SUPPLEMENTAL METHODS

Animal Husbandry

Six week-old male, 8 week-old female C57BL/6J, and 8 week-old male BALB/cJ mice intruder males were ordered from Jackson Laboratories (Bar Harbor, ME, USA) and housed in a 12L:12D animal room until the resident-intruder paradigm was undertaken. Before testing, resident males were cohoused with members of the same sex for two weeks, housed alone for a week, and then housed with a single C57BL/6J female for a week to establish a territory. Three hours before testing, females were removed from the resident males' cages. Immediately before the trial, residents' cages were inserted into a blank-walled chamber. We introduced unfamiliar intruder BALB/cJ male mice contained within a wire mesh cage to prevent injury. Control animals were exposed to the same cage, but a paper cup was introduced instead of an intruder mouse. The intruders or objects were removed after five minutes, after which resident animals were kept in a dark, quiet place for 30 minutes, 60 minutes, or 120 minutes. Residents (5 animals per time point) were then immediately euthanized by cervical dislocation. Immediately after euthanasia we extracted frontal cortex, hypothalamus, and amygdala.

Dissection

After the brain was extracted from the skull and the olfactory bulbs removed, dissection of these tissues began with coronal sectioning of the brain into four sections in a 1 mm coronal acrylic tissue matrix (Cellpoint Scientific, Gaithersburg, MD, USA) for mouse brains using razor blades. These sections, labeled A, B1, B2, and C from caudal to rostral, are described in Supplemental Figure S1. The cut dividing A from B1 was at the level of the rhombencephalon boundary, the cut dividing B1 from B2 was two millimeters rostral of the A/B1 cut, and the cut dividing B2 and C was two millimeters rostral of the B1/B2 cut. These cuts divided the whole hypothalamus approximately in half. A schematic of the sectioning appears in Supplemental Figure S1A.

After sectioning, tissue was laid flat on a cutting mat. The amygdala was extracted from section B2. The hypothalamus was taken from sections B2 and B1. The frontal cortex was taken from section C. A schematic of the cuts made to the sections to extract these tissues can be found in Supplemental Figure S1B.

RNA Extraction and Library Preparation

Dissected tissue was disrupted in Trizol (Life Technologies, Carlsbad, CA, USA) with a mechanical pestle according manufacturer's specifications. The aqueous phase was precipitated in isopropanol, resuspended in nuclease-free water, treated with DNase I (New England Biolabs, Ipswich, MA, USA), and cleaned up using a Zymo RNA Clean & Concentrator™-25 kit (Zymo Research, Irvine, CA, USA) according to manufacturer's specifications. Prior to library preparation, total RNA was checked for purity using a NanoDrop ND-1000 spectrophotometer, integrity using RNA Nano chips on an Agilent 2100 Bioanalyzer, and concentration using a Qubit fluormeter. RNA-Seq

libraries were prepared from total RNA robotically using TruSeq Stranded mRNA HT (Illumina, San Diego, CA, USA) on an epMotion 5075 robot (Eppendorf, Hamburg, Germany). Libraries were pooled and sequenced on an Illumina HiSeq 2500 sequencer by the UIUC W. M. Keck Biotechnology Center using an Illumina TruSeq SBS sequencing kit, version 3 (Illumina, San Diego, CA, USA). All samples were sequenced in single end format with fragment length of 100 bp. Base calling and demultiplexing into FASTQ files was done using CASAVA version 1.8.2 (Illumina, San Diego, CA, USA). Read depth ranged from 48,345,410 reads to 72,161,138 reads per sample.

RNA-Seq Bioinformatics

FASTQ files were aligned to the Ensembl annotation of the NCBIM37 version of the mouse genome using TopHat2 version 2.0.8 (Kim et al. 2013). Reads inside of exon features were counted in union mode using htseq version 0.6.1 (Anders et al. 2015). Differential expression analysis was done in R using the Bioconductor package edgeR (Robinson et al. 2010) after filtering for genes with expression ≥ 1 CPM in at least 3 samples in the GLM and within the smallest group for pairwise comparisons. Pairwise comparisons between control and intruder conditions in each tissue and time after challenge were analyzed using the bin.loess version of trended dispersion in edgeR version 3.2.4 in R version 3.0.0. For the 9 tables produced in this analysis, we performed a global FDR correction of all raw p-values produced instead of the edgeR default table-wise FDR correction. Generalized linear modeling looking at tissue, challenge status, time after challenge, and all possible interactions between these factors was performed in edgeR version 3.8.6 in R version 3.1.2. We performed global FDR correction of all raw p-values produced in the seven tables corresponding to each factor instead of using the edgeR default of table-wise FDR correction.

Functional Enrichment and Clustering

To enrich for biological systems and visualize the results of the pairwise comparisons, we used enrichment and visualization techniques similar to the online tool REVIGO (Supek et al. 2011). We used the weight GO tree-pruning algorithm with Fisher's exact testing in topGO to find significantly enriched GO BP terms in each pairwise comparison (Alexa et al. 2006). We found their dissimilarity using the simRel algorithm in the GOSemSim package (Yu et al. 2010). We then plotted their similarity using the non-metric isoMDS function in MASS. We used the individual terms and the genes inside each term to manually annotate names for clusters appearing in MDS plots. Systems enrichment using DAVID v. 6.8 (Huang da et al. 2009a; Huang da et al. 2009b) utilized genes with an FDR < 0.10 except the tissue and tissue:time factors, where we chose the top 3,000 genes. DAVID analysis was done using functional clustering with default settings. For GLM enrichment analyses, we chose a background of all genes that made it through the GLM's filtering criteria, which are discussed in the RNA-seq Bioinformatics subsection of these supplemental methods. For WGCNA enrichment analyses, we chose a background of all genes that made it through WGCNA's filtering criteria, which are discussed in the WGCNA subsection of these supplemental methods.

WGCNA and Network Analysis

To find modules of genes coexpressed with one another, we used signed WGCNA (Langfelder et al. 2008) on all tissues and times after challenge. After log-transforming our data using voom+limma, we filtered zero variance genes, selected a soft thresholding coefficient of 8, then used a signed Pearson correlation analysis with a minimum module size of 30. We used standard linear modeling on the resultant eigengenes with all experimental factors of interest as well as hypergeometric overlap tests to find modules with more DEGs than expected by chance. Hypergeometric overlap p-values were calculated using the function hypergeo.overlap.test() in version 1.16.1 of the R package msaul (https://github.com/msaul/msaul). Results are reported in Supplemental Table S9.

To construct a coexpression network with only the most stable of these relationships, we calculated Pearson correlation coefficients between all gene pairs in all three tissues from the experiment: amygdala, frontal cortex, and hypothalamus. We drew edges for only those correlations with an absolute value ≥ 0.85 in all three tissues and in which all correlations had the same sign. After importing these high-stability edges into Cytoscape v. 3.2.0, we extracted the largest connected component and used edge-weighted spring embedded layout on the sign of edges to separate the network into two components. We calculated network statistics like betweenness centrality in Cytoscape and used this information to draw the network in this paper. Further, we used DAVID as described above to perform functional enrichment on the genes in WGCNA modules contained in this high stability network.

Cell Type Deconvolution Analysis

We used a modification of population-specific expression analysis (PSEA) to deconvolve our samples and identify genes associated with some of the many cellular components of brain tissue (Kuhn et al. 2011). We used the PSEA R package to calculate reference signals for five different cell types — astrocytes, neurons, oligodendrocytes, microglia, and endothelial cells — from a previous RNA-Seq experiment on sorted cells from adult mouse frontal cortex (Zhang et al. 2014). After finding genes whose expression values were at least 1 FPKM and at least 5-fold higher in one cell type than in all other cell types, we used PSEA to identify the core signal from each cell type. Using a customized high-throughput model selection and averaging script built with the R package MuMIn that tests models of each gene's expression as a function of zero, one, or multiple cell type core signals, we selected the models with the lowest Bayesian Information Criterion (BIC) value. In cases where we identified multiple good models with BICs within 2 of one another, we used MuMIn to create a polymodel weighted by log-likelihood. The best models, BICs, and p-values of these models or weighted polymodels are reported in Supplemental Table S7.

Transcriptional Regulatory Network Reconstruction

The ASTRIX (Analyzing Subsets of Transcriptional Regulators Influencing eXpression) algorithm generates a network of high-confidence TF-gene interactions

using ARACNE (Accurate Reconstruction of Cellular Networks), and uses these interactions to predict expression in new conditions using LARS (Least Angle Regression). Transcriptomics data for network inference using ASTRIX was first quantile normalized and then standardized to have row variances of 1. This normalization procedure allowed us to uniformly interpret the magnitude of the regression coefficients and use their magnitudes to rank the individual interactions. We quantified the accuracy of the inferred model by measuring the Root Mean Square Deviation (RMSD). RMSD has the same units as variance, thus providing an estimate for the amount of variance of the gene explained by the model. The predicted targets of TFs were defined as those genes that share very high mutual information ($P < 10^{-6}$) with a TF and have high predictive ability (RMSD < 0.33 i.e greater than 66% of each gene expression's standard deviation can be predicted by the TRN model). The putative regulators with regression coefficients less than 0.1 were pruned out and the final network was determined, which consists of 1211 target genes and 253 TFs. This set of 1211 targets were strongly enriched for differentially expressed genes (DEGs) across different regions and time points (p-value < 10^{-14}). Enrichment of TFs targets and DEGs from both the model and pairwise results were tested using a hypergeometric overlap test, and p-values were FDR-corrected for multiple comparisons.

Validation of the TRN was done by comparative bioinformatics analyses. The interactions in the present dataset were found to have strong overlap with TRNs from mouse adult brain (p-value < 10^{-11}) and mouse fetal brain (p-value < 10^{-12}) that were reconstructed using DNAse foot printing as part of the ENCODE project (Stergachis et al. 2014). The observed overlap with mouse fetal brain and adult brain TRN were 180-fold and 74-fold higher compared to a random brain TRN data constructed with the same set of TFs and target genes. 67 out of 98 TFs with greater than ten target genes had a common cis-motif enriched among its targets (FDR < 0.10, based on motif annotation from the TRANSFAC database). 29 out of 98 TFs had strong enrichment for KEGG metabolic pathways (FDR < 0.10) among its targets. Further, many neural-related pathways like "axon guidance" and "long term potentiation", were overrepresented among the target genes, indicating that the modules (targets of individual TFs) capture known brain processes.

RT-qPCR Confirmation

RT-qPCR on 120 minute RNA samples from each region and from both control and challenged animals were used for RT-qPCR confirmation on seven genes: *Dnajb1l*, *Ide*, *Igf2*, *Oxt*, *Pmch*, *Tcf7l2*, and *Zic1*. The gene *Ywhaz*, whose expression is known to be stable in brain tissue, was used as a reference gene. The primer sequences are contained in Supplemental Table S17. All primers passed stringent bioinformatics specificity requirements using Primer BLAST and had single melt curve peaks.

Reverse transcription was performed with random hexamer primers in 20 μL reactions on 2 μg of RNA template using an M-MuLV Reverse Transcriptase Kit (NEB, Ipswich, MA, USA) on an Eppendorf MasterCycler Nexus Gradient thermocycler (Eppendorf, Hamburg, Germany) according to the kit manufacturer's specifications and using the kit manufacturer's thermocycling conditions.

Real-time reactions were performed in triplicate. Each reaction contained 2 μL of template (20X dilution of cDNA) in 10 μL reactions with 300 nM primer concentrations using 5 μL of 2X Power SYBR Green Master Mix (Applied Biosystems, Waltham, MA, USA). Reaction setup was done using manual pipettes for master mix preparation and using electronic repeating pipettes for final reaction setup in MicroAmp® Optical 384-Well Reaction Plate with Barcode (Product # 4309849, Applied Biosystems, Waltham, MA, USA) that were sealed with MicroAmp® Optical Adhesive Film (Product # 4311971, Applied Biosystems, Waltham, MA, USA). After cenrtrifugation to concentrate reactions at the bottoms of wells, real-time thermocycling was performed on Applied Biosystems QuantStudio 6 Flex 384-well real-time thermocycler (Applied Biosystems, Waltham, MA, USA) using the following thermocycling parameters: 105° C heated cover temperature, 10 minutes hot start, 45 cycles of 95° C for 20 sec, 60° C for 25 sec, and 72° C for 25 sec (measurement of SYBR and ROX fluorescence at 60° C), and a melt curve from 60° C to 95° C in 0.5° C increments to measure primer specificity.

Cq was measured using a template-specific threshold auto-calculated by the QuantStudio Real-Time PCR Software (version 1.0, Applied Biosystems, Waltham, MA, USA). Quantification of RNA relative abundance was performed using the $\Delta\Delta$Cq method with *Ywhaz* used as a reference ("housekeeping") gene. Plotting of transformed relative abundances was performed using the $2^{-\Delta\Delta Cq}$ method (Supplemental Table S17, Supplemental Figure S1).

ChIP Tissue Preparation, Chromatin Immunoprecipitation, and Library Preparation

Brain tissue dissected from 5 animals was pooled and homogenization in PBS with protease inhibitor cocktail (PIC, Roche, Basel, Switzerland) using a motorized pestle. Homogenized cells were fixed in PBS with 1% formaldehyde for 10 minutes and the fixing reaction was stopped by addition of Glycine to 0.125M. Fixed cells were washed 3x with PBS+PIC to remove formaldehyde and resuspended in lysis solution – 50 mM Tris-HCl (pH 8.0), 2 mM EDTA, 0.1% v/v NP-40, 10% v/v glycerol, and PIC – for 30 minutes on ice. Cell debris was washed away with PBS with PIC. Nuclei were pelleted and flash-frozen on dry ice and stored until use. Frozen nuclei were thawed on ice in lysis solution (1% SDS, 10mM EDTA, 50mM Tris, pH 8.1 with protease inhibitor cocktail) and nuclei, counted using a hemocytometer, were sonicated at high power for 7 x 7 minute cycles (30 s on, 30 s off) in a Biorupter^{TM} UCD-200 (Diagenode, Liège, Belgium) sonicator. Remaining cellular debris was pelleted by centrifugation for 10 minutes at 13,000 x g.

Fragmented chromatin was processed for histone H3K27Ac ChIP (Abcam ab4729). One million nuclei were used for each IP. 25 μl of each IP was reserved for input samples. Technical replicate inputs were pooled to 50 μl. 2 ug of h3k27ac antibody was used for each IP. An additional wash in TE buffer was performed after the initial four IP washes. Chromatin was processed for ESRRA ChIP using a customized protocol. Sonicated samples were pre-incubated with Protein G Dynabeads (Invitrogen 10009D) for three hours. Beads were removed and 10 μg of ESRRA antibody (SC-66882, Santa Cruz Biotechnology, Dallas, TX, USA) was added overnight with rotation

at 4° C. Protein G beads were added for 3 hours to bind antibodies. Beads were washed with high salt, low salt, LiCl, and TE buffers for 5 minutes each in succession. Precipitated chromatin was eluted in ChIP elution buffer (1% SDS, 0.1 M NaHCO3) for 15 minutes twice in 25 μl. Samples were reverse cross-linked at 65° C with 1,300 rpm rotation overnight. Samples were phenol-chloroform extracted with standard methods and eluted into 20 μl of nuclease-free water.

After ChIP, immunoprecipitated DNA was quantified using a Qubit 2.0 (Life Technologies, Carlsbad, CA, USA) with a dsDNA HS Assay kit (Life Technologies #Q32854). Libraries were prepared using KAPA LTP library kits (KK8230), with protocol as written, using Bioo Scientific index adapters. Libraries were size selected using AmpureXP beads (Beckman Coulter, Brea, CA, USA), with protocol as written, selecting for DNA between 200-500bp in size. Library quality was checked by Qubit 2.0 and Bioanalyzer (Agilent 2100). Samples were sequenced with an Illumina HiSeq 2500 sequencer using a TruSeq SBS sequencing kit, version 4. All samples were sequenced in single end format with fragment length of 100 bp. Base calling and demultiplexing into FASTQ files was done using bcl2fastq v1.8.4 software (Illumina, San Diego, CA, USA).

ChIP-Seq Bioinformatics

Sequence data were mapped with Bowtie2 (Langmead and Salzberg 2012) to the UCSC *Mus musculus* mm9 genome, using default settings. Mapped sequence data were analyzed for peaks using HOMER (Hypergeometric Optimization of Motif EnRichment) v4.7 (Heinz et al. 2010). Samples were converted into tag directories, and QC was performed using read mapping and GC bias statistics. Histone peaks were then called from the Tag Directories with default factor settings, except local filtering was disabled (-L 0) and input filtering was set at three-fold over background (-F 3), to increase the sensitivity of the peak calling and identify individual subunits of multi-histone peaks. After peak calling, peak files were annotated to the mouse mm9 genome using HOMER's annotation script to assign peaks to genes, and associate peaks with differential expression data. BigWiggle pileup files were generated using HOMER's makeBigWig.pl script with default settings.

Differential chromatin peaks were identified using the HOMER getDifferentialPeak.pl script, looking for any peaks that changed at least two-fold between conditions with a significance cutoff of 1×10^{-4}. Differential peak sets were then annotated as previously described and using a custom R script to search for the nearest transcription start site on all Ensembl-annotated splice variants built using biomaRt. Genes annotated nearby differential H3k27ac peaks were submitted for GO analysis to DAVID and GREAT (Dennis et al. 2003; McLean et al. 2010).

The overlap between differential accessibility assayed by H3K27Ac ChIP-Seq and differential expression assayed by RNA-seq was assessed by using a hypergeometric test for list overlap, using as a background the intersection of expressed genes and all gene with nearby peaks in the ChIP-seq experiment (Supplemental Table S13A).

Cis Motif Analysis

We used the Stubb algorithm (Sinha et al. 2003) to identify sequence segments with significant presence of a TF binding motif (position weight matrix), scanning the genome with 500 bp windows with a 250 bp shift size. A tandem repeat masker (Benson 1999) was used prior to scanning the genome. Our motif collection included 129 PWMs from the JASPAR database (Portales-Casamar et al. 2010) and 239 non-redundant PWMs from (Jolma et al. 2013). The Stubb score of a window was compared to an empirical distribution of analogous scores from windows of similar G/C content, and converted to an empirical p-value. A gene promoter (5 kbp upstream and 2 kbp downstream of transcription start site) was scored by the minimum of empirical p-values assigned to windows within it. To incorporate accessibility information (captured by H3K27ac ChIP-seq data), we required that the motif score of a 500 bp window be considered only if the window is deemed "accessible" by the following criteria: we considered windows that either overlapped with identified H3K27Ac ChIP peaks, or were proximal to such peaks (separated by at most three windows from the peak) and had average read count above that from a corresponding input control experiment. All such windows were assigned scores equaling their average read count, and the resulting profile of genome-wide scores was smoothed as described in (Kazemian et al. 2013). Finally, windows scoring in the top 3 percentile were considered accessible.

The top 500 promoters (with an additional requirement that their Stubb empirical p-value is < 0.05) for each given motif were then identified, and the respective genes were the "motif target set." Hypergeometric tests were performed between each motif target set and each up- and down-regulated gene set. (Note that we incorporated accessibility information from the same time point and brain region as the DEG set, except for DEGs at 60 m for which we used accessibility at 30 m) Hypergeometric test p-values were subjected to an empirical FDR estimation to correct for multiple hypothesis testing (368 motifs tested for each DEG set). The Tomtom program (Gupta et al. 2007) was used to calculate the similarity between motifs in our collection. Motif pairs with a q-value below 0.25 were considered similar.

To test for cis motif enrichment in DAP-DEGs, we adapted the method above as follows: for each motif, the Stubb score p-value corresponding to the best-scoring 500 bp window that overlapped each DAP-DEG was assigned as the score of that DAP-DEG. The number of DAP-DEGs with scores < 0.05 were counted, and subjected to a Binomial test where the success probability parameter was learned from the frequency of such motif scores in size-matched background sequences that were sampled from gene deserts and did not contain the H3K27Ac mark.

Thick Slice CLARITY Immunohistochemistry

To assess the cellular and sub-cellular localization of specific transcription factors, we used a CLARITY protocol modified to work on 200 μM thick slices of brain (Chung et al. 2013). Male animals were transcardially perfused with 4% PFA and 1% acrylamide in PBS. Brains were extracted and fixed in the perfusion solution overnight at 4° C. The brains were embedded in 6% agarose and sectioned in 200 μm coronal or

sagittal slices on a vibrating microtome. Sections were fixed for an additional 3 hours in perfusion solution at 4° C before they were embedded in hydrogel under a vacuum at 37° C. After hydrogel embedding, tissue slices were cleared overnight using electrophoretic tissue clearing in 2% SDS. Cleared tissues were washed with PBS with Triton-X100, then incubated with primary antibodies (ERR-alpha: Santa Cruz sc-66882; CNPase: Millipore #MAB326) for three days. After three more washes, cleared tissues were incubated with Alexa Fluor secondary antibodies (Donkey anti rabbit, chicken against mouse) for three days before three washes in PBS with Triton-X100. The final wash included the nuclear counterstain Hoechst 33342. Cleared tissue slices were cleared in RIMS made from 70% Histodenz (Sigma #D2158) in PBS with Triton-X100 and mounted on lifter slides before being imaged on a Zeiss LSM 710 confocal microscope.

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