



Sex-Specific Parent-of-Origin Allelic Expression in the Mouse Brain

Christopher Gregg *et al.*
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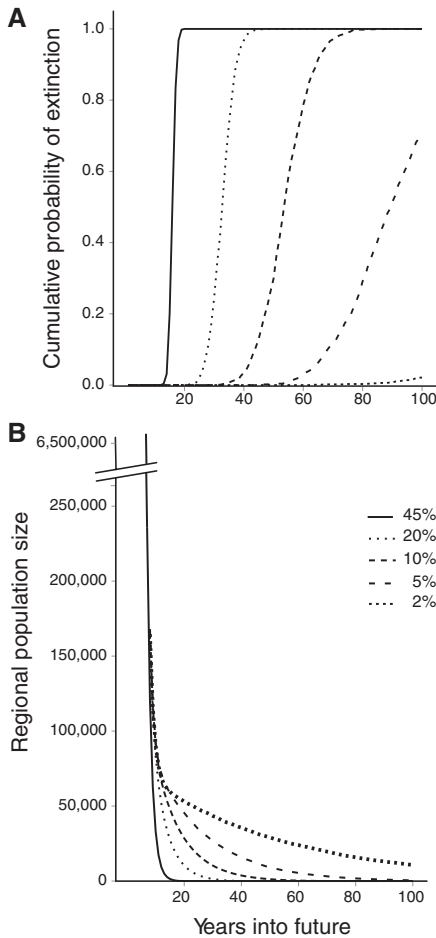


Fig. 4. (A) Cumulative probability of regional extinction of little brown myotis for five scenarios of time-dependent amelioration of disease mortality from WNS, based on matrix model simulation results. Each scenario represents predicted time-dependent declines for a specified number of years after infection and then holds the decline rate constant at either 45, 20, 10, 5, or 2% to demonstrate the impact of amelioration on the probability of extinction over the next 100 years. **(B)** Population size in each year averaged across 1000 simulations for each of the five scenarios of time-dependent amelioration of mortality from WNS.

structure and function (27, 28). The rapid geographic spread of WNS since 2006, coupled with the severity and rapidity of population declines, support the hypothesis of introduction of a novel pathogen into a naïve population and demonstrate the seriousness of pathogen pollution as a conservation issue (1). Our analysis focused on little brown myotis in the northeastern United States, but several other bat species are experiencing similar mortality from WNS and may also be at significant risk of population collapse or extinction. This rapid decline of a common bat species from WNS draws attention to the need for increased research, monitoring, and management to better understand and combat this invasive wildlife disease (1).

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Supporting Online Material

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Sex-Specific Parent-of-Origin Allelic Expression in the Mouse Brain

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Genomic imprinting results in preferential gene expression from paternally versus maternally inherited chromosomes. We used a genome-wide approach to uncover sex-specific parent-of-origin allelic effects in the adult mouse brain. Our study identified preferential selection of the maternally inherited X chromosome in glutamatergic neurons of the female cortex. Moreover, analysis of the cortex and hypothalamus identified 347 autosomal genes with sex-specific imprinting features. In the hypothalamus, sex-specific imprinted genes were mostly found in females, which suggests parental influence over the hypothalamic function of daughters. We show that *interleukin-18*, a gene linked to diseases with sex-specific prevalence, is subject to complex, regional, and sex-specific parental effects in the brain. Parent-of-origin effects thus provide new avenues for investigation of sexual dimorphism in brain function and disease.

Genomic imprinting is an epigenetic mode of gene regulation involving preferential expression of the paternally or maternally inherited allele (1). Sexual dimorphism is a central characteristic of mammalian brain function and behavior that influences major neurological diseases in humans (2). Here we address the potential existence of differential genomic imprinting in the brain according to the sex of individuals. Imprinting refers to gene expression differences between maternal and paternal chro-

mosomes (3) and is also used more strictly to define complete allele-specific silencing (4). Our analysis encompasses sex differences in parent-

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of-origin allelic effects involving all-or-none allele-specific expression and parental biases in gene expression.

Three processes may underlie sexually dimorphic genomic imprinting (fig. S1, A to C). Nonrandom X inactivation, such as the imprinted X inactivation observed in marsupials and the mouse extra-embryonic lineages, could result in the preferential silencing of one of the parentally inherited X chromosomes in females (fig. S1A) (5). In addition, imprinting of individual X-linked loci in females results in gene expression from the active paternally inherited X that differs from the active maternally inherited X (fig. S1B). Studies of Turner syndrome suggested imprinting of X chromosome loci with relevance to brain function (6), and X-linked imprinted genes have indeed been identified in the brain (7, 8). Finally, autosomal genes might be imprinted in one sex but not the other (fig. S1C). A recent study of quantitative trait loci influencing growth and body composition in mice indicates that such mechanisms may exist (9).

We have used Illumina transcriptome sequencing of F₁ hybrid mice generated from initial (F₁i) and reciprocal (F₁r) crosses of CAST/EiJ (CAST) and C57BL/6J (C57) mice to investigate genomic imprinting in the brain with high resolution (10, 11). Here we compare parental effects in the transcriptome of the adult male versus adult female preoptic area (POA) of the hypothalamus and medial prefrontal cortex (mPFC). Detailed methods are described in (10) and in our companion paper (11).

We first assessed global levels of X-linked gene expression from the maternal X chromo-

some (Xm) versus the paternal X chromosome (Xp) in the adult female POA and mPFC. A significant strain-effect favoring expression from the CAST X chromosome was observed in F₁ females (Fig. 1, A and B). This difference is likely due to preferential selection of the CAST X-chromosome in the hybrids (12). In addition, we identified a parent-of-origin effect (Fig. 1, A and C), such that total levels of expression from the Xm were increased by 19% and 11% relative to the Xp in the mPFC and POA, respectively. The Xm bias was significantly greater in the mPFC than in the POA ($P < 0.0001$, two-tailed Fisher's exact test).

This elevated expression from the Xm versus the Xp (Fig. 1, A and C) may indicate a bias in X

inactivation in the brain, a hypothesis further investigated with a transgenic mouse line expressing X-linked *egfp* under the control of the cytomegalovirus (CMV) promoter as a reporter of the active X chromosome (13). Control studies confirmed that the *egfp* transgene reports X inactivation (fig. S2), and *egfp* expression was found restricted to a subpopulation of vesicular glutamate transporter 2-positive (vGLUT2⁺) glutamatergic neurons (~72%) (fig. S3). We compared the number of Xm- versus Xp-expressing glutamatergic neurons in adult Xm^{*egfp*}/Xp and Xm/Xp^{*egfp*} females (Fig. 2). In cortical regions, 40 to 50% more neurons expressed the Xm than the Xp in the mPFC, the sensory CTX, and the piriform CTX (Fig. 2A). We also observed a significant Xm bias in

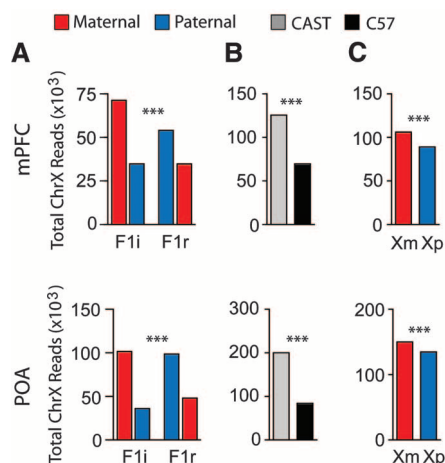


Fig. 1. Sex-specific imprinting and preferential expression of the Xm in the female brain. (A) Total maternal and paternal X-linked reads for the adult female mPFC and POA in F₁i and F₁r crosses reveals a highly significant association between strain and cross (mPFC, $P < 0.0001$; POA, $P < 0.0001$, two-tailed Fisher's exact test). (B) Identification of a significant strain effect favoring CAST X-chromosome expression (χ^2 analysis). (C) Preferential expression of the Xm in the mPFC and POA (χ^2 analysis). *** $P < 0.001$; * $P < 0.05$.

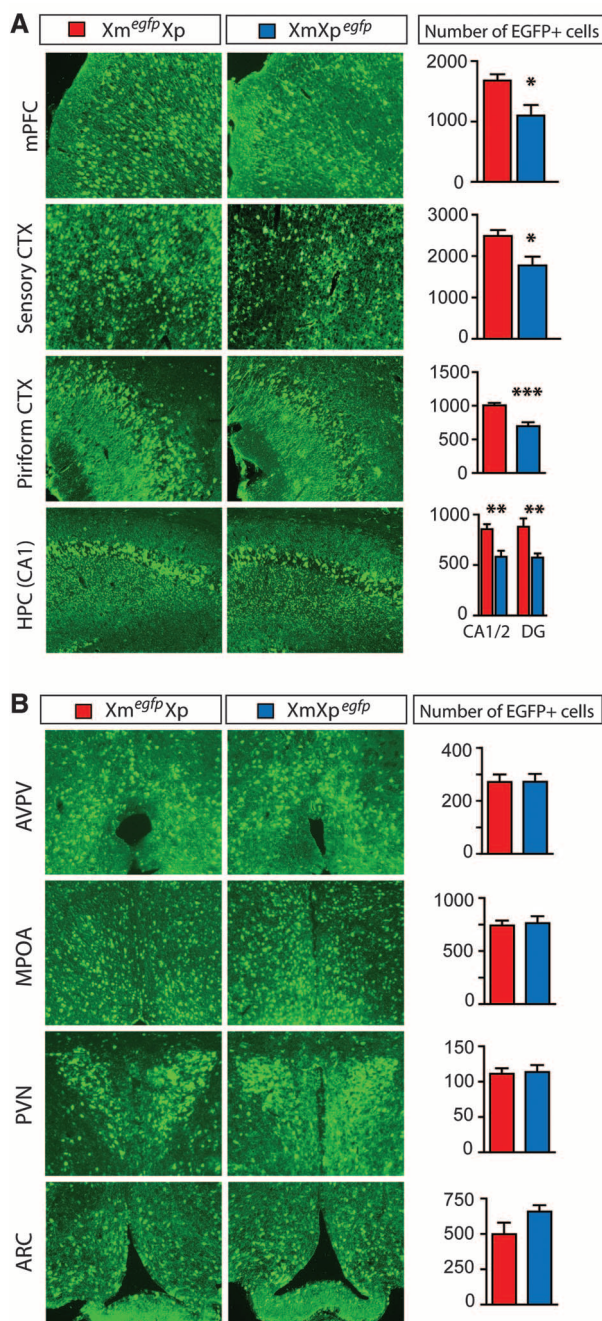


Fig. 2. Preferential expression of Xm in female cortical regions indicated by Xm^{*egfp*}/Xp and Xm/Xp^{*egfp*} transgenic mice. (A and B) The number of EGFP⁺ cells in different cortical (A) and hypothalamic (B) brain regions of Xm^{*egfp*}/Xp (red) versus Xm/Xp^{*egfp*} (blue) 5-week-old females. Hypothalamic regions: anteroventricular nucleus (AVPV), medial preoptic area (MPOA), periventricular nucleus (PVN), or arcuate nucleus (ARC). Two-tailed unpaired t test; $n = 7$; *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$. Red bars, Xm^{*egfp*}/Xp; blue bars, Xm/Xp^{*egfp*}. Scale bar, 50 μ m.

the CA1/2 and dentate gyrus (DG) regions of the hippocampus (HPC) (Fig. 2A). In contrast, no difference in the number of Xm- versus Xp-expressing cells was detected in the hypothalamus (Fig. 2B). We then asked whether the bias observed in cortical versus hypothalamic glutamatergic neurons could be generalized to all or a few neuronal populations in these brain regions. We summed the Xm and Xp reads for seven well-characterized neuron-specific X-linked genes and found a significant Xm expression bias in both the mPFC (21% Xm bias; $P < 0.0001$) and POA (15% Xm bias; $P < 0.0001$, two-tailed Fisher's exact test) (fig. S4). Therefore, whereas $X^{egfp}+$ glutamatergic neurons in POA do not preferentially select the Xm, some other neuronal populations of the hypothalamus likely do (fig. S4).

We then assessed X-linked imprinting at the level of individual genes using a chi-square test in which the expected value was adjusted for strain and maternal X selection biases. Using the stringent cutoff of $P < 0.05$ in the F_{1i} and F_{1r} cross used in our companion study (11) to assess imprinting, we failed to identify X-linked imprinted loci. Using a less stringent cutoff ($P < 0.1$), the previously known maternally expressed imprinted gene (MEG) *Xr13b* (7, 8) was correctly identified, and this approach further identified nine candidate imprinted genes in the POA and three in the mPFC (table S1), such as *yipf6*, which was identified in the POA (maternal bias) and mPFC (paternal bias).

Finally, we searched for sex-specific parental allelic effects on the autosomes. As reported in

our companion paper, parental expression biases in the male and female data sets were highly correlated (Fig. 3, A and B). However, single-nucleotide polymorphism (SNP) sites that exhibited a strong parental bias in one sex but not the other were also apparent in the data (Fig. 3, A and B). A chi-square test was applied in the F_{1i} and F_{1r} cross to identify SNP sites (cutoff $P < 0.05$) significantly imprinted in one sex but not the other ($P > 0.05$).

This study identified 347 candidate genes associated with sex-specific parental allelic effects in the adult brain, as defined by the presence of one or more SNP sites statistically imprinted in one sex but not the other (tables S2 and S3). The average parental expression bias exhibited by sex-specific imprinted SNP sites was 73% (POA) and 68% (mPFC), whereas the average bias for the same sites in the opposite sex was 52% (POA) and 51% (mPFC). Females had three times the total number of genes with sex-specific imprinted features (Fig. 3C) [150 genes (1.3% of 11,241 genes assessed)] as males in the POA [48 genes (0.5% of 9235 genes assessed)], but no difference was observed in the mPFC. This correlates well with the facts that the POA is a highly sexually dimorphic region of the brain involved in the control of maternal and mating behaviors and that imprinting is known to influence maternal behavior (14). We noted a paternal bias in the number of sex-specific genes identified in all samples (Fig. 3C).

We carried out an in-depth analysis of two candidate genes subject to sex-specific paren-

tal effects: *mitochondrial ribosomal protein 48* (*Mrpl48*) and *interleukin-18* (*Il18*). Mitochondria are strictly maternally inherited, and mitochondrial ribosomal proteins regulate translation in mitochondria but are encoded in the nuclear DNA (15). *Mrpl48* is one of four *Mrpl* genes found in our companion studies, which indicates parental control over the bioenergetics of neural cells. In the present study, *Mrpl48* was identified as paternally expressed in the female POA but not the male POA (Fig. 4A and fig. S5A). In the female POA, eight out of nine *Mrpl48* SNP sites exhibited a paternal expression bias in the F_{1i} and F_{1r} cross, four of which achieved statistical significance ($P < 0.05$) (Fig. 4A). In contrast, none of the nine SNP sites exhibited a paternal expression bias in the male POA. The female-specific paternal expression bias was confirmed in the POA by Sequenom matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry (MALDI-TOF) analysis (Fig. 4A).

Il18 encodes a cytokine expressed by neurons, astrocytes, and microglia that modulates neuroinflammation as well as homeostatic processes and behavior (16). *Il18* has been linked to multiple sclerosis, a highly sexually dimorphic disease that predominates in women and is associated with parent-of-origin effects through the maternal lineage (17). We found *Il18* to be preferentially expressed from the maternal allele in the female but not male mPFC or the POA. We identified two SNP sites (three bases apart) in one exon of *Il18* in the female mPFC that indicate that 74% of transcription from this region

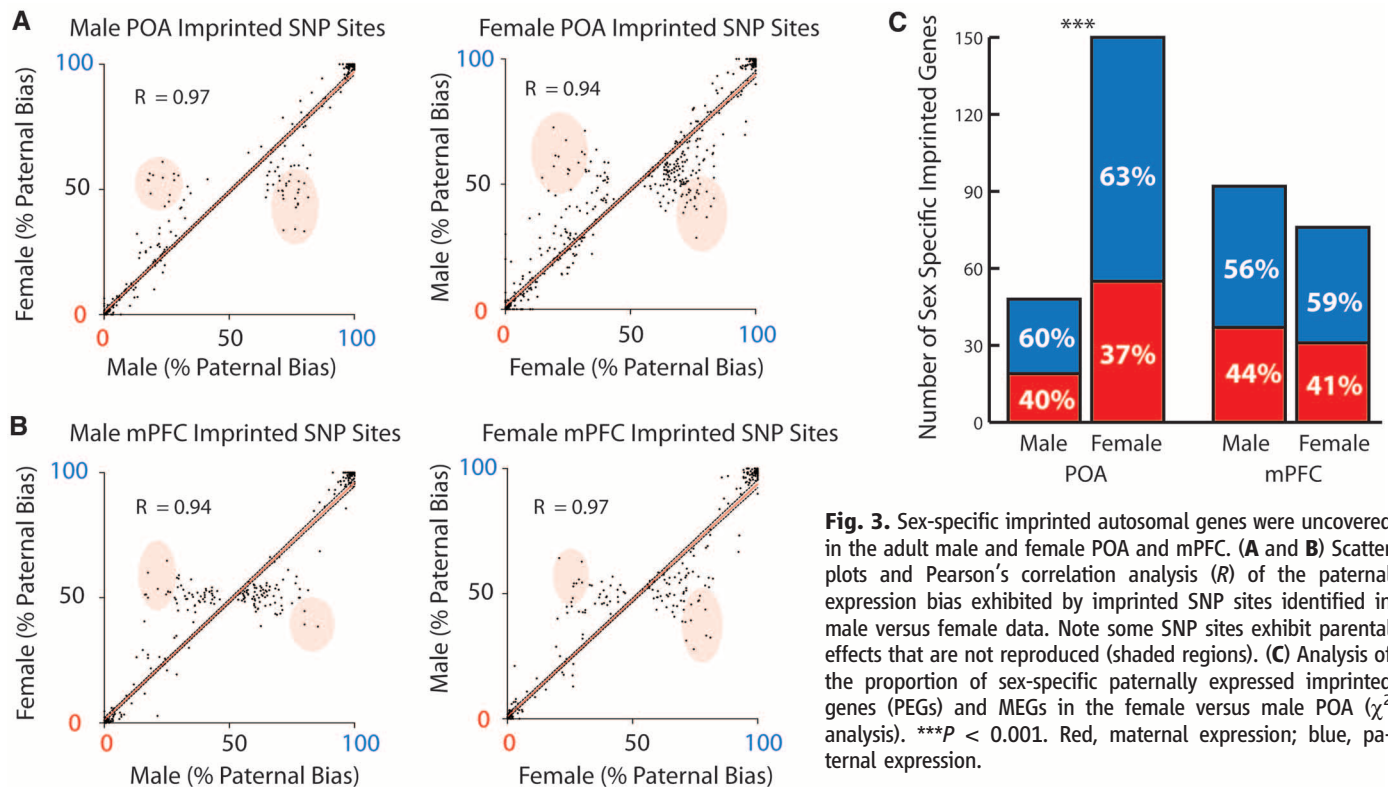


Fig. 3. Sex-specific imprinted autosomal genes were uncovered in the adult male and female POA and mPFC. (A and B) Scatter plots and Pearson's correlation analysis (R) of the paternal expression bias exhibited by imprinted SNP sites identified in male versus female data. Note some SNP sites exhibit parental effects that are not reproduced (shaded regions). (C) Analysis of the proportion of sex-specific paternally expressed imprinted genes (PEGs) and MEGs in the female versus male POA (χ^2 analysis). *** $P < 0.001$. Red, maternal expression; blue, paternal expression.

of the locus arises from the maternal allele (Fig. 4B and fig. S5B).

I118 signaling has anorectic effects, and heterozygous *I118* female, but not male, mice exhibit hyperphagia (18). We used quantitative polymerase chain reaction (QPCR) to assess *I118* levels in the mPFC and the hypothalamus of *I118* heterozygous mice on a C57 background (Fig. 4C and fig. S5B). Loss of the maternal allele in the mPFC of *I118*^{+/−} females, but not males, resulted in a reduction by a factor of 2.3 in the level of *I118* expression relative to animals in which the paternal allele was deleted (Fig. 4C). No significant parent-of-origin effects were observed in the hypothalamus in males or females (Fig. 4C). These results are consistent with the preferential expression of the maternal allele in the female mPFC uncovered by the Illumina RNA-sequencing (RNA-Seq) analysis.

I118 is adjacent to *SDHD* (succinate dehydrogenase complex, subunit D) and *Bcd2* (beta, beta-carotene 9',10'-dioxygenase variant 2) in mouse and human. Mutations in *SDHD* lead to head and neck paragangliomas in humans only when paternally inherited, yet previous studies have failed to detect imprinting at this locus

(19). We found evidence for sex-specific parent-of-origin effects in the mPFC, but not the POA, for both *SDHD* (male maternal bias) and *Bcd2* (female paternal bias) (fig. S6), which suggested a putative gene cluster with highly complex, region-specific and sex-specific parent-of-origin effects. Future studies will be required to determine the existence of an imprinting control region or other defining features of bona fide imprinted gene clusters.

Our data present evidence for epigenetic mechanisms by which parents may differentially influence gene expression in the brain of daughters versus sons and provide insights into sexually dimorphic epigenetic pathways recently uncovered in the brain (20). Some of the genes identified have known relevance to behavior and disease, although the mechanisms and functions of these parental effects are unclear. Previous analysis of X inactivation in the brain focused on very early stages of neural development and failed to observe any parental bias (21). The Xm bias may emerge during development through differential cell proliferation or survival, although a few studies have suggested that X inactivation in female somatic lineages favors selection of

the Xm (22–24). The Xm enrichment contrasts with the paternal bias found among autosomal genes subject to sex-specific imprinting and the 70% paternal bias of autosomal genes identified in our companion study (11). The X chromosome is enriched for genes involved in brain function (25, 26), and theoretical work has postulated that the maternally biased inheritance of the X selects for maternal interests (27, 28). Investigating the potential relations between maternal and paternal gene expression programs may shed light on brain function, evolution, and disease.

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Supporting Online Material

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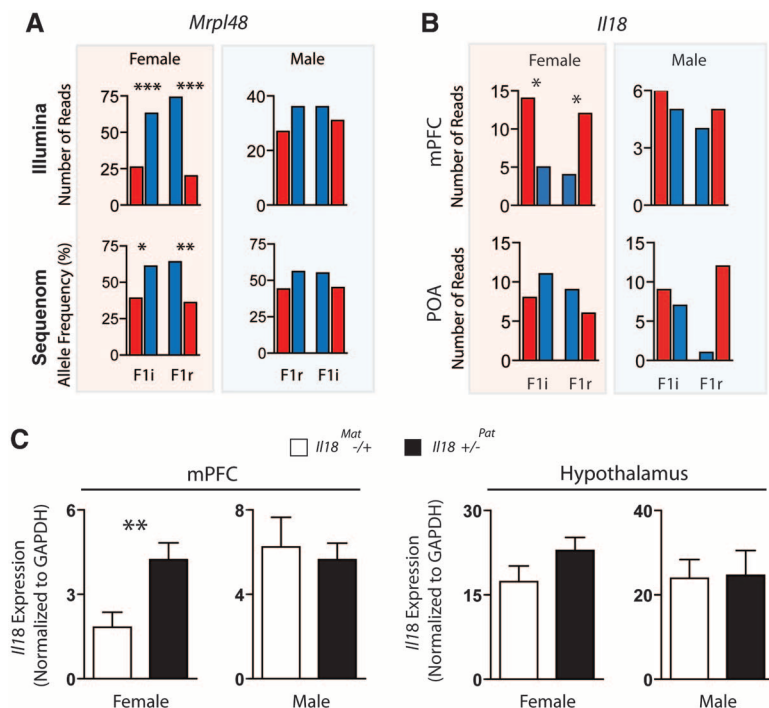


Fig. 4. Sex-specific imprinted expression of *Mrpl48* and *I118* in the female brain. (A) Illumina read data for an imprinted SNP in the 3' untranslated region (3' UTR) of *Mrpl48* [highlighted in blue in (A); SNP_ID: uc009inh.1_801] indicate preferential expression of the paternal allele in the female but not male POA (χ^2 analysis). Sequenom analysis confirmed the result (average allele frequency from three biological and three technical replicates). (B) Illumina read data for the imprinted SNP in *I118* (SNP_ID: uc009inh.1_801) indicate preferential expression of the maternal allele in the female mPFC, but not the male mPFC or the POA (χ^2 analysis). (C) QPCR analysis of *I118* expression in maternal- versus paternal-deletion *I118* heterozygous mice on C57 background reveals reduced expression in the mPFC of female maternal-deletion mice relative to paternal-deletion mice ($n = 10$, two-tailed, unpaired t test, $P = 0.0086$). No difference was observed in the male mPFC ($n = 5$) or the hypothalamus (females: $n = 5$, males: $n = 6$). *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$. Red, maternal expression; blue, paternal expression. GAPDH, glyceraldehyde-3-phosphate dehydrogenase.