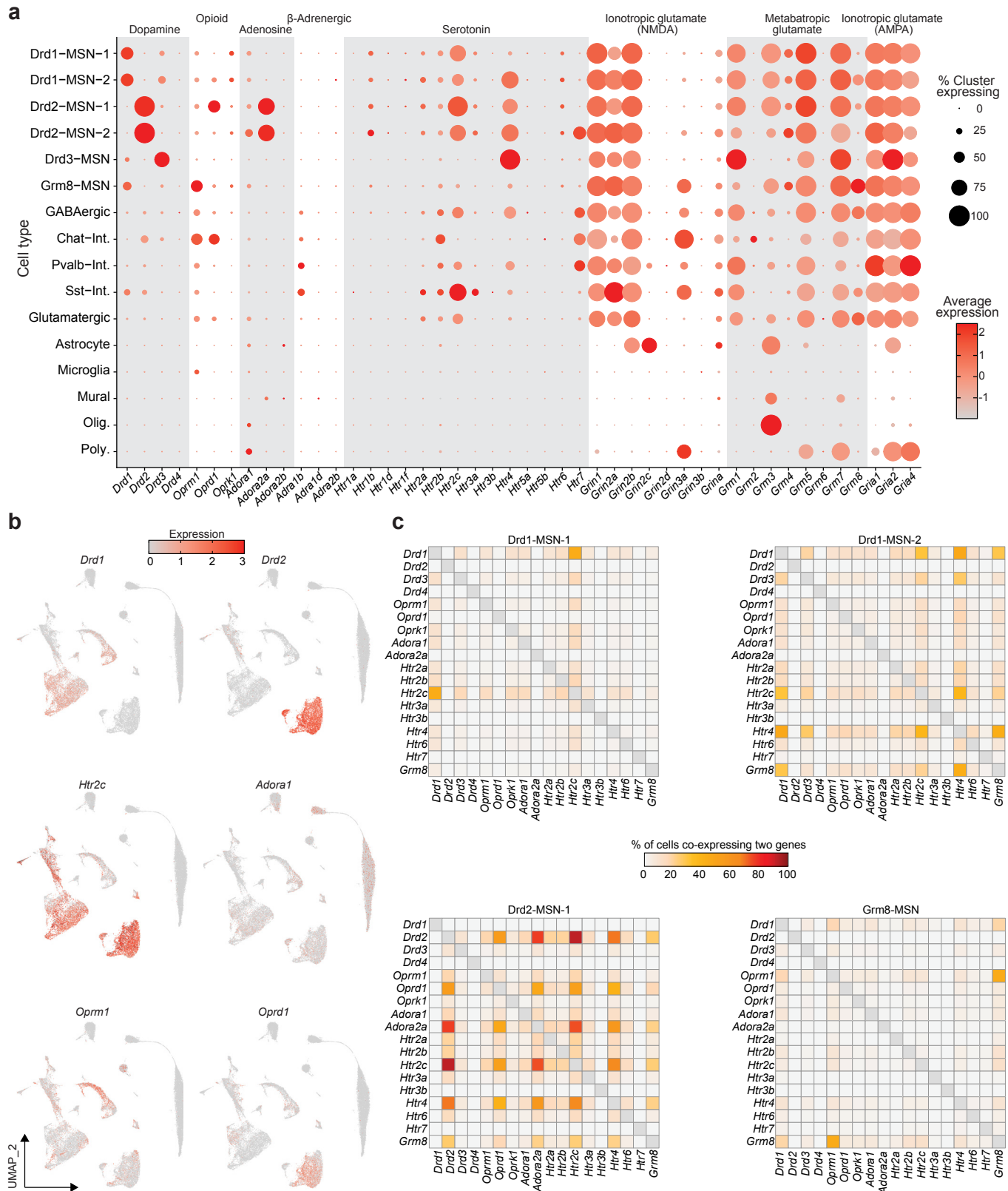
Supplemetnary Figure 5. Distribution of expression of genes encoding several receptor systems and subtypes. **a**, Dotplot demonstrating level of expression, and percentage of cells, expressing 46 genes invovled in 8 receptor systems. **b**, UMAPs colored by level of expression of *Drd1*, *Drd2*, *Htr2c*, *Adora1*, *Oprm1*, and *Oprd1*. **c**, Co-expression heatmaps for several receptor systems demonstrating differential expression of serotonic receptors in *Drd1*-express-ing MSNs, co-expression of *Drd2* and *Adora2a* in the Drd2-MSN population, and *Grm8* and *Oprm1* in the Grm8-MSN population.

Supplementary Figure 6. Sex- and cell type-specific comparison of cocaine-induced transcriptional changes identified using pseudobulk differential expression analysis. **a**, Interpretation key for rank-rank hypergeometric overlap (RRHO) heatmaps for sex- and population- specific cocaine genes. Quadrants I and III contain discordant gene changes; quadrants II and IV highlight concordant gene changes. **b-d,** RRHO plots for D1-MSN-1, Astrocyte and Sst-Interneuron populations. Bar graphs illustrating respresentative example genes with similar transcriptional responses to cocaine across populations (**e-f**) and dynamic regulation across populations (**g**).