Published in final edited form as:

Front Neuroendocrinol. 2016 July ; 42: 1–17. doi:10.1016/j.yfrne.2016.05.002.

Genetic and neuroendocrine regulation of the postpartum brain

Stephen C. Gammie^{a,b,*}, Terri M. Driessen^a, Changjiu Zhao^a, Michael C. Saul^a, and Brian E. Eisinger^a

^aDepartment of Zoology, University of Wisconsin-Madison, Madison, WI, USA

^bNeuroscience Training Program, University of Wisconsin-Madison, Madison, WI, USA

Abstract

Changes in expression of hundreds of genes occur during the production and function of the maternal brain that support a wide range of processes. In this review, we synthesize findings from four microarray studies of different maternal brain regions and identify a core group of 700 maternal genes that show significant expression changes across multiple regions. With those maternal genes, we provide new insights into reward-related pathways (maternal bonding), postpartum depression, social behaviors, mental health disorders, and nervous system plasticity/developmental events. We also integrate the new genes into well-studied maternal signaling pathways, including those for prolactin, oxytocin/vasopressin, endogenous opioids, and steroid receptors (estradiol, progesterone, cortisol). A newer transcriptional regulation model for the maternal brain is provided that incorporates recent work on maternal microRNAs. We also compare the top 700 genes with other maternal gene expression studies. Together, we highlight new genes and new directions for studies on the postpartum brain.

Keywords

Maternal; Postpartum; Depression; Addiction; Reward; Social behavior; Mental health; MicroRNA; Oxytocin; Prolactin

1. Introduction

The transformation from a non-parental to a maternal state involves a number of dramatic and wide ranging alterations, including changes in the CNS, behavior, and physiology (Numan and Insel, 2003). As recently reviewed, an interplay between the neuroendocrine system, including estradiol, progesterone, and prolactin, and CNS neuromodulators, including oxytocin, dopamine, and vasopressin, helps to orchestrate multiple maternal functions (Bridges, 2015). Many of the known target genes of these neuroendocrine pathways have been specifically examined, but the vast majority of genes still have not been evaluated for contributions to the maternal brain. Thus, it is likely that there are many genes that play critical, but currently unknown roles in producing the maternal brain and that our understanding of the maternal brain will advance significantly by adding in this currently

*Corresponding author at: 430 Lincoln Drive, University of Wisconsin, Madison, WI 53706, USA. scgammie@wisc.edu (S.C. Gammie).

hidden information. In this review, we aim to identify potential new critical maternal brain genes by synthesizing findings from multiple large scale gene expression studies from different CNS regions in the postpartum condition. With the potential newly identified maternal brain genes, we use various analytic tools to determine the mechanisms by which they might support the maternal phenotype.

2. The genetic complexity of the postpartum brain

The human and mouse genomes both include over 20,000 protein coding genes (Zerbino et al., 2015) (Fig. 1). Recent studies have evaluated how many genes are actually expressed in the CNS for humans and rodents (mouse or rat) and these numbers are approximately 18,000 (Hawrylycz et al., 2012) and 16,000 (Lein et al., 2007; Stansberg et al., 2007), respectively. These latter numbers are important because they indicate the size of the universe of genes that could be making contributions to the maternal brain, yet relatively few have been examined. As indicated in Fig. 1, a subset of genes (~50) have been well-studied (including via pharmacological manipulations) in the context of the postpartum brain or maternal phenotype and most of these are related to known modulators of maternal behavior and physiology, including estradiol, oxytocin, vasopressin, prolactin, progesterone, dopamine, and GABA (Francis et al., 2002; Salzberg et al., 2002; Numan and Insel, 2003; Zhao et al., 2012a; Akbari et al., 2013; Bridges, 2015; de Moura et al., 2015; Keebaugh et al., 2015; Mileva-Seitz et al., 2015). Further, the Jackson Laboratory maintains a database of modifications of genes that lead to overt maternal behavioral or physiological disruptions in mice and currently about 150 genes have been identified (www.jax.org) (Grubb et al., 2014). The contributions of some of these genes to maternal care were recently reviewed (Kuroda et al., 2011). Unfortunately, for most transgenic lines maternal phenotype is not examined or reported, so the genetic contributions to the maternal brain are not known. Together, over 99% of genes that could be making important contributions to the postpartum brain have yet to be examined (Fig. 1). While some signals (e.g., certain cytokines or hormones such as cortisol) are produced outside the CNS and act back on the CNS, we focus here on genes within the CNS, including those that might respond to outside signals (e.g., glucocorticoid/cortisol receptors).

3. Synthesis of recent multiple large scale gene expression studies of the maternal brain

In recent studies, we used high density microarrays that allowed for assessment of over 20,000 protein coding genes to assay gene expression changes in the postpartum CNS in four brain regions that contribute to the maternal phenotype: medial preoptic area (MPOA) (Driessen et al., 2014b), medial prefrontal cortex (mPFC) (Eisinger et al., 2014), lateral septum (LS) (Eisinger et al., 2013b), and nucleus accumbens (NAC) (Zhao et al., 2014). In these studies we compared the CNS of maternal to virgin mice and typically identified over 1000 genes per region with significant alterations in expression, suggesting a high level of change in the postpartum condition. Further, while some genes were unique to a region, we also noticed that many of the same genes were altered in multiple brain regions. Using a hypergeometric test (Saul et al., 2016), we confirm here that each of the four regions are

enriched for one another in terms of high overlap of significantly altered genes (Fig. 2). The connections between LS with MPOA ($p < 10^{-16}$) and mPFC with NAC ($p < 10^{-8}$) were particularly high. Together then, the findings suggest that there is a core group of maternal genes that act across multiple brain regions. In order to synthesize the overlap of common genes in multiple brain regions and identify core maternal genes, we decided to use a ranking approach. As shown in Supplementary Table 1, the ranking and p-value (from most to least significant) of genes for each of the four brain regions is provided using analysis as previously described. Further, an overall rank is provided that is based on the average of the top three ranks for a given gene from all four regions. The rationale is that if a gene is significantly altered in three regions, then those changes are not ignored simply due to lack of change in a fourth region. We considered multiple cutoffs for subsequent analysis and determined that the top 700 genes was a useful cutoff given high likely biological validity (significance in 3 or more regions would remove most false positives) and 700 works well with most of the analysis tools we employed. Because this review focusses on these core 700 maternal genes identified using this novel approach and performs novel analysis, it is not a typical review of the existing literature and attempts to make new progress in the analysis of the maternal brain.

4. Bonding, reward, and addiction pathways in the postpartum brain

Offspring are highly rewarding and previous studies have demonstrated alterations in reward systems in the maternal brain (Wilsoncroft, 1968; Hauser and Gandelman, 1985; Lee et al., 1999; Mattson et al., 2001, 2003; Febo et al., 2005; Ferris et al., 2005; Mattson and Morrell, 2005; Seip and Morrell, 2007; Noriuchi et al., 2008; Strathearn et al., 2008; Febo, 2011). For example, naïve prepartum female rodents find social interactions with mouse pups to have low valence (Lonstein and De Vries, 2000), but postpartum females find social interactions with pups to be intensely rewarding (Hauser and Gandelman, 1985). In our recent study on NAC, a key region involved in reward (and coopted during addiction), we used bioinformatics to demonstrate for the first time a significant link between maternal gene expression and known databases for genes involved in reward and addiction (Zhao et al., 2014). Here we use the same approach and find that the top 700 maternal genes are significantly enriched (contain significantly more than expected by chance) for the 986 known addiction-related genes gathered from five independent databases ($p = 0.004$) (Fig. 3A). Our tests used either Modular Single-set Enrichment Tests (MSET) when the target is <500 genes or BigTest when the target is >500 genes. We developed both enrichment tests and details on MSET (Eisinger et al., 2013a) and BigTest (Saul et al., 2016) are provided in our recent publications. In general, the tests use the gene expression background to determine a probability distribution of matches to the target list and the p-value is determined by the actual number of matches to the target list as shown in Fig. 3A. When focusing on matches to 304 addiction genes in two or more databases, the top 700 maternal genes show significant enrichment ($p < 0.0001$) as do three of the four regions when these are analyzed separately; mPFC is just above significance ($p = 0.07$) (Fig. 3A). The top 700 maternal genes that matched addiction genes included genes previously connected to maternal reward or bonding, including the mu opioid receptor, *Oprm1*, the dopamine receptor, *Drd1a*, the serotonin receptor, *Htr1a*, and the opioid peptides, enkephalin (*Penk*)

and dynorphin (*Pdyn*) (Panksepp et al., 1994; Parada et al., 2008; Higham et al., 2011; Mileva-Seitz et al., 2012; de Moura et al., 2015); shown in red circles in Fig. 3B. Interestingly, a number of genes previously linked to reward or addiction, but not to maternal reward or bonding per se, are identified and these include glutamate related signaling genes (*Grm3*, *Gria2*, *Homer1*, and *Homer2*), the hypocretin receptor (*Hcrtr1*), the dopamine and glutamate related phosphatase inhibitor (*Ppp1r1b*; also known as Darpp32), the adenosine receptor (*Adora2a*), and the transcription factors (*Nr1d1* and *Nr4a2*); shown in green circles in Fig. 3B. We plotted the top 700 maternal genes matching addiction genes (in black) using Gene-Mania (Warde-Farley et al., 2010), which provides an interaction network based on multiple databases and types of evidence, including co-expression, co-localization, shared protein domains, physical interaction, and predicted interaction. The more lines between two genes and the closer the genes to one another in the graph indicates a stronger connection between two genes. GeneMania also provides connecting genes (in gray) that can help explain gene network connections (Fig. 3B). The few genes that did not show a strong connection with other genes were omitted from the figure. A complete listing of all matching genes is provided in Supplementary Table 1. Of the promising new candidate reward genes, *Nr1d1* (also known as Rev erb alpha) is of particular interest because it is involved in circadian rhythm feedback and an increasing number of studies are linking it to reward/addiction pathways (Belluardo et al., 2005; Wang et al., 2008; Piechota et al., 2012; Wongchitrat et al., 2013). The nuclear receptor, *Nr4a2*, and the phosphatase inhibitor, *Ppp1r1b*, both are connected to dopamine signaling and reward (Le et al., 1999; Frank et al., 2009) and thus may be relevant to numerous dopamine-related studies on maternal reward (Numan, 2007, 2012; Stolzenberg and Numan, 2011; Olazábal et al., 2013; Kikuchi and Noriuchi, 2015). Any of the genes shown could play a key role in maternal bonding, but follow up hypothesis directed studies will be required to assess the impact.

As an additional approach for reward/addiction analysis, we used the on-line tool ToppCluster (Kaimal et al., 2010) to analyze the top 700 maternal genes. As shown in Fig. 3C, top 700 maternal genes were found to be highly significantly enriched ($p < 10^{-5}$) for targets of multiple drugs of abuse, including nicotine, alcohol, dronabinol (cannabinoid analogue), methamphetamine, morphine, and cocaine. As seen in the cluster diagram, while some genes are common to multiple drugs, others are common to only two or one. A main take home message is that using multiple approaches, the postpartum brain has a striking connection to genes associated with reward or addiction. Drugs of abuse act on natural reward systems and genes linked to addiction in turn reflect upon natural reward genes. The strong connection of the maternal brain to addiction/reward related genes suggests the genetic mechanisms by which large changes in natural rewards occurs in mother. The maternal brain provides a natural model for how a brain modulates bonding and reward and the genes identified here may add to our understanding of how that works.

5. Depression and postpartum depression

The state of maternity includes an increased risk for depression, termed postpartum depression (PPD) (Miller, 2002; Couto et al., 2015). One view of the elevated risk for depression is that with a number of genes normally altered in producing the postpartum brain, if a subset are dysregulated or not changed from baseline appropriately, then this

could lead to increased risk for PPD. In our previous microarrays we found high enrichment of maternal genes for depression-related genes in LS, MPOA, and NAC using multiple databases. As shown in Fig. 4, we also find here high overlap of the top 700 maternal genes with depression genes that are found in at least 2 independent databases. Because prior depression is a risk factor for PPD (Miller, 2002) and depression per se is much more studied than PPD, many depression genes could be relevant to PPD. We also found enrichment with PPD genes that were produced by combining two small lists from DISEASES (Copenhagen) (Pletscher-Frankild et al., 2015) and Malacards (Rappaport et al., 2013). By combining matches of top 700 maternal genes with either depression (2 or more databases) or PPD, we identify a subset of genes that may be new high priority PPD genes (Fig. 4). Among the genes already included in PPD databases are: *Sult1a1*, *Nr1d1*, *Penk*, *Lipa*, *Grm3*, *Fabp7*, *Htr1a*, and *Npepps*; red circles in Fig. 4. Any of these could now be considered higher priority PPD genes because each exhibits a strong change in expression with the postpartum condition and thus could leave women vulnerable to PPD. Additional genes linked to depression databases, but not PPD databases, include: *Drd1a*, *Oprm1*, *Npas2*, *Cry2*, *Grik1*, *Ephb1*, *Dbp*, *Csnk1e*, and *Ped4b*; green circles in Fig. 4. Some of the genes identified here are also part of the reward/addiction pathway genes highlighted above and this is consistent with studies suggesting dysregulation of the reward pathways may underlie depression (Henriques and Davidson, 2000; Nestler and Carlezon, 2006; Schlaepfer et al., 2008; Eshel and Roiser, 2010). *Nr1d1* is again of high interest because a number of studies link it to depression, including a recent one in humans showing high dysregulation of *Nr1d1* expression with depression (Li et al., 2013). *Nr1d1* interacts with other molecular clock related genes (Reppert and Weaver, 2002; Guillaumond et al., 2005; Burris, 2008), including *Cry2*, *Dbp*, and *Npas2*, that are in the top 700 maternal genes and are involved in depression (shown in black in Fig. 4B). *Fabp7* is noteworthy as it involved in different forms of depression and can both alter endocannabinoid signaling as well as cell differentiation (Arai et al., 2005; Liu et al., 2010; Berger et al., 2012; Matsumata et al., 2012; Yun et al., 2012). Interestingly, in two separate studies in humans, PPD was associated with decreased levels of free fatty acids (De Vriese et al., 2003; Otto et al., 2003) while increased free fatty acids or a high fat diet alleviate PPD-like traits in rats (Maniam and Morris, 2010; Arbabi et al., 2014). Recent work indicates a role for the inhibitory glutamate receptor, *Grm3*, in major depression in humans (Tsunoka et al., 2009) and our findings indicate this could be a top PPD candidate gene. A role for *Penk* in PPD is also of interest given its function as a neuropeptide and that it provides an intersection of reward and depression pathways. Together, a number of new interesting targets for PPD are identified and could be evaluated in follow up studies.

6. Association with other mental health disorder genes that include social deficits

Many mental health disorders include social deficits as a component, including autism, schizophrenia, and bipolar disorder (BPD) (Mundy et al., 1986; Häfner et al., 1995; Goldstein et al., 2006). As suggested above, hundreds of genes could have altered expression to heighten bonding or sociability in a mother, but if the same genes are dysregulated in certain mental health disorders, then deficits in sociability or bonding could occur. For each

of the three disorders, multiple independently curated databases exist (>5) which provide lists of genes associated with the disorder. To limit analysis to likely high quality genes, we performed enrichment of the top 700 maternal genes against genes from 3 or more autism databases (321 genes), 2 or more BPD databases (337 genes), and 4 or more schizophrenia databases (429 genes). We found highly significant enrichment for each of the disorders (Fig. 5). We identified 5 genes that were common to high quality genes from all three disorders (*Htr1a*, *Csnk1e*, *Nr4a2*, *Ppp1r1b*, and *Drd1a* (green circles) and 11 genes that were common to 2 disorders (*Pde4b*, *Homer1*, *Ncan*, *Igf1*, *Npas2*, *Gria2*, *Nr4a1*, *Grm3*, *Adora2a*, *Ptprz1*, and *Fabp7*) (red circles) (Fig. 5). Additional top 700 genes were matched with high quality genes from one disorder using our strict criterion, but it is worth pointing out that using less restrictive cutoffs, a number of these genes are found in databases in multiple disorders. Given that these disorders include social deficits, one interpretation of the matches is that these are genes that contribute to social behaviors. If hundreds of genes have altered expression to heighten sociability in a mother and the same genes are dysregulated in some mental health disorders, then deficits in sociability or bonding would be expected to be part of the phenotype. The matching genes (maternal and mental health), then, may underlie the continuum of social behavior ranging from highly social to asocial. This is speculative, but it is noteworthy how tightly the genes are interconnected in the GeneMania network analysis (Fig. 5), which suggests this is a core network regulating an important process. Some of the genes of interest include *Nr1d1*, *Grm3*, *Htr1a*, *Penk*, and *Drd1a* and these were also linked above to reward pathways and depression, which are connected to social behaviors.

Although a link to social behavior could explain some of the connections of the maternal brain to mental health disorders, other explanations are possible. Certainly, a healthy mother is not a model for a mental health disorder. However, if one looks at the individual disorders, some possible connections are found. For example, in schizophrenia a dysregulation of sensory motor gating occurs (Braff and Geyer, 1990) and in mothers, changes in sensory motor gating also transpire (Byrnes et al., 2007). Thus, the same genes promoting alterations in sensory motor gating may be involved in both mothers and individuals with schizophrenia. For BPD, there is an increase incidence of BPD in mothers (Brockington, 2004; Maina et al., 2014), so certain genes that are normally changing could make mothers more vulnerable to BPD. How the maternal brain may provide novel insights into mental health disorders is a promising area for future research.

7. Novel insights into well studied maternal signaling pathways

The majority of studies into the maternal brain have focused on neuroendocrine pathways known to be modified during reproduction. Using Web of Science and the search term, “maternal behavior”, we confirmed that the top studied pathways or modulators include oxytocin/vasopressin, estradiol, cortisol (glucocorticoids), prolactin, progesterone, and endogenous opioids. Here we examine how our top 700 maternal genes interact with these pathways. Other maternal pathways or modulators include dopamine, serotonin, GABA, and norepinephrine and although these are not analyzed here the reader is encouraged to use the tools described to analyze any pathway of interest. As a side note, a key serotonin (*Htr1a*) and dopamine (*Drd1a*) receptor are in the top 700 maternal genes. In this analysis, we used the on-line tool, STRING (<http://string-db.org/>) (Szklarczyk et al., 2011) and began with

genes involved in a given pathway (e.g., *Esr1* and *Esr2* for estrogen signaling as these are the receptors for estradiol) and then looked for interactions with the top 700 maternal genes. We focus on the genes with the strongest direct or indirect connections to the core pathway genes. STRING provides information ranging from known physical interactions, to coexpression, to presumed interactions based on text mining (Szkarczyk et al., 2011).

7.1. Prolactin

Neither prolactin (*Prl*) nor the prolactin receptor (*Prlr*) are among the top 700 maternal genes, but they interact with a subset of these genes (Fig. 6). For analysis here and below, we begin with the target genes (e.g., *Prl* and *Prlr*) and then test for interactions with top 700 maternal genes. Further, this conservative approach does not use linking genes provided by the program, so the results only show top 700 genes and the core target genes. For prolactin signaling, three top 700 genes are from the suppressor of cytokine signaling family (*Cish*, *Socs2*, and *Socs3*) that is part of the JAK-STAT signaling pathway. These genes play an important role in negative feedback on the prolactin receptor, including the long receptor isoform (Bole-Feysot et al., 1998; Kisseleva et al., 2002; O'Shea et al., 2002; Nicolas et al., 2013). Because of this negative feedback role, changes in expression of these molecules would modulate prolactin effects in the maternal brain. Because the genes are involved in prolactin receptor feedback, it is possible that changes in expression are a response to endogenous changes in prolactin release in mothers. *Btrc* is of interest as it is involved in ubiquitination (Maniatis, 1999) and could modulate prolactin receptor actions and it is linked to other top 700 genes, *Npas2* and *Cry2*, that are involved in circadian rhythm regulation (Wang et al., 2009). Prolactin signaling is also found to be associated with development and differentiation events in the CNS and additional information on how top 700 genes interact with prolactin signaling are provided below (see Section 9 on plasticity and development).

7.2. Oxytocin/vasopressin

The oxytocin (*Oxt*) and vasopressin (*Avp*) system signaling pathways are closely linked and were analyzed together. A subset of top 700 maternal genes appear to modulate these pathways (Fig. 7). Interestingly, receptors for hypocretin (orexin) (*Hcrtr1* and *Hcrtr2*) are among those most tightly connected to oxytocin and vasopressin signaling (Fig. 7). We previously identified postpartum changes in *Hcrt* activity (Espana et al., 2004) and found that central manipulations of the arousal peptide action alter aspects of maternal care in mice, including licking and grooming (D'Anna and Gammie, 2006). Neuromedin S (*Nms*) is of interest because it can modulate oxytocin release (Sakamoto et al., 2008). Further, *Nms* may act as an intermediate between enkephalin (*Penk*) and dynorphin (*Pdyn*) action on oxytocin and vasopressin signaling (Fig. 7) and could be a key player in orchestrating action of multiple neuropeptides. Another noteworthy candidate is kalirin (*Kalrn*) that regulates neuropeptide processing and G protein signaling (*Oxt* and *Avp* receptors are both G-protein coupled) (Ma et al., 2001). The *Kalrn* gene produces multiple mRNA variants and has been associated with a number of CNS processes, including plasticity and anxiety (Sommer and Budreck, 2009; Mandela et al., 2014). The voltage-gated calcium channel, *Cacna2d3*, was recently linked in an exploratory study to attachment behavior in humans (Pappa et al., 2015) and a connection to oxytocin signaling could help to explain this finding. *Gna11* is

also of interest as the knockout of this gene along with *Gnaq* led to maternal behavior disruption in mice (Wettschureck et al., 2004). As a side note, many previously identified maternal genes, such as oxytocin receptor (*Oxtr*), are found to have significantly altered expression in one or more region from the microarray studies (e.g., *Oxtr* is elevated in MPOA) (Driessen et al., 2014b), but are not listed among the top 700 maternal genes because the changes were not found in 3 or more regions.

7.3. Endogenous opioid signaling

The endogenous opioids, *Penk* and *Pdyn*, as well as the mu opioid receptor, *Oprm1*, all show dynamic changes in multiple maternal brain regions and all three are part of the top 700 maternal genes. When examining how other top 700 maternal genes interact with these three, we identified the somatostatin receptor (*Sstr4*), the acetylcholine receptor (*Chrm4*), the histamine receptor (*Hrh3*), the serotonin receptor (*Htr1a*), the glutamate receptor (*Grm3*), the adenosine receptor (*Adora2a*), and the dopamine receptor (*Drd1a*) (Fig. 8). *Sstr4* is of interest as it was recently implicated in depressive and anxiety-like traits (Scheich et al., 2016). *Chrm4* has been linked to psychiatric disorders (Dean and Scarr, 2015) and is coexpressed with *Pdyn* in neurons (Heiman et al., 2008), suggesting a role in dynorphin signaling. The neuropeptide, *Nms* (described above), could be interacting with *Pdyn* and *Penk* release or action and the *Nms* peptide has multiple functions, including feeding regulation (Ida et al., 2005). A strong link for *Grm3* with *Pdyn* and *Penk* is found and recently *Grm3* was associated with dependence on the opioid derivative, heroin, in humans (Jia et al., 2014), suggesting *Grm3* could be critical in how endogenous opioids act, including within the maternal brain. An additional discussion on endogenous opioid signaling and maternal reward is provided below.

7.4. Estradiol, progesterone, and glucocorticoids

When examining estrogen/estradiol signaling with the top 700 via the estrogen receptors (*Esr1* and *Esr2*), we found the receptors closely interacted with both the progesterone receptor (*Pgr*) and the glucocorticoid (cortisol or corticosterone) receptor (*Nr3c1*). Thus, in looking for interactions with the top 700 maternal genes, the estrogen, progesterone, and glucocorticoid systems were evaluated together. Not surprisingly, the steroid receptors interact with other transcriptional regulators, including top 700 maternal genes, *Nr4a1*, *Nr4a2*, and *Nr4a3*. *Nr4a2* (also known as *Nurr1*) is noteworthy as it has been implicated in dopamine signaling (Perlmann and Wallén-Mackenzie, 2004) and its expression responds to estrogen treatment in the CNS (Wang et al., 2004) (Fig. 9). Transcriptional regulators *Ep300*, *Hif1a*, and *Creb1* can interact with one another and estradiol activates *Hif1a* (Kazi et al., 2009). *Nr1d1* may play an integrative role because it is linked to the steroid receptors in the network diagram (Fig. 8) and numerous other transcription regulators in the top 700, including *Npas2*, *Ep300*, two retinoic acid receptors (*Rxrg* and *Rarb*), and the retinoic acid signaling modulator, *Ncor2*. *Nr1d1* expression is affected by estradiol (Miyamoto et al., 2010), glucocorticoid (Torra et al., 2000; Kiessling et al., 2010), and progesterone treatment (Zucchi et al., 2013). *Nr1d1* continues to emerge as a key maternal gene. The serum and glucocorticoid regulated kinase 3 (*Sgk3*) is regulated by glucocorticoids as well as estradiol (Wang et al., 2011) and in turn regulates ion channel expression (Munoz et al., 2014). It is

possible that this top 700 gene plays a key role in mediating steroid hormone actions in the maternal brain.

8. Transcriptional and microRNA regulation of the postpartum brain

Typical transcriptional regulators, including steroid receptors for estradiol and progesterone, can target hundreds to thousands of genes. When examining the DRAGON Estrogen Responsive Genes Database (Tang et al., 2004), we found significant enrichment of the top 700 maternal genes for estrogen responsive genes ($p < 10^{-6}$) (Supplementary Table 1). Using the Nuclear Receptor Signaling Atlas (NURSA) that includes data from hormone manipulation and knockout studies, enrichment of the top 700 occurred for potential *Esr1* targets in both mice ($p = 0.003$) and humans ($p = 0.02$) (Supplementary Table 1). No enrichment for potential progesterone targets was found in NURSA, although some progesterone targets were among the top 700 (Supplementary Table 1).

Using the enrichment tool, NIH DAVID, we identified 149 transcriptional regulators of the top 700 maternal genes ($FDR < 0.05$). Among these was estrogen receptor, which ranked 125 out of 149 (Supplementary Table 1). Because changes in levels of a given transcriptional regulator (e.g. steroid receptor) can in turn alter expression of other transcriptional regulators that in turn alter expression of other genes and yet more transcriptional regulators, it is perhaps not surprising to see a large number of transcriptional regulators the maternal brain. Just over 10% of the top 700 maternal genes are transcriptional regulators (85/700) and this is consistent with the overall percentage of transcriptional regulators in the genome. Interestingly, *Elk1*, *Creb1*, *Arid5b*, and *Irf2* are genes both in the top 700 and also connected to transcriptional regulation of the top 700. Using the GATHER enrichment tool (Chang and Nevins, 2006), we also identified 77 transcriptional regulators of the top 700 genes ($p < 0.05$) and from these, 22 genes for transcriptional regulation were in common between the two approaches (Supplementary Table 1). *Elk1*, *Arid5b*, *Creb1*, and *Tef* were genes in the top 700 and amongst the transcriptional regulators identified in GATHER. Transcriptional regulators can be either single genes or a complex of genes and this adds to the complexity of determining how gene expression regulation occurs. Further, for a given gene target, multiple expression regulation binding sites exist, so no single regulation region is expected to have complete control over expression.

In addition to traditional transcriptional regulators, micro-RNAs (miRNAs) are emerging as an important way to control gene expression. In a recent study, we examined for the first time miRNA expression changes in the postpartum brain using RNA sequencing approaches (Saul et al., 2016). As indicated in Fig. 10, we identified 32 miRNAs that were reliably upregulated in maternal LS and 25 that were downregulated across multiple reproductive stages. We conducted that study because bioinformatics analysis of our microarray studies suggested a role for miRNAs in shaping gene expression (Zhao et al., 2012b; Driessen et al., 2014b; Eisinger et al., 2014). MiRNAs are small, non-coding RNAs that regulate gene expression by inhibiting RNA targets (Bartel, 2009). The mRNA targets for miRNAs are determined using computational analysis and direct testing (Bartel, 2009; Thomas et al., 2010) and as seen in Fig. 10, we identified over 4000 genes that were targeted by maternal miRNAs. Interestingly, about half of the target genes were modulated by both up and

downregulated maternal miRNAs, suggesting strong homeostatic regulation of expression (Saul et al., 2016). As expected, we found that maternal LS miRNA target genes provided significant enrichment for the maternal mRNA genes from our LS microarray study. Interestingly, though, we found enrichment for MPOA, mPFC, and NAC mRNA maternal genes with the miRNA targets. This finding could also be expected given the strong overlap of significant genes among the four regions described above. Given that miRNAs can move across cells, this finding suggested there may be a core group of maternal miRNAs that act across multiple brain regions. Here, we analyze the top 700 maternal genes with the maternal miRNA targets from LS and also find significant enrichment (Fig. 10). It is noteworthy that maternal miRNA brain targets did not match genes that were altered in the mammary glands of mothers (Saul et al., 2016), suggesting that the maternal miRNAs in the CNS are specific only to the CNS (and not mammary glands) and play a key role in shaping gene expression across multiple regions.

An extra level of complexity to the production of the maternal brain is that transcription factors can be targeted by miRNAs and transcription factors not only influence expression of other genes, but miRNAs as well (Fig. 10). Thus, there is an ongoing and dynamic interplay between miRNAs, transcriptional regulators, and gene expression. In the top 700 maternal genes, 46 transcriptional regulators were found to be targeted by maternal miRNAs, including *Nr1d1*, *Nr4a2*, *Creb1*, *Hif1a*, *Elk1*, and *Uhrf2* (Fig. 10). In terms of level of change in mRNA expression, most significant genes in the maternal brain show changes <40%. For example, *Nr1d1* is decreased about 20% in NAC, while *Lipa* is increased about 30% (Zhao et al., 2014). Together, our findings that genes can be targeted by multiple maternal miRNAs, that up and down regulated maternal miRNAs can target the same genes, and that a dynamic interplay of miRNAs and transcriptional regulators is likely occurring, suggests there is strong homeostatic regulation of genes that is critical for significantly altering gene expression, but also keeping those changes within a restricted range. Maternal miRNAs add a critical new piece for helping to understand how the maternal brain is created.

9. CNS development, plasticity, neurogenesis, and differentiation pathways

The top 700 postpartum genes showed enrichment for pathways involved in CNS plasticity, development, and neurogenesis using various on-line tools, including NIH DAVID (Huang da et al., 2009), ToppCluster (Kaimal et al., 2010), and GATHER (Chang and Nevins, 2006). This finding is consistent with enrichment analysis within specific regions (Eisinger et al., 2013b, 2014; Driessen et al., 2014b; Zhao et al., 2014) and suggests that the maternal brain may represent a developmental endpoint in mammals. Structural changes in mothers across various regions (Leuner and Gould, 2010; Shams et al., 2012) suggests widespread CNS developmental and plasticity events occur in mothers. Changes in neurogenesis in mothers within hippocampus and the subventricular zone have been documented (Pawluski and Galea, 2007; Levy et al., 2011; Galea et al., 2013) and both are noted areas of high neurogenesis. Low levels of neurogenesis can occur in other brain regions, including cortex, nucleus accumbens, and hypothalamus, and there is some evidence that aspects of neurogenesis (e.g., cell survival) may differ in mothers (Leuner and Sabihi, 2016). While the regions examined here have low neurogenesis, it is still possible some aspects of

neurogenesis are altered in mothers in these regions or that the genes are involved in differentiation or plasticity events rather than neurogenesis per se. As indicated below, we found a clustering of upregulated maternal miRNAs in the *Dlk1-Dio3* region and miRNAs in this region have been strongly connected to development and differentiation events. Because these changes occur as adults, it is possible the maternal brain provides a unique insight into how to modulate the architecture of the adult brain. Fig. 11 shows top 700 maternal genes that are connected to development, plasticity, neurogenesis, or differentiation pathways from GATHER. Interestingly, when the genes are analyzed in GeneMania, the prolactin receptor (*Prlr*) is added by the program as a connecting gene (Fig. 11) and this is due in part because prolactin interacting genes, *Cish* and *Socs3*, are also involved in differentiation and development. A role for prolactin in plasticity aspects of the maternal brain has been supported by multiple studies, including a focus on neurogenesis and white matter regeneration (Shingo et al., 2003; Larsen et al., 2008; Gregg, 2009; Torner et al., 2009; Larsen and Grattan, 2012), and the network shown may highlight additional ways by which prolactin acts (see also section on prolactin signaling above). Because we see a strong signature for development and differentiation events, it raised the question of whether the top 700 genes may shed some insight into adult degenerative disorders, such as Alzheimer's. Interestingly, we found the top 700 maternal genes to be significantly enriched for Alzheimer's genes in the DISEASES database ($p = 0.016$). Further, some of the genes are also part of the plasticity/development related genes (see red circles in Fig. 11), including the differentiation genes, *Nes* and *Olig2*, as well as *Socs2*, *Elavl3*, *Creb1*, *Ppp1r9b*, *Nr4a2*, and *Gulp1*. Stem cell fate and neurogenesis are closely linked to blood vessels, including endothelial cells (Shen et al., 2004) and as indicated in the next section, remodeling of blood vessels likely occurs in the maternal state. One intriguing future direction would be to understand whether or how alteration of maternal gene expression that promotes plasticity or developmental events could benefit the treatment of adult CNS disorders by reactivating a developmental event.

10. Maternal gene expression changes in glial cells and blood vessels

While of number of the genes described above are known to be expressed in neurons and contribute to neuronal functions, some of top 700 maternal genes are expressed in glial cells and endothelial (blood vessel) cells. Previous research has suggested changes in blood flow during reproduction (Belfort et al., 2001; Cipolla et al., 2004) and using the on-line cell-type tool based on RNA-Seq data from cerebral cortex, (Zhang et al., 2014), we were able to identify 25 genes with typically high expression in endothelial cells relative to other cells types, including a member of the vascular endothelial growth factor (VEGF) receptor family, *Flt1*, a mediator of VEGF action, *Fgd5*, well as *Acer2*, and *Pltp*. As indicted above, blood vessels and endothelial cells can provide important signals for cell differentiation (Shen et al., 2004). The maternal brain, then, may be providing specific insights into how to remodel blood vessel systems within adults.

There are numerous types of glial cells, including astrocytes, oligodendrocytes, and microglia. For astrocytes, we find 30 genes with relatively high expression relative to neurons, including the genes, *Vcam1*, *Fam107a*, *Gldc*, *Alpl*, *Ptprz1*, and *Aldoc*. For the myelin producing oligodendrocytes, we identified 7 genes with known high expression

relative to other cells types, and these included *Ablim2*, *Synj2*, *Ephb1*, and *Cryab*. Eight genes have typically high microglia expression relative to neurons, and these included *Sult1a1*, *Cd180*, *Hspa1a*, *Crybb1*, and *Ctsh*. While relative expression in a given cell type versus another is useful for developing ideas on where and how specific genes are acting in the maternal brain, it is rare for any gene to be exclusive to a cell type and follow up studies are required to evaluate cellular function.

11. Comparisons to other maternal brain microarray studies

As indicated above, the maternal MPOA, LS, mPFC, and NAC datasets were synthesized because they involved similar microarray platforms and the >20,000 protein coding mouse genes could be compared across regions. For two previous maternal microarrays performed by us on whole septum (Zhao et al., 2012b) and preoptic/hypothalamic tissue (Gammie et al., 2005), significant enrichment was found with top 700 maternal genes, which again highlights a conserved maternal gene expression signature. Supplementary Table 1 provides a list of the gene matches. Some earlier maternal microarray publications focused on only a small subset of gene expression changes, but without a full list of significant changes along with unambiguous gene symbols, enrichment analysis is not possible. However, even with that limitation, in a maternal rat arcuate/ventromedial nucleus study (Xiao et al., 2005), six genes were found to be significantly altered that were also found in the top 700 and of those, four also matched our previous hypothalamic array, namely *Fabp7*, *Sult1a1*, *Penk*, and *Pdyn*. Thus, these are four robust maternal genes. *Penk* was also found to be differentially expressed in a study on rat hippocampus (Kinsley et al., 2008). In a relatively recent maternal rat study on MPOA and amygdala (Akbari et al., 2013), two of the genes were also in the top 700 maternal genes, namely *Drd1a* and *Oprm1*.

Interestingly, a large scale gene expression analysis (using RNA-seq) of the maternal brain was just published that focused on four brain regions, namely, prefrontal cortex, hippocampus, hypothalamus, and cerebellum (Ray et al., 2016). In that study in C57/B16 mice, multiple time-points were analyzed including virgin, two time-points during pregnancy, and three postpartum time-points. In order to compare our top 700 maternal genes to this new dataset, we created a top 700 genes separately for the new data for postpartum day 3 (PPD3) relative to virgin and for postpartum day 10 (PPD10) relative to virgin. In creating the top 700 we ranked the genes based on significance for each region and then created an overall rank based on the top three ranks from the four brain regions. We found a remarkably high concordance between our top 700 and the new top 700s from both PPD3 (hypergeometric p-value = 9×10^{-11}) and PPD10 (hypergeometric p-value = 2×10^{-13}) and this occurred with strain differences, maternal stage differences, and that three of the four brain regions differed between groups (see Fig. 12). A full list of the 34 common genes among the three different top 700 maternal genes is provided in Supplementary Table 1. Some of the noteworthy genes appearing in all three top 700 lists are: *Nr1d1*, *Nr4a1*, *Dbp*, *Egr1*, *Pilp*, *Nr4a3*, *Cish*, *Cryab*, *Socs2*, *Peg10*, *Kcna1*, *Elk1*, and *Fabp7*. Any of these genes could be considered high importance maternal brain genes. 108 of the top 700 maternal genes were found in either of the two new lists and these also provide a valuable list of high quality maternal genes. In both of the new top 700 lists (PPD3 and PPD10) were also a small number of genes of interest that were not among our top 700 maternal genes, including *Prlr*,

Bdnf, *Grin2a* (a component of the NMDA receptor), and *Htr2c* (a serotonin receptor). Additionally, the RNA seq study included some annotations not included in our microarray background with 80 of the top 700 PPD3 not being found in the microarrays and 93 of the top 700 PPD10 not being found. 33 RNA seq gene annotations were among both top 700 lists (PPD3 and PPD10) and these are provided in Supplementary Table 1.

12. Genes of interest and direction of expression change

For some notable genes, including *Nr1d1* and *Fabp7*, direction of change is highly consistent across the maternal brain. For example, both *Nr1d1* and *Fabp7* have been found to be downregulated in almost every region examined (or unaltered in the other regions). Decreased *Fabp7* leads to differentiation events (Kurtz et al., 1994; Anthony et al., 2004; Arai et al., 2005; Liu et al., 2010; Matsumata et al., 2012; Yun et al., 2012), so those decreases in mothers may provide global and consistent alterations in plasticity, while also providing consistent changes in endocannabinoid signaling (Kaczocha et al., 2009; Berger et al., 2012). Decreases in *Nr1d1* can have multiple effects, including altering expression of downstream transcriptional targets and modulating mood and behavior (Ueda et al., 2005; Wang et al., 2008; Kripke et al., 2009; Etain et al., 2011; Mohawk et al., 2012; Piechota et al., 2012; Li et al., 2013; Banerjee et al., 2014). As noted above, *Nr1d1* is integrated into a wide range of pathways. The endogenous opioid peptides, *Penk* and *Pdyn*, are both significantly upregulated in MPOA, but down regulated elsewhere, including in NAC, LS, and PFC. We have previously suggested that this pattern of change could play a key role in altering maternal reward behavior whereby signals that include a strong MPOA component (including maternal interaction with offspring) have an increased reward, while responses to other stimuli have decreased reward (Zhao et al., 2014). Thus, direction of change for a gene can be different across regions and this may be critical for proper maternal brain function.

Another gene of high interest is the metabotropic glutamate receptor, *Grm3*. Unlike the ionotropic receptors, *Grm3* leads to neuronal inhibition when bound by glutamate (Cartmell and Schoepp, 2000). *Grm3* has been associated with multiple mental health disorders (Mössner et al., 2008; Tsunoka et al., 2009) as well as reward/addiction related behaviors (O'Brien et al., 2014; Xia et al., 2014). In terms of expression changes, *Grm3* is found in both neurons and glial cells and we recently documented an overall significant downregulation of *Grm3* in LS that occurred in neurons, but not in glial cells (Zhao and Gammie, 2015). In maternal mPFC and NAC, *Grm3* expression was also downregulated (Eisinger et al., 2014; Zhao et al., 2014), but whether this only occurred in neurons has yet to be investigated. In MPOA changes did not reach significance (Driessen et al., 2014b). Together then, *Grm3* appears to be playing an important role in the maternal brain, but changes are not uniform in all regions and different actions in neurons versus glial cells may drive *Grm3*'s overall effect.

13. Associations with transgenic studies

Thousands of transgenic mouse lines have been produced and of those, a subset show overt disruptions of maternal care or physiology. Unfortunately, for most transgenic lines, maternal behaviors are not explicitly tested, so it is possible that interesting phenotypes

exist, but have yet to be documented. Of those lines listed by Jackson labs (www.jax.org) as having parental disruptions, *Shank2* and *Gria2* are also among the top maternal 700 genes. *Shank2* is involved in postsynaptic localization of ionotropic glutamate receptors and in neuronal plasticity (Brandstätter et al., 2004; de Bartolomeis and Fiore, 2004). *Shank2* has widespread CNS expression and has been connected to multiple disorders with social deficits, including autism (Berkel et al., 2012; Leblond et al., 2012; Won et al., 2012). *Gria2* is an ionotropic glutamate receptor that has been associated with reward related processing (Mead et al., 2005) as well as mood disorders (Russo and Nestler, 2013). Both *Shank2* and *Gria2* could be important maternal genes.

14. False positives, false negatives, and other considerations

It is likely that most of the top 700 maternal genes evaluated are high quality and have relevance to the maternal brain. However, the 700 genes are derived from microarray studies and as with any approach, there are limitations. In our previous studies, we have been able to confirm most microarray expression changes via qPCR, although there are a few that are not confirmed. By focusing on consistent significant changes across multiple regions, it is hoped that here most false positives would be eliminated, but additional testing for any gene of interest is needed for confirmation. As highlighted above, the recent RNA seq maternal brain study of four brain regions (Ray et al., 2016) allowed us to identify additional conserved maternal gene expression changes and it is hoped that future studies will promote the identification of even more high quality maternal genes. Further, we know from our focused studies using qPCR, that neurotensin and its receptors (Driessen et al., 2014a) and the genes for the enzymes that produce GABA, namely *Gad1* and *Gad2*, show dynamic postpartum changes in expression across multiple CNS regions (Zhao et al., 2012a; Zhao and Gammie, 2014), but these are not identified in the microarray. Thus, these represent false negatives and highlight that additional key maternal genes may exist, but remain to be identified. Contributing to the issue of false negatives is that some genes may undergo an important posttranslational modification and this would not be apparent from a gene expression level. An additional technical point is that while most genes on the microarrays had one probeset, some genes had multiple probesets. Additional probesets often target different parts of the gene and could reflect splicing differences. For this analysis we needed to collapse the probeset results to compare across regions and platforms and it is possible that some useful information was lost. In a recent study on sex differences in gene expression in humans, splice differences accounted for a great deal of intersex variability (Trabzuni et al., 2013) and it is possible splice changes contribute to the maternal brain. A focus on exon expression in future studies (as opposed to whole gene results here) and/or RNA seq that distinguishes splice variants may also yield new insights.

An additional issue is highlighted by GABA signaling. In work on regions such as LS, we found a number of altered GABA A receptor subunits and confirmed these via qPCR (Eisinger et al., 2013b). However, in different regions, such as MPOA (Driessen et al., 2014b), different subunits showed expression changes. Changes of receptor subunit expression is region specific and no genes coding for GABA receptor subunits are among the top 700. A number of interesting and important genes, in addition to GABA receptor subunits, are region specific and these also need to be considered for future studies. A

related confound is that even within a brain region, expression of a given gene could be moving in opposite directions within different cell types and thus the overall gene expression remains constant. Cell type specific expression studies provide one approach for addressing this potential problem.

15. Chromosome location of maternal genes and miRNAs

In terms of chromosome location, in general, most of the top 700 maternal genes are evenly distributed across the chromosomes, with no regions showing enrichment of postpartum genes. One explanation is that the even distribution decreases the vulnerability of key maternal genes to perturbations. However, in the maternal microRNAs study, we found a group of upregulated microRNAs to be tightly clustered to the 12qF1 region of chromosome 12 (Fig. 13); the other miRNAs were evenly distributed. MiRNAs from within this subregion, referred to as the Dlk1-Dio3 gene cluster, are implicated in stem cell and neuronal differentiation (Stadtfield et al., 2010). Silencing of miRNAs in this region affects the status of induced pluripotent stem cell (Stadtfield et al., 2010). Most genes within 12qF1 are imprinted and the region has shared synteny with 14q32 on chromosome 14 in humans (Laufer and Singh, 2012). One unexpected finding was that the ratio of maternal genes to total genes in a chromosome was lowest for the X chromosome (Fig. 13).

16. Summary and future directions

One goal of this review was to provide novel insights into the genetic regulation of the maternal brain. Here, we created a top 700 maternal brain gene list based on consistent high rankings in microarray studies of multiple CNS regions known to contribute to the maternal phenotype. An advantage of this approach is that the rankings are based on statistics only and not any previous link to maternal processes. Thus, the approach provides a means for highlighting for the first time additional key maternal brain players from the 20,000+ genes in the mammalian brain. By using bioinformatics, we find potential new key players in the maternal brain with relevance to multiple processes, including reward, bonding, and addiction; depression and PPD; mental health disorders; prolactin signaling; oxytocin/vasopressin signaling; estrogen/progesterone signaling; endogenous opioid signaling; transcriptional regulation, including miRNAs; and adult developmental plasticity events.

For a researcher interested in any of the above areas, a focus on the new maternal genes may provide a useful approach. For example, research on prolactin, could add to studies analysis of *Cish*, *Socs2*, *Socs3*, and *Cntfr*. Studies of oxytocin/vasopressin systems might now include analysis of *Hcrtr1*, *Hcrtr2*, *Kalrn*, *Nms*, *Gna11*, and *Adcy6*. For studies on postpartum depression, any of the maternal genes highlighted in Fig. 4 may be of interest, but *Nr1d1*, *Fabp7*, *Dbp*, *Cry2*, *Oprm1*, *Sult1a1*, *Npas2*, *Penk*, and *Grm3* may merit additional attention. A researcher interested in adult plasticity may examine the network of developmental/plasticity genes in the maternal brain as a guide for CNS changes within an adult.

Overall, a few top maternal genes do stand out as worthy of particular attention. *Nr1d1* has interesting connections to reward addiction processes, multiple mental health disorders,

including depression, steroid receptor activity, and endogenous opioid signaling. Further, it is regulated by maternal miRNAs and it is also found in the two top 700 maternal lists derived from the recent RNA seq study. Together, *Nr1d1* is poised to have important widespread action and its consistent decreased expression across the postpartum CNS suggests an important conserved role in the maternal brain and phenotype. Additional genes that are likely worthy of attention for reasons described above include *Fabp7*, *Penk*, *Pdyn*, *Grm3*, *Nr4a1*, *Ppp1r1b*, *Htr1a*, *Drd1a*, *Nms*, and *Oprm1*. However, the results from this review suggest that gene networks (rather than single genes) regulate multiple processes within the maternal brain. Thus, one take home message for future maternal brain research is that studies on only a few genes would benefit from expansion to include interactions with multiple other genes. The use of a gene networks perspective may be critical for advancing the field.

While 700 genes are used here, this is not meant to be definitive list and the reader is encouraged to use all the data in Supplementary Table 1 to evaluate results from individual regions and/or use different criteria/cutoffs to compare or combine results across regions. As highlighted in Section 11, the recent publication of maternal brain expression changes in four regions using RNA seq approaches allowed us to identify even more highly significant maternal gene changes. It is hoped large scale datasets on the maternal brain will continue to be produced and that researchers will use similar approaches as described here to uncover gene networks of interest that guide research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the United States National Institutes of Health Grant R01 MH 085642 to Stephen Gammie.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.yfrne.2016.05.002>.

References

- Akbari EM, Shams S, Belay HT, Kaiguo M, Razak Z, Kent CF, Westwood T, Sokolowski MB, Fleming AS. The effects of parity and maternal behavior on gene expression in the medial preoptic area and the medial amygdala in postpartum and virgin female rats: a microarray study. *Behav Neurosci*. 2013; 127:913. [PubMed: 24341715]
- Anthony TE, Klein C, Fishell G, Heintz N. Radial glia serve as neuronal progenitors in all regions of the central nervous system. *Neuron*. 2004; 41:881–890. [PubMed: 15046721]
- Arai Y, Funatsu N, Numayama-Tsuruta K, Nomura T, Nakamura S, Osumi N. Role of *Fabp7*, a downstream gene of Pax6, in the maintenance of neuroepithelial cells during early embryonic development of the rat cortex. *J Neurosci*. 2005; 25:9752–9761. [PubMed: 16237179]
- Arbabi L, Baharuldin MTH, Moklas MaM, Fakurazi S, Muhammad SI. Antidepressant-like effects of omega-3 fatty acids in postpartum model of depression in rats. *Behav Brain Res*. 2014;65–71. [PubMed: 24867329]

- Banerjee S, Wang Y, Solt LA, Griffett K, Kazantzis M, Amador A, El-Gendy BM, Huitron-Resendiz S, Roberts AJ, Shin Y. Pharmacological targeting of the mammalian clock regulates sleep architecture and emotional behaviour. *Nat Commun.* 2014; 5
- Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell.* 2009; 136:215–233. [PubMed: 19167326]
- Belfort MA, Tooke-Miller C, Allen JC, Saade GR, Dildy GA, Grunewald C, Nisell H, Herd JA. Changes in flow velocity, resistance indices, and cerebral perfusion pressure in the maternal middle cerebral artery distribution during normal pregnancy. *Acta Obstet Gynecol Scand.* 2001; 80:104–112. [PubMed: 11167203]
- Belluardo N, Olsson P, Mudo G, Sommer W, Amato G, Fuxe K. Transcription factor gene expression profiling after acute intermittent nicotine treatment in the rat cerebral cortex. *Neuroscience.* 2005; 133:787–796. [PubMed: 15890456]
- Berger WT, Ralph BP, Kaczocha M, Sun J, Balius TE, Rizzo RC, Haj-Dahmane S, Ojima I, Deutsch DG. Targeting fatty acid binding protein (FABP) anandamide transporters – a novel strategy for development of anti-inflammatory and anti-nociceptive drugs. *PLoS ONE.* 2012; 7:e50968. [PubMed: 23236415]
- Berkel S, Tang W, Treviño M, Vogt M, Obenhaus HA, Gass P, Scherer SW, Sprengel R, Schrat G, Rappold GA. Inherited and de novo SHANK2 variants associated with autism spectrum disorder impair neuronal morphogenesis and physiology. *Hum Mol Genet.* 2012; 21:344–357. [PubMed: 21994763]
- Bole-Feysot C, Goffin V, Edery M, Binart N, Kelly PA. Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. *Endocr Rev.* 1998; 19:225–268. [PubMed: 9626554]
- Braff DL, Geyer MA. Sensorimotor gating and schizophrenia: human and animal model studies. *Arch Gen Psychiatry.* 1990; 47:181–188. [PubMed: 2405807]
- Brandstätter JH, Dick O, Boeckers TM. The postsynaptic scaffold proteins ProSAP1/*Shank2* and Homer1 are associated with glutamate receptor complexes at rat retinal synapses. *J Comp Neurol.* 2004; 475:551–563. [PubMed: 15236236]
- Bridges RS. Neuroendocrine regulation of maternal behavior. *Front Neuroendocrinol.* 2015; 36:178–196. [PubMed: 25500107]
- Brockington I. Postpartum psychiatric disorders. *The Lancet.* 2004; 363:303–310.
- Burris TP. Nuclear hormone receptors for heme: REV-ERBa and REV-ERBb are ligand-regulated components of the mammalian clock. *Mol Endocrinol.* 2008; 22:1509–1520. [PubMed: 18218725]
- Byrnes EM, Bridges RS, Scanlan VF, Babb JA, Byrnes JJ. Sensorimotor gating and dopamine function in postpartum rats. *Neuropsychopharmacology.* 2007; 32:1021–1031. [PubMed: 17047669]
- Cartmell J, Schoepp DD. Regulation of neurotransmitter release by metabotropic glutamate receptors. *J Neurochem.* 2000; 75:889–907. [PubMed: 10936169]
- Chang JT, Nevins JR. GATHER: a systems approach to interpreting genomic signatures. *Bioinformatics.* 2006; 22:2926–2933. [PubMed: 17000751]
- Cipolla MJ, Vitullo L, Mckinnon J. Cerebral artery reactivity changes during pregnancy and the postpartum period: a role in eclampsia? *Am J Physiol – Heart Circul Physiol.* 2004; 286:H2127–H2132.
- Couto T, Brancaglion M, Alvim-Soares A, Moreira L, Garcia FD, Nicolato R, Aguiar R, Leite HV, Corrêa H. Postpartum depression: a systematic review of the genetics involved. *World J Psychiatry.* 2015; 5:103–111. [PubMed: 25815259]
- D’anna KL, Gammie SC. Hypocretin-1 dose-dependently modulates maternal behaviour in mice. *J Neuroendocrinol.* 2006; 18:553–566. <http://dx.doi.org/10.1111/j.1365-2826.2006.01448.x>. [PubMed: 16867176]
- De Bartolomeis A, Fiore G. Postsynaptic density scaffolding proteins at excitatory synapse and disorders of synaptic plasticity: implications for human behavior pathologies. *Int Rev Neurobiol.* 2004; 59:221–254. [PubMed: 15006490]
- De Moura AC, Lazzari VM, Becker RO, Gil MS, Ruthschilling CA, Agnes G, Almeida S, Da Veiga ABG, Lucion AB, Giovenardi M. Gene expression in the CNS of lactating rats with different patterns of maternal behavior. *Neurosci Res.* 2015:8–15. [PubMed: 26003743]

- De Vriese S, Christophe A, Maes M. Lowered serum n-3 polyunsaturated fatty acid (PUFA) levels predict the occurrence of postpartum depression: further evidence that lowered n-PUFAs are related to major depression. *Life Sci.* 2003; 73:3181–3187. [PubMed: 14561523]
- Dean B, Scarr E. Possible involvement of muscarinic receptors in psychiatric disorders: a focus on schizophrenia and mood disorders. *Curr Mol Med.* 2015; 15:253–264. [PubMed: 25817858]
- Driessen T, Zhao C, Whittlinger A, Williams H, Gammie SC. Endogenous CNS expression of neurotensin and neurotensin receptors is altered during the postpartum period in outbred mice. *Publ Library Sci ONE.* 2014a:e83098.
- Driessen TM, Eisinger BE, Zhao C, Stevenson SA, Saul MC, Gammie SC. Genes showing altered expression in the medial preoptic area in the highly social maternal phenotype are related to autism and other disorders with social deficits. *BMC Neurosci.* 2014b; 15:11. [PubMed: 24423034]
- Eisinger BE, Driessen TM, Zhao C, Gammie S. Medial prefrontal cortex: genes linked to bipolar disorder and schizophrenia have altered expression in the highly social maternal phenotype. *Front Behav Neurosci.* 2014; 8 <http://dx.doi.org/10.3389/fnbeh.2014.00110>.
- Eisinger BE, Saul MC, Driessen TM, Gammie SC. Development of a versatile enrichment analysis tool reveals associations between the maternal brain and mental health disorders, including autism. *BMC Neurosci.* 2013a; 14:147. <http://dx.doi.org/10.1186/1471-2202-14-147>. [PubMed: 24245670]
- Eisinger BE, Zhao C, Driessen TM, Saul MC, Gammie SC. Large scale expression changes of genes related to neuronal signaling and developmental processes found in lateral septum of postpartum outbred mice. *PLoS ONE.* 2013b; 8:e63824. <http://dx.doi.org/10.1371/journal.pone.0063824>. [PubMed: 23717492]
- Eshel N, Roiser JP. Reward and punishment processing in depression. *Biol Psychiatry.* 2010; 68:118–124. [PubMed: 20303067]
- Espana RA, Berridge CW, Gammie SC. Diurnal levels of Fos immunoreactivity are elevated within hypocretin neurons in lactating mice. *Peptides.* 2004; 25:1927–1934. <http://dx.doi.org/10.1016/j.peptides.2004.06.006>. [PubMed: 15501524]
- Etain B, Milhiet V, Bellivier F, Leboyer M. Genetics of circadian rhythms and mood spectrum disorders. *Eur Neuropsychopharmacol.* 2011; 21:S676–S682. [PubMed: 21835597]
- Febo M. A bold view of the lactating brain: functional magnetic resonance imaging studies of suckling in awake dams. *J Neuroendocrinol.* 2011; 23:1009–1019. [PubMed: 21722215]
- Febo M, Numan M, Ferris CF. Functional magnetic resonance imaging shows oxytocin activates brain regions associated with mother–pup bonding during suckling. *J Neurosci.* 2005; 25:11637–11644. [PubMed: 16354922]
- Ferris CF, Kulkarni P, Sullivan JM, Harder JA, Messenger TL, Febo M. Pup suckling is more rewarding than cocaine: evidence from functional magnetic resonance imaging and three-dimensional computational analysis. *J Neurosci.* 2005; 25:149–156. [PubMed: 15634776]
- Francis DD, Young L, Meaney M, Insel T. Naturally occurring differences in maternal care are associated with the expression of oxytocin and vasopressin (V1a) receptors: gender differences. *J Neuroendocrinol.* 2002; 14:349–353. [PubMed: 12000539]
- Frank MJ, Doll BB, Oas-Terpstra J, Moreno F. Prefrontal and striatal dopaminergic genes predict individual differences in exploration and exploitation. *Nat Neurosci.* 2009; 12:1062–1068. [PubMed: 19620978]
- Galea LA, Wainwright SR, Roes MM, Duarte-Guterman P, Chow C, Hamson DK. Sex, hormones and neurogenesis in the hippocampus: hormonal modulation of neurogenesis and potential functional implications. *J Neuroendocrinol.* 2013; 25:1039–1061. [PubMed: 23822747]
- Gammie SC, Hasen NS, Awad TA, Auger AP, Jessen HM, Panksepp JB, Bronikowski AM. Gene array profiling of large hypothalamic CNS regions in lactating and randomly cycling virgin mice. *Brain Res Mol Brain Res.* 2005; 139:201–211. <http://dx.doi.org/10.1016/j.molbrainres.2005.05.011>. [PubMed: 15953654]
- Goldstein TR, Miklowitz DJ, Mullen KL. Social skills knowledge and performance among adolescents with bipolar disorder. *Bipolar Disord.* 2006; 8:350–361. [PubMed: 16879136]
- Gregg C. Pregnancy, prolactin and white matter regeneration. *J Neurol Sci.* 2009; 285:22–27. [PubMed: 19608204]

- Grubb SC, Bult CJ, Bogue MA. Mouse phenome database. *Nucleic Acids Res.* 2014; 42:D825–D834. [PubMed: 24243846]
- Guillaumond F, Dardente H, Giguère V, Cermakian N. Differential control of Bmal1 circadian transcription by REV-ERB and ROR nuclear receptors. *J Biol Rhythms.* 2005; 20:391–403. [PubMed: 16267379]
- Häfner H, Nowotny B, Löffler W, An Der Heiden W, Maurer K. When and how does schizophrenia produce social deficits? *Eur Arch Psychiatry Clin Neurosci.* 1995; 246:17–28. [PubMed: 8773215]
- Hauser H, Gandelman R. Lever pressing for pups: evidence for hormonal influence upon maternal behavior of mice. *Horm Behav.* 1985; 19:454–468. [PubMed: 4085998]
- Hawrylycz MJ, Lein ES, Guillozet-Bongaarts AL, Shen EH, Ng L, Miller JA, Van De Lagemaat LN, Smith KA, Ebbert A, Riley ZL. An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature.* 2012; 489:391–399. [PubMed: 22996553]
- Heiman M, Schaefer A, Gong S, Peterson JD, Day M, Ramsey KE, Suárez-Fariñas M, Schwarz C, Stephan DA, Surmeier DJ. A translational profiling approach for the molecular characterization of CNS cell types. *Cell.* 2008; 135:738–748. [PubMed: 19013281]
- Henriques JB, Davidson RJ. Decreased responsiveness to reward in depression. *Cogn Emot.* 2000; 14:711–724.
- Higham JP, Barr CS, Hoffman CL, Mandalaywala TM, Parker KJ, Maestripieri D. Mu-opioid receptor (OPRM1) variation, oxytocin levels and maternal attachment in free-ranging rhesus macaques *Macaca mulatta*. *Behav Neurosci.* 2011; 125:131. [PubMed: 21463018]
- Huang Da W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat Protoc.* 2009; 4:44–57. <http://dx.doi.org/10.1038/nprot.2008.211>. [PubMed: 19131956]
- Ida T, Mori K, Miyazato M, Egi Y, Abe S, Nakahara K, Nishihara M, Kangawa K, Murakami N. Neuromedin S is a novel anorexigenic hormone. *Endocrinology.* 2005; 146:4217–4223. [PubMed: 15976061]
- Jia W, Zhang R, Wu B, Dai ZX, Zhu YS, Li PP, Zhu F. Metabotropic glutamate receptor 3 is associated with heroin dependence but not depression or schizophrenia in a Chinese population. *PLoS ONE.* 2014; 9
- Kaczocha M, Glaser ST, Deutsch DG. Identification of intracellular carriers for the endocannabinoid anandamide. *Proc Natl Acad Sci.* 2009; 106:6375–6380. [PubMed: 19307565]
- Kaimal V, Bardes EE, Tabar SC, Jegga AG, Aronow BJ. ToppCluster: a multiple gene list feature analyzer for comparative enrichment clustering and network-based dissection of biological systems. *Nucleic Acids Res.* 2010; 38:W96–W102. <http://dx.doi.org/10.1093/nar/gkq418>. [PubMed: 20484371]
- Kazi AA, Molitoris KH, Koos RD. Estrogen rapidly activates the PI3K/AKT pathway and hypoxia-inducible factor 1 and induces vascular endothelial growth factor A expression in luminal epithelial cells of the rat uterus. *Biol Reprod.* 2009; 81:378–387. [PubMed: 19420388]
- Keebaugh AC, Barrett CE, Laprairie JL, Jenkins JJ, Young LJ. RNAi knockdown of oxytocin receptor in the nucleus accumbens inhibits social attachment and parental care in monogamous female prairie voles. *Soc Neurosci.* 2015:1–10.
- Kent WJ, Sugnet CW, Furey TS, Roskin KM, Pringle TH, Zahler AM, Haussler D. The human genome browser at UCSC. *Genome Res.* 2002; 12:996–1006. [PubMed: 12045153]
- Kiessling S, Eichele G, Oster H. Adrenal glucocorticoids have a key role in circadian resynchronization in a mouse model of jet lag. *J Clin Invest.* 2010; 120:2600. [PubMed: 20577050]
- Kikuchi Y, Noriuchi M. The neuroscience of maternal love. *Neurosci Commun.* 2015; 1
- Kinsley CH, Bardi M, Karelina K, Rima B, Christon L, Friedenber J, Griffin G. Motherhood induces and maintains behavioral and neural plasticity across the lifespan in the rat. *Arch Sex Behav.* 2008; 37:43–56. [PubMed: 18074214]
- Kisseleva T, Bhattacharya S, Braunstein J, Schindler C. Signaling through the JAK/STAT pathway, recent advances and future challenges. *Gene.* 2002; 285:1–24. [PubMed: 12039028]
- Kripke DF, Nievergelt CM, Joo E, Shekhtman T, Kelsoe JR. Circadian polymorphisms associated with affective disorders. *J Circad Rhyth.* 2009; 7:2.

- Kuroda KO, Tachikawa K, Yoshida S, Tsuneoka Y, Numan M. Neuromolecular basis of parental behavior in laboratory mice and rats: with special emphasis on technical issues of using mouse genetics. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011; 35:1205–1231. [PubMed: 21338647]
- Kurtz A, Zimmer A, Schnutgen F, Bruning G, Spener F, Muller T. The expression pattern of a novel gene encoding brain-fatty acid binding protein correlates with neuronal and glial cell development. *Development*. 1994; 120:2637–2649. [PubMed: 7956838]
- Larsen C, Grattan D. Prolactin, neurogenesis, and maternal behaviors. *Brain Behav Immun*. 2012; 26:201–209. [PubMed: 21820505]
- Larsen CM, Kokay IC, Grattan DR. Male pheromones initiate prolactin-induced neurogenesis and advance maternal behavior in female mice. *Horm Behav*. 2008; 53:509–517. [PubMed: 18258236]
- Laufer BI, Singh SM. A macro role for imprinted clusters of MicroRNAs in the brain. *MicroRNA*. 2012; 1:59–64. [PubMed: 25048091]
- Le WD, Conneely OM, Zou L, He Y, Saucedo-Cardenas O, Jankovic J, Mosier DR, Appel SH. Selective agenesis of mesencephalic dopaminergic neurons in *Nurr1*-deficient mice. *Exp Neurol*. 1999; 159:451–458. [PubMed: 10506516]
- Leblond CS, Heinrich J, Delorme R, Proepper C, Betancur C, Huguet G, Konyukh M, Chaste P, Ey E, Rastam M. Genetic and functional analyses of SHANK2 mutations suggest a multiple hit model of autism spectrum disorders. *PLoS Genet*. 2012; 8:e1002521. [PubMed: 22346768]
- Lee A, Clancy S, Fleming AS. Mother rats bar-press for pups: effects of lesions of the mpoa and limbic sites on maternal behavior and operant responding for pup-reinforcement. *Behav Brain Res*. 1999; 100:15–31. [PubMed: 10212050]
- Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, Bernard A, Boe AF, Boguski MS, Brockway KS, Byrnes EJ. Genome-wide atlas of gene expression in the adult mouse brain. *Nature*. 2007; 445:168–176. [PubMed: 17151600]
- Leuner B, Gould E. Dendritic growth in medial prefrontal cortex and cognitive flexibility are enhanced during the postpartum period. *J Neurosci*. 2010; 30:13499–13503. [PubMed: 20926675]
- Leuner B, Sabihi S. The birth of new neurons in the maternal brain: hormonal regulation and functional implications. *Front Neuroendocrinol*. 2016
- Levy F, Gheusi G, Keller M. Plasticity of the parental brain: a case for neurogenesis. *J Neuroendocrinol*. 2011; 23:984–993. <http://dx.doi.org/10.1111/j.1365-2826.2011.02203.x>. [PubMed: 21824205]
- Li JZ, Bunney BG, Meng F, Hagenauer MH, Walsh DM, Vawter MP, Evans SJ, Choudary PV, Cartagena P, Barchas JD. Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. *Proc Natl Acad Sci*. 2013; 110:9950–9955. [PubMed: 23671070]
- Liu RZ, Mita R, Beaulieu M, Gao Z, Godbout R. Fatty acid binding proteins in brain development and disease. *Int J Dev Biol*. 2010; 54:1229. [PubMed: 20563994]
- Lonstein JS, De Vries GJ. Sex differences in the parental behavior of rodents. *Neurosci Biobehav Rev*. 2000; 24:669–686. [PubMed: 10940441]
- Ma XM, Johnson RC, Mains RE, Eipper BA. Expression of kalirin, a neuronal GDP/GTP exchange factor of the trio family, in the central nervous system of the adult rat. *J Comp Neurol*. 2001; 429:388–402. [PubMed: 11116227]
- Maina G, Rosso G, Aguglia A, Bogetto F. Recurrence rates of bipolar disorder during the postpartum period: a study on 276 medication-free Italian women. *Arch Women's Mental Health*. 2014:1–6.
- Mandela P, Yan Y, Larese T, Eipper BA, Mains RE. Elimination of *Kalrn* expression in POMC cells reduces anxiety-like behavior and contextual fear learning. *Horm Behav*. 2014; 66:430–438. [PubMed: 25014196]
- Maniam J, Morris MJ. Long-term postpartum anxiety and depression-like behavior in mother rats subjected to maternal separation are ameliorated by palatable high fat diet. *Behav Brain Res*. 2010; 208:72–79. [PubMed: 19896506]
- Maniatis T. A ubiquitin ligase complex essential for the NF- κ B, Wnt/Wingless, and Hedgehog signaling pathways. *Genes Dev*. 1999; 13:505–510. [PubMed: 10072378]

- Matsumata M, Sakayori N, Maekawa M, Owada Y, Yoshikawa T, Osumi N. The effects of *Fabp7* and *Fabp5* on postnatal hippocampal neurogenesis in the mouse. *Stem Cells*. 2012; 30:1532–1543. [PubMed: 22581784]
- Mattson B, Morrell J. Preference for cocaine-versus pup-associated cues differentially activates neurons expressing either Fos or cocaine-and amphetamine-regulated transcript in lactating, maternal rodents. *Neuroscience*. 2005; 135:315–328. [PubMed: 16112474]
- Mattson BJ, Williams S, Rosenblatt JS, Morrell JI. Comparison of two positive reinforcing stimuli: pups and cocaine throughout the postpartum period. *Behav Neurosci*. 2001; 115:683. [PubMed: 11439457]
- Mattson BJ, Williams SE, Rosenblatt JS, Morrell JI. Preferences for cocaine- or pup-associated chambers differentiates otherwise behaviorally identical postpartum maternal rats. *Psychopharmacology*. 2003; 167:1–8. [PubMed: 12607073]
- Mead AN, Brown G, Le Merrer J, Stephens DN. Effects of deletion of *gria1* or *gria2* genes encoding glutamatergic AMPA-receptor subunits on place preference conditioning in mice. *Psychopharmacology*. 2005; 179:164–171. [PubMed: 15619119]
- Mileva-Seitz VR, Bakermans-Kranenburg MJ, Van Ijzendoorn MH. Genetic mechanisms of parenting. *Horm Behav*. 2015; 77:211–223. [PubMed: 26112881]
- Mileva-Seitz V, Fleming A, Meaney M, Mastroianni A, Sinnwell J, Steiner M, Atkinson L, Levitan R, Matthews S, Kennedy J. Dopamine receptors D1 and D2 are related to observed maternal behavior. *Genes Brain Behav*. 2012; 11:684–694. [PubMed: 22574669]
- Miller LJ. Postpartum depression. *JAMA*. 2002; 287:762–765. [PubMed: 11851544]
- Miyamoto A, Shimizu T, Krebs S, Bauersachs S, Blum H, Wolf E. Actions and interactions of progesterone and estrogen. *Physiol Genom*. 2010; 42:290–300.
- Mohawk JA, Green CB, Takahashi JS. Central and peripheral circadian clocks in mammals. *Annu Rev Neurosci*. 2012; 35:445. [PubMed: 22483041]
- Mössner R, Schuhmacher A, Schulze-Rauschenbach S, Kühn KU, Rujescu D, Rietschel M, Zobel A, Franke P, Wölwer W, Gaebel W. Further evidence for a functional role of the glutamate receptor gene *GRM3* in schizophrenia. *Eur Neuropsychopharmacol*. 2008; 18:768–772. [PubMed: 18614340]
- Mundy P, Sigman M, Ungerer J, Sherman T. Defining the social deficits of autism: the contribution of non-verbal communication measures. *J Child Psychol Psychiatry*. 1986; 27:657–669. [PubMed: 3771682]
- Munoz C, Pakladok T, Almilaji A, Elvira B, Decher N, Shumilina E, Lang F. Up-regulation of Kir2.1 (KCNJ2) by the serum & glucocorticoid inducible SGK3. *Cell Physiol Biochem*. 2014; 33:491–500. [PubMed: 24556932]
- Nestler EJ, Carlezon WA. The mesolimbic dopamine reward circuit in depression. *Biol Psychiatry*. 2006; 59:1151–1159. [PubMed: 16566899]
- Nicolas CS, Amici M, Bortolotto ZA, Doherty A, Csaba Z, Fafouri A, Dournaud P, Gressens P, Collingridge GL, Peineau S. The role of JAK-STAT signaling within the CNS. *JAK-STAT*. 2013; 2:e22925. [PubMed: 24058789]
- Noriuchi M, Kikuchi Y, Senoo A. The functional neuroanatomy of maternal love: mother's response to infant's attachment behaviors. *Biol Psychiatry*. 2008; 63:415–423. <http://dx.doi.org/10.1016/j.biopsych.2007.05.018>. [PubMed: 17686467]
- Numan M. Motivational systems and the neural circuitry of maternal behavior in the rat. *Dev Psychobiol*. 2007; 49:12–21. [PubMed: 17186513]
- Numan M. Maternal behavior: neural circuits, stimulus valence, and motivational processes. *Parenting*. 2012; 12:105–114.
- Numan, M.; Insel, TR. *The Neurobiology of Parental Behavior*. Springer; New York: 2003.
- O'shea JJ, Gadina M, Schreiber RD. Cytokine signaling in 2002: new surprises in the Jak/Stat pathway. *Cell*. 2002; 109:S121–S131. [PubMed: 11983158]
- O'brien NL, Way MJ, Kandaswamy R, Fiorentino A, Sharp SI, Quadri G, Alex J, Anjorin A, Ball D, Cherian R. The functional *GRM3* Kozak sequence variant rs148754219 affects the risk of schizophrenia and alcohol dependence as well as bipolar disorder. *Psychiatr Genet*. 2014; 24:277–278. [PubMed: 25046171]

- Olazábal DE, Pereira M, Agrati D, Ferreira A, Fleming AS, González-Mariscal G, Lévy F, Lucion AB, Morrell JI, Numan M. New theoretical and experimental approaches on maternal motivation in mammals. *Neurosci Biobehav Rev*. 2013; 37:1860–1874. [PubMed: 23608127]
- Oliveros JC. Venny: An Interactive Tool for Comparing Lists with Venn Diagrams. 2007
- Otto S, De Groot R, Hornstra G. Increased risk of postpartum depressive symptoms is associated with slower normalization after pregnancy of the functional docosahexaenoic acid status. *Prostaglandins Leukot Essent Fatty Acids*. 2003; 69:237–243. [PubMed: 12907133]
- Panksepp J, Nelson E, Siviý S. Brain opioids and mother-infant social motivation. *Acta Paediatr Suppl*. 1994; 397:40–46. [PubMed: 7981473]
- Pappa I, Szekely E, Mileva-Seitz VR, Luijk MP, Bakermans-Kranenburg MJ, Van Ijzendoorn MH, Temeier H. Beyond the usual suspects: a multidimensional genetic exploration of infant attachment disorganization and security. *Attach Hum Develop*. 2015:1–14.
- Parada M, King S, Li M, Fleming AS. The roles of accumbal dopamine D1 and D2 receptors in maternal memory in rats. *Behav Neurosci*. 2008; 122:368. [PubMed: 18410175]
- Pawluski J, Galea L. Reproductive experience alters hippocampal neurogenesis during the postpartum period in the dam. *Neuroscience*. 2007; 149:53–67. [PubMed: 17869008]
- Perlmann T, Wallén-Mackenzie Å. Nurrl, an orphan nuclear receptor with essential functions in developing dopamine cells. *Cell Tissue Res*. 2004; 318:45–52. [PubMed: 15340833]
- Piechota M, Korostynski M, Sikora M, Golda S, Dzbek J, Przewlocki R. Common transcriptional effects in the mouse striatum following chronic treatment with heroin and methamphetamine. *Genes Brain Behav*. 2012; 11:404–414. [PubMed: 22390687]
- Pletscher-Frankild S, Pallegà A, Tsafou K, Binder JX, Jensen LJ. DISEASES: text mining and data integration of disease–gene associations. *Methods*. 2015; 74:83–89. [PubMed: 25484339]
- Rappaport N, Nativ N, Stelzer G, Twik M, Guan-Golan Y, Stein TI, Bahir I, Belinky F, Morrey CP, Safran M. MalaCards: an integrated compendium for diseases and their annotation. *Database: J Biol Databases Curat*. 2013:2013.
- Ray S, Tzeng RY, Dicarlo LM, Bundy JL, Vied C, Tyson G, Nowakowski R, Arbeitman MN. An examination of dynamic gene expression changes in the mouse brain during pregnancy and the postpartum period. *G3: Genes|Genomes| Genetics*. 2016; 6:221–233. [PubMed: 26596646]
- Reppert SM, Weaver DR. Coordination of circadian timing in mammals. *Nature*. 2002; 418:935–941. [PubMed: 12198538]
- Russo SJ, Nestler EJ. The brain reward circuitry in mood disorders. *Nat Rev Neurosci*. 2013; 14:609–625. [PubMed: 23942470]
- Sakamoto T, Mori K, Miyazato M, Kangawa K, Sameshima H, Nakahara K, Murakami N. Involvement of neuromedin S in the oxytocin release response to suckling stimulus. *Biochem Biophys Res Commun*. 2008; 375:49–53. [PubMed: 18675786]
- Salzberg H, Lonstein J, Stern J. GABA A receptor regulation of kyphotic nursing and female sexual behavior in the caudal ventrolateral periaqueductal gray of postpartum rats. *Neuroscience*. 2002; 114:675–687. [PubMed: 12220569]
- Saul M, Zhao C, Driessen T, Eisinger B, Gammie S. MicroRNA expression is altered in lateral septum across reproductive stages. *Neuroscience*. 2016; 312:130–140. [PubMed: 26592715]
- Scheich B, Gaszner B, Kormos V, László K, Ádori C, Borbély É, Hajna Z, Tékus V, Bölcskei K, Ábrahám I. Somatostatin receptor subtype 4 activation is involved in anxiety and depression-like behavior in mouse models. *Neuropharmacology*. 2016; 101:204–215. [PubMed: 26387439]
- Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, Joe AY, Kreft M, Lenartz D, Sturm V. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology*. 2008; 33:368–377. [PubMed: 17429407]
- Seip KM, Morrell JI. Increasing the incentive salience of cocaine challenges preference for pup-over cocaine-associated stimuli during early postpartum: place preference and locomotor analyses in the lactating female rat. *Psychopharmacology*. 2007; 194:309–319. [PubMed: 17589831]
- Shams S, Pawluski JL, Chatterjee-Chakraborty M, Oatley H, Mastroianni A, Fleming AS. Dendritic morphology in the striatum and hypothalamus differentially exhibits experience-dependent changes in response to maternal care and early social isolation. *Behav Brain Res*. 2012; 233:79–89. [PubMed: 22569575]

- Shen Q, Goderie SK, Jin L, Karanth N, Sun Y, Abramova N, Vincent P, Pumiglia K, Temple S. Endothelial cells stimulate self-renewal and expand neurogenesis of neural stem cells. *Science*. 2004; 304:1338–1340. [PubMed: 15060285]
- Shingo T, Gregg C, Enwere E, Fujikawa H, Hassam R, Geary C, Cross JC, Weiss S. Pregnancy-stimulated neurogenesis in the adult female forebrain mediated by prolactin. *Science*. 2003; 299:117–120. [PubMed: 12511652]
- Sommer JE, Budreck EC. Kalirin-7: linking spine plasticity and behavior. *J Neurosci*. 2009; 29:5367–5369. [PubMed: 19403804]
- Stadtfield M, Apostolou E, Akutsu H, Fukuda A, Follett P, Natesan S, Kono T, Shioda T, Hochedlinger K. Aberrant silencing of imprinted genes on chromosome 12qF1 in mouse induced pluripotent stem cells. *Nature*. 2010; 465:175–181. [PubMed: 20418860]
- Stansberg C, Vik-Mo AO, Holdhus R, Breilid H, Srebro B, Petersen K, Jørgensen HA, Jonassen I, Steen VM. Gene expression profiles in rat brain disclose CNS signature genes and regional patterns of functional specialisation. *BMC Genom*. 2007; 8:94.
- Stolzenberg DS, Numan M. Hypothalamic interaction with the mesolimbic DA system in the control of the maternal and sexual behaviors in rats. *Neurosci Biobehav Rev*. 2011; 35:826–847. [PubMed: 20955733]
- Strathearn L, Li J, Fonagy P, Montague PR. What's in a smile? Maternal brain responses to infant facial cues. *Pediatrics*. 2008; 122:40–51. <http://dx.doi.org/10.1542/peds.2007-1566>. [PubMed: 18595985]
- Szklarczyk D, Franceschini A, Kuhn M, Simonovic M, Roth A, Minguéz P, Doerks T, Stark M, Müller J, Bork P. The STRING database in 2011: functional interaction networks of proteins, globally integrated and scored. *Nucleic Acids Res*. 2011; 39:D561–D568. [PubMed: 21045058]
- Tang S, Han H, Bajic VB. ERGDB: estrogen responsive genes database. *Nucleic Acids Res*. 2004; 32:D533–D536. [PubMed: 14681475]
- Thomas M, Lieberman J, Lal A. Desperately seeking microRNA targets. *Nat Struct Mol Biol*. 2010; 17:1169–1174. [PubMed: 20924405]
- Torner L, Karg S, Blume A, Kandasamy M, Kuhn HG, Winkler J, Aigner L, Neumann ID. Prolactin prevents chronic stress-induced decrease of adult hippocampal neurogenesis and promotes neuronal fate. *J Neurosci*. 2009; 29:1826–1833. [PubMed: 19211889]
- Torra ISP, Tsubulsky V, Delaunay F, Saladin RG, Laudet V, Fruchart JC, Kosykh V, Staels B. Circadian and glucocorticoid regulation of Rev-erba expression in liver 1. *Endocrinology*. 2000; 141:3799–3806. [PubMed: 11014236]
- Trabzuni D, Ramasamy A, Imran S, Walker R, Smith C, Weale ME, Hardy J, Ryten M, Consortium, N.A.B.E. Widespread sex differences in gene expression and splicing in the adult human brain. *Nat Commun*. 2013;4.
- Tsunoka T, Kishi T, Ikeda M, Kitajima T, Yamanouchi Y, Kinoshita Y, Kawashima K, Okochi T, Okumura T, Inada T. Association analysis of group II metabotropic glutamate receptor genes (*GRM2* and *GRM3*) with mood disorders and fluvoxamine response in a Japanese population. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009; 33:875–879. [PubMed: 19386277]
- Ueda HR, Hayashi S, Chen W, Sano M, Machida M, Shigeyoshi Y, Iino M, Hashimoto S. System-level identification of transcriptional circuits underlying mammalian circadian clocks. *Nat Genet*. 2005; 37:187–192. [PubMed: 15665827]
- Wang J, Cheng C, Zhou J, Smith A, Weickert CS, Perlman W, Becker K, Powell D, Bondy C. Estradiol alters transcription factor gene expression in primate prefrontal cortex. *J Neurosci Res*. 2004; 76:306–314. [PubMed: 15079859]
- Wang J, Gutala R, Hwang Y, Kim JM, Konu O, Ma J, Li M. Strain-and region-specific gene expression profiles in mouse brain in response to chronic nicotine treatment. *Genes Brain Behav*. 2008; 7:78–87. [PubMed: 17504244]
- Wang Y, Zhang XS, Chen L. A network biology study on circadian rhythm by integrating various omics data. *OMICS*. 2009; 13:313–324. [PubMed: 19645592]
- Wang Y, Zhou D, Phung S, Masri S, Smith D, Chen S. SGK3 is an estrogen-inducible kinase promoting estrogen-mediated survival of breast cancer cells. *Mol Endocrinol*. 2011; 25:72–82. [PubMed: 21084382]

- Warde-Farley D, Donaldson SL, Comes O, Zuberi K, Badrawi R, Chao P, Franz M, Grouios C, Kazi F, Lopes CT. The GeneMANIA prediction server: biological network integration for gene prioritization and predicting gene function. *Nucleic Acids Res.* 2010; 38:W214–W220. [PubMed: 20576703]
- Wettschurek N, Moers A, Hamalainen T, Lemberger T, Schütz G, Offermanns S. Heterotrimeric G proteins of the Gq/11 family are crucial for the induction of maternal behavior in mice. *Mol Cell Biol.* 2004; 24:8048–8054. [PubMed: 15340067]
- Wilsoncroft W. Babies by bar-press: maternal behavior in the rat. *Behav Res Methods Instrum.* 1968; 1:229–230.
- Won H, Lee HR, Gee HY, Mah W, Kim JI, Lee J, Ha S, Chung C, Jung ES, Cho YS. Autistic-like social behaviour in *Shank2*-mutant mice improved by restoring NMDA receptor function. *Nature.* 2012; 486:261–265. [PubMed: 22699620]
- Wongchitrat P, Mukda S, Phansuwan-Pujito P, Govitrapong P. Effect of amphetamine on the clock gene expression in rat striatum. *Neurosci Lett.* 2013; 542:126–130. [PubMed: 23518151]
- Xia Y, Wu Z, Ma D, Tang C, Liu L, Xin F, Zhu D, Hu J. Association of single-nucleotide polymorphisms in a metabotropic glutamate receptor GRM3 gene subunit to alcohol-dependent male subjects. *Alcohol Alcohol.* 2014 agu004.
- Xiao XQ, Grove KL, Lau SY, Mcweeney S, Smith MS. Deoxyribonucleic acid microarray analysis of gene expression pattern in the arcuate nucleus/ventromedial nucleus of hypothalamus during lactation. *Endocrinology.* 2005; 146:4391–4398. [PubMed: 16002521]
- Yun SW, Leong C, Zhai D, Tan YL, Lim L, Bi X, Lee JJ, Kim HJ, Kang NY, Ng SH. Neural stem cell specific fluorescent chemical probe binding to *FABP7*. *Proc Natl Acad Sci.* 2012; 109:10214–10217. [PubMed: 22689954]
- Zerbino DR, Wilder SP, Johnson N, Juettemann T, Flicek PR. The ensembl regulatory build. *Genome Biol.* 2015; 16:56. [PubMed: 25887522]
- Zhang Y, Chen K, Sloan SA, Bennett ML, Scholze AR, O'keeffe S, Phatnani HP, Guarnieri P, Caneda C, Ruderisch N. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J Neurosci.* 2014; 34:11929–11947. [PubMed: 25186741]
- Zhao C, Driessen T, Gammie SC. Glutamic acid decarboxylase 65 and 67 expression in the lateral septum is up-regulated in association with the postpartum period in mice. *Brain Res.* 2012a; 1470:35–44. <http://dx.doi.org/10.1016/j.brainres.2012.06.002>. [PubMed: 22750123]
- Zhao C, Eisinger BE, Driessen TM, Gammie SC. Addiction and reward-related genes show altered expression in the postpartum nucleus accumbens. *Front Behav Neurosci.* 2014; 8:388. [PubMed: 25414651]
- Zhao C, Gammie SC. Glutamate, GABA, and glutamine are synchronously upregulated in the mouse lateral septum during the postpartum period. *Brain Res.* 2014
- Zhao C, Gammie SC. Metabotropic glutamate receptor 3 is downregulated and its expression is shifted from neurons to astrocytes in the mouse lateral septum during the postpartum period. *J Histochem Cytochem.* 2015; 63:417–426. [PubMed: 25739438]
- Zhao C, Saul MC, Driessen T, Gammie SC. Gene expression changes in the septum: possible implications for microRNAs in sculpting the maternal brain. *PLoS ONE.* 2012b; 7:e38602. <http://dx.doi.org/10.1371/journal.pone.0038602>. [PubMed: 22701680]
- Zucchi S, Castiglioni S, Fent K. Progesterone alters global transcription profiles at environmental concentrations in brain and ovary of female zebrafish (*Danio rerio*). *Environ Sci Technol.* 2013; 47:12548–12556. [PubMed: 24083816]

Fig. 1.

Overview of possible genetic contributions to the maternal brain. While a subset of genes (~50) have been well-studied in the postpartum brain and additional genes (~150) have been identified as relevant to maternal processing via transgenic studies (left panel), most genes have not been examined in a maternal context (right panel). With over 20,000 genes in mice and humans and of those about 16–18,000 expressed in the CNS (right panel), over 99% of genes that could be involved in shaping the maternal brain still remain unexamined.

Fig. 2.

Overview of synthesis of recent maternal microarray studies and outline of analysis of top 700 maternal genes. From microarray analysis of NAC, mPFC, LS, and MPOA with over 20,000 protein coding RNAs, we found high overlap of significant genes between each region and identified the top 700 maternal genes based on alterations in 3 or more regions (left part of figure; see text for additional details). Steps of analysis for the top 700 maternal genes in this review are provided in the right panel. Abbreviation: TF, transcription factor or transcriptional regulator. Overlap diagram drawn using Venny (Oliveros, 2007).

Fig. 3. Top 700 maternal genes show high enrichment with reward or addiction-related genes. (A) BigTest or MSET analysis (Eisinger et al., 2013a; Saul et al., 2016), where Y -axis represents the probability of X matches to database appearing in a randomly generated set of simulated results from the microarray background. The red arrow shows how many matches were found in the top 700 maternal genes changes and where that number falls on the probability density distribution. Enrichment is significant when evaluating top 700 maternal genes against either all reward/addiction genes (pooled from 5 databases) or against only reward/addiction genes appearing in at least two databases. When each maternal brain region is analyzed separately, enrichment is shown for all regions except mPFC, which is just above significance (top right). (B) Interaction network of matches between top 700 maternal genes and reward/addiction genes (in black) using GeneMania (see text for details). Genes in red circles have previously been associated with maternal reward, while genes in green circles are new candidates for maternal reward. GeneMania adds linking genes (in gray). Lines indicate type of evidence for interaction; yellow, predicted; red, physical interaction; purple,

co-expression; gray, other; aqua blue, pathway; light blue, co-localization, gold, shared protein domain. (C) ToppCluster results showing significant enrichment of top 700 maternal genes with genes associated with six chemicals of abuse, namely nicotine, alcohol, dronabinol, methamphetamine, morphine, and cocaine. Graph on right shows the general pattern whereby some genes are only linked to one drug, but others are linked to two or three or more.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 4.

Top 700 maternal genes show high enrichment with depression and (postpartum depression) PPD genes. Significant enrichment is found evaluating top 700 maternal genes against either depression genes found in two or more databases or against PPD genes within two databases using MSET analysis. The red arrow shows how many matches were found in the top 700 maternal genes changes and where that number falls on the probability density distribution (top panel). Interaction network of matches between top 700 maternal genes and depression or PPD genes (in black) using GeneMania (bottom panel). Genes in red circles are in PPD databases, while genes in green circles are new candidates for PPD. GeneMania adds linking genes (in gray).

Fig. 5.

Top 700 maternal genes show high enrichment with mental health disorders that include social deficits. Significant enrichment is found evaluating top 700 maternal genes against either autism genes found in 3 or more databases, BPD genes found in 2 or more databases, or schizophrenia genes in 4 or more databases using MSET analysis. The red arrow shows how many matches were found in the top 700 maternal genes changes and where that number falls on the probability density distribution (left panel). All three disorders include social deficits (see text for details). Interaction network of matches between top 700 maternal genes and mental health genes (in black) using GeneMania (right panel). Genes in green circles are in all three disorders, while genes in red circles are in two of three disorders. GeneMania adds linking genes (in gray). Genes are tightly clustered, suggesting they may act as a functional unit, but whether they relate in general to social behavior (which is promoted in mothers and disrupted with certain mental health disorders) is not known.

Prolactin signaling and top 700 maternal genes

Fig. 6.

Overview of prolactin signaling intersection with top 700 maternal genes. Although neither prolactin (yellow circle) nor prolactin receptor (red circle), were in the top 700, both interact with a subset of top 700 maternal genes as assessed using STRING network analysis (see text for details; color of other circles are arbitrary and do not provide additional information). *Cish*, *Socs2*, and *Socs3* are part of negative feedback on the prolactin receptor and thus expression changes in these genes could alter prolactin action in mothers or expression change could be due to alterations in prolactin signaling. *Btrc* is involved in ubiquitination events and could affect prolactin receptor action. Line colors indicate type of evidence connecting gene in STRING; blue, cooccurrence; black, coexpression; purple, experiments; aqua blue, databases; light green, text mining; light blue, homology.

Oxytocin/ vasopressin signaling and top 700 maternal genes

Fig. 7.

Overview of oxytocin/vasopressin signaling intersection with top 700 maternal genes. Genes for oxytocin signaling (yellow circles) and vasopressin signaling (red circles), were not in the top 700, but interact with a subset of top 700 maternal genes as assessed using STRING network analysis (see text for details; color of other circles are arbitrary and do not provide additional information). Receptors for hypocretin (orexin) (*Hcrt1* and *Hcrt2*) are among those most tightly connected to oxytocin and vasopressin signaling and the HCRT system has previously been implicated in maternal care (see text for details). Neuromedin S (*Nms*) may modulate oxytocin release and/or act as an intermediate between enkephalin (*Penk*) and dynorphin (*Pdyn*) action on oxytocin and vasopressin signaling. Kalirin (*Kalrn*) regulates neuropeptide processing and G protein signaling and multiple mRNA variants and has been associated with a number of CNS processes, including plasticity and anxiety. *Cacna2d3* is of interest as it has recently linked to attachment behavior (see text). Knockout of *Gna11* (along with *Gnaq*) disrupts maternal care, so this gene could be critical in oxytocin action. Line colors indicate type of evidence connecting genes in STRING; red, gene fusion; blue, co-occurrence; black, coexpression; purple, experiments; aqua blue, databases; light green, text mining; light blue, homology.

Fig. 8.

Overview of endogenous opioid signaling intersection with top 700 maternal genes. *Penk*, *Pdyn*, and *Oprm1* are all top 700 maternal genes and interact with multiple other top 700 genes as assessed using STRING network analysis (see text for details; color of other circles are arbitrary and do not provide additional information). Among genes of interest are the somatostatin receptor (*Sstr4*), the acetylcholine receptor (*Chrm4*), the histamine receptor (*Hrh3*), the serotonin receptor (*Htr1a*), the glutamate receptor (*Grm3*), the adenosine receptor (*Adora2a*), and the dopamine receptor (*Drd1a*) (see text for more details on these genes). The neuropeptide, *Nms* (described above), could be interacting with *Pdyn* and *Penk* release or action. Recently, *Grm3* was associated with dependence on the opioid (see text for details), so *Grm3* could be critical in how endogenous opioids acts. Line colors indicate type of evidence connecting gene in STRING; red, gene fusion; blue, co-occurrence; black, coexpression; purple, experiments; aqua blue, databases; light green, text mining; light blue, homology.

Estrogen/ progesterone/ glucocorticoid signaling and top 700 maternal genes

Fig. 9.

Overview of steroid receptor signaling (estradiol, progesterone, and glucocorticoid) intersection with top 700 maternal genes. Genes for estradiol signaling (yellow circles), glucocorticoid signaling (red circle), and progesterone signaling (green circle) were not in the top 700, but interact with a subset of top 700 maternal genes as assessed using STRING network analysis (see text for details; color of other circles are arbitrary and do not provide additional information). A high number of transcriptional regulators are identified, including *Nr1d1*, *Hif1a*, *Nr4a1*, *Ncor2*, *Ep300*, *Egr1*, *Nr4a3*, *Npas2*, *Fkbp4*, *Rarb*, *Rarg*, and *Creb1* (see text for information on known interactions with the steroid receptors). Line colors indicate type of evidence connecting gene in STRING; red, gene fusion; blue, co-occurrence; black, coexpression; purple, experiments; aqua blue, databases; light green, text mining; light blue, homology.

miRNA regulation of the maternal brain

Postpartum LS

32 miRNAs upregulated → 4626 genes targeted
25 miRNAs downregulated

Top 700 highly enriched
for miRNA targets
287/700 (41%) are targets

Hypergeometric p-value < 0.00000001

maternal miRNAs → top 700 (TFs in top 700)

Subset of TFs targeted by maternal miRNAs (46)

Nr1d1	Egr1	Eny2	Zdhhc5	Btbd11	Zfp46
Zfp687	Hmg20a	Ell2	Ep300	Phf12	Bcl6
Arid5b	Rbfox2	Rab8b	Tef	Irf2	Zxdb
Uhrf2	Rfx4	Tmpo	Rabl3	Ivns1abp	Ppp1r12b
Nr4a3	Hmgb3	Hdac4	Foxp1	E2f6	Zbtb16
Mafg	Creb1	Nr4a2	Rarb	Etv5	Tox3
Skil	Hif1a	Tsc22d3	Grlf1	Morf4l1	
Hif3a	Ascl1	Ncoa5	Bcl11b	Elk1	

Fig. 10.

Transcriptional regulation and the production of the maternal brain. In recent work directly examining miRNA expression across reproduction, we found 32 miRNAs consistently upregulated miRNAs (pregnant/postpartum relative to virgin) and 25 miRNAs consistently downregulated (Saul et al., 2016). Each miRNA can have multiple RNA targets and combined, the up and downregulated miRNAs target 4626 genes (top panel). The top 700 maternal genes showed extremely high enrichment for the miRNA targets with 41% of the top 700 being targets (BigTest p-value = 0.002; hypergeometric p-value < 10^{-8}). Within the 41% are 46 transcription regulators (bottom panel) that in turn can regulate miRNAs and/or other genes within the top 700 maternal genes. Thus, a complex interaction occurs whereby miRNAs target numerous maternal genes and a subset of these genes then can transcriptionally regulate other maternal genes as well as the miRNAs (middle diagram).

CNS plasticity/ development/ neurogenesis in top 700 maternal genes

Fig. 11.

Overview of top 700 maternal genes involved in development, differentiation, neurogenesis, and plasticity pathways. Interaction network of matches between top 700 maternal genes and genes associated with various CNS plasticity events (in black) using GeneMania.

GeneMania adds the prolactin receptor (green circle) as a linking gene, which is consistent with its known role in cellular plasticity (see text). Because these genes represent adult changes in plasticity/development, we tested and found a significant overlap of top 700 maternal genes with the adult degenerative disorders, such as Alzheimer's. The common genes are shown in red circles and may provide insight into how changes in the maternal brain could indicate a pathway for restoring the CNS from degeneration in adults.

Top 700 maternal genes and enrichment with top genes from new maternal RNA seq study

Fig. 12.

Top 700 maternal genes show high enrichment with top genes from new maternal RNA seq study. Significant enrichment (hypergeometric test) is found evaluating top 700 maternal genes against new RNA seq top 700 genes for postpartum day 3 (PPD3) or PPD10 relative to virgin. For comparisons, data from the maternal RNA seq study from hippocampus, cortex, hypothalamus, and cerebellum for PPD3 and PPD10 (Ray et al., 2016) was combined to provide a top 700 list (high rank in at least three of four regions; see text for details). The red arrow shows how many matches were found in the top 700 maternal genes changes and where that number falls on the probability density distribution (left panel). 108 top 700 genes were found in at least one of the two other lists (PPD3 or PPD10) and 34 genes were found in the top 700 of all three lists.

Fig. 13.

Chromosome distribution of top 700 maternal genes. Blue dots indicate top 700 maternal genes and as shown, most are evenly distributed across chromosomes. The X chromosome had the lowest ratio of maternal genes per total genes. For miRNAs, one region on chromosome 12 (12qF1) is highly enriched for upregulated miRNAs (Saul et al., 2016) and this region has been connected to cell differentiation events (see text for details). Background image taken from UCSC Genome Browser (<http://genome.ucsc.edu>) (Kent et al., 2002).