Figure Legends:

**Figure 1: Overview of the BrainSpan resource.** (a) The developmental timespan of the human brain, from embryonic ages (≤ 8 pcw), through fetal development, infancy, childhood, adolescence, and adulthood. The human brain grows in size and complexity until roughly 3 years of age (top panel), at which time development continues on a cellular, synaptic, and molecular levels. (b) Brain regions sampled for the BrainSpan resource include eleven regions of the neocortex, three additional regions of the cerebrum, and two additional regions, the thalamus and cerebellum. (c) Data modalities generated by the BrainSpan consortium, and accessible online at brainspan.org, include surveys of the transcriptome, key histone modifications, DNA methylation and the genome as well as *in situ* hybridization, histology, and high-resolution web-based reference atlases.

**Figure 2: The global transcriptional architecture of the human brain is driven by a broad perinatal transition.** (a) Distribution of samples across developmental windows. Prenatal samples are labeled in blue, postnatal samples are labeled in red, and the perinatal window, w5, is labeled in goldenrod. (b) Circular dendrogram plotting unsupervised hierarchical clustering shows samples from late fetal ages and early infancy (w5) cluster with postnatal samples (w6-9) rather than with prenatal samples (w1-4). (c) Principle component analysis (PCA) for samples from all brain regions at late midfetal ages (w4), late fetal ages and early infancy (w5), and early adulthood (w9) shows that interregional differences are generally reduced across a perinatal window before expanding again postnatally. (e) Distance vectors across the first two principal components show that the cerebellum is largely responsible for increased interregional diversity in postnatal samples. The perinatal window is highlighted in yellow. (f) PCA for neocortical areas shows a perinatal transition similar to that seen for all brain regions. (g) Distance vectors for neocortical samples show a stereotypical “hourglass” pattern. (h) Gene expression within brain regions correlates across early prenatal and late postnatal windows but not across a perinatal transition. (i) Gene co-expression modules also correlate across early prenatal and late postnatal windows but not across a perinatal transition. (j) Differences in the rate at which the transcriptome changes are greatest between midfetal and late fetal/early infancy (w4/5) in the neocortex and infancy/early childhood (w5/6) in the cerebellum. (k) The interwindow periods where co-expression modules experience the greatest shift are plotted as percentages of the total number of spatiotemporally distinct modules for each region. For all regions except the CBC, the vast majority of the most major transcriptional rearrangements are complete by the w4/5 transition.

**Figure 3: Sex-different gene expression is associated with both microglia and ASD.** (a) We found that 872 protein-coding genes were expressed at significantly higher levels in at least one sex for at least one developmental window, with 430 protein-coding genes expressed more highly only in males, 420 expressed more highly only in females, and 71 expressed to a significantly greater extent in both sexes at different developmental times. However, suggesting that sex-different gene expression is tightly spatiotemporally specific, only a small number of genes on chromosome Y and the *XIST* locus on chromosome X showed consistent and robust sex-different expression across all brain regions and developmental windows. (b) Modules enriched for sex-DEX gene expression include several modules (M3, M7, M33, M68) also enriched for glial or microglial markers. In contrast, neither M35 nor any other module enriched for neuron-specific gene expression exhibited male-high, sex-DEX gene expression. The sexual dimorphic expression of collagen genes mirrors that of the glial and microglial markers. Here again the perinatal window is highlighted in goldenrod. (c) Several gene sets associated with autism spectrum disorder show a depletion for genes identified in the BrainSpan resource as differentially expressed between males and females, as do several modules identified in postmortem ASD samples and enriched for markers for neurons. However, several modules enriched for glial-specific gene expression and either upregulated in postmortem ASD brain or associated with a module upregulated in postmortem ASD brain are enriched for sex-DEX genes (PMID 25494366; 2164001; 25752243; 25294932; 21784246).

**Figure 4: Regional patterns of gene expression in the human are more similar to those seen in macaque than in mouse.** (a) Evidence exists for regionally-specific patterns of expression for 6,083 genes in human and 4,099 genes in macaque. Of these, 3,113 orthologous genes exhibit regionally-specific expression patterns in both species. (b) Density plots showing the across-region correlation of all genes (dotted line) and DEX genes (solid lines) between human and macaque (left), human and mouse (center), and macaque and mouse (right). Most genes show consistent patterning (R >= 0.5) between different trios of human individuals (100 bootstrap iterations; grey dashed lines), while many more genes show consistent patterning between human and macaque than between either primate and mouse (inset pie charts). (c) SLC17A7 shows consistent regional differential expression across nine regions commonly annotated in mouse, macaque, and human datasets. (d,e) *In situ* hybridization of SLC17A7 expression in macaque (d) and mouse € shows high expression in excitatory neurons in macaque NCX and CBC and mouse NCX, CBC, and HIP. Insets show a magnified view of boxed region in macaque V2 and mouse visual cortex. (f) The expression pattern for *PDE1A* appears similar in both human datasets and in macaque, but the expression of *PDE1A* differs in mouse MD and CBC. (g,h) Additionally, while PDE1A is expressed in both macaque and mouse NCX, the expression of PDE1A in macaque is restricted to deep layers of the NCX (g) while expression is present in both deep and upper layers in mouse (h). (i) CRYM expression is distinct in human datasets as compared to mouse and macaque. (j,k) Laminar expression of CRYM appears conserved in NCX from both macaque (j) amd mouse (k). ISH for macaque from the NIH Blueprint Non-human Primate Atlas. ISH for mouse from the Allen Mouse Brain Atlas.

**Figure 5: Integrative analysis of BrainSpan resource provides key functional insights.** (a) Categories of methylation sites defined by whether the methylation of that site increases, decreases, or remains constant across prenatal and postnatal ages. (b) Plots of beta values showing representative methylation changes for up to 100 methylation sites in each category. (c) Distribution of average methylation levels for sites in these categories at prenatal and postnatal ages. (d) Enrichment of genomic, cell-type specific, and age-related features among categories of methylation sites show multi-modal trends as well as the potential utility of integrating BrainSpan datasets. For example, categories of methylation sites enriched for non-NUM sites also tend to be most enriched in introns, for adult enhancers, and for glial-selective genes. (e) Gene ontology terms enriched among these categories of methylation sites further supports the validity and utility of integration, with glial-associated methylation trajectories linked to ontological terms including myelination and CNS myelination while neuronal-linked trajectories are linked to terms including neurogenesis, regulation of neurogenesis, and neuron development, among others. (f) The presence of H3K27ac marks in fetal, infant, and adult samples correlates with patterns of gene expression suggesting these marks identify putatively active enhancers. (g) Gene ontology terms enriched among genes associated with putative fetal-active or fetal/infant-active enhancers (top half of g) include terms generally associated with nervous system development. Ontology terms enriched among putative infant/adult-active or adult-active enhancers (bottom half of g) include terms such as negative regulation of neurogenesis, glial cell development, myelination, synaptic transmission, and other terms more associated with later developmental ages and function.

**Figure 6: Regulatory elements identified in the BrainSpan resource are enriched, in disease-specific patterns, for loci associated with schizophrenia, bipolar disorder, and Parkinson’s Disease.** (a) H3K27ac peaks identified by the BrainSpan consortium are generally more enriched for SNPs implicated in genome-wide association studies on the neurological disorders schizophrenia, bipolar disease, and Parkinson’s disease than are putative enhancers identified from the liver, aorta, and other non-brain tissues. Conversely, H3K27ac peaks identified in this study are less likely to intersect with SNPs associated with Type 2 diabetes, coronary artery disease, and asthma than are similar peaks identified in non-brain tissues or cell types. (b) Putative super enhancers show patterns of enrichment for disease-associated loci similar to the patterns seen for enhancers. (c) Several categories of methylation sites exhibiting methylation trajectories described in Figure 6 are enriched for SNPs associated with neurological disorders, including two associated with glia and several enriched for sites that are hypermethylated in centenarians.

**EDF 1: Regions collected for analysis by the BrainSpan consortium.**  (a) Schematic showing an adult brain as well as regions dissected to procure the samples indicated. (b) Similar schematic for a generic fetal brain. Region color is coded to that used in Figure 2.

**EDF 2: Basic characteristics of the transcriptome in the human brain.** (a)

**EDF 3: Basic characteristics of methylation in the human brain.**  (a) Distribution of methylation levels at the sites assayed in this survey. Most methylation sites were either highly (Beta-value greater than 0.8) or lowly (less than 0.2) methylated. (b) Principle Component Analysis of methylation in the postnatal human brain suggests interregional differences and sex-specific differences drive the first two components. Prenatal samples were not included in this analysis, so the influence of developmental age is likely minimal among these samples. (c) Heatmap showing the z-score for 1,000 randomly selected methylation sites. The distinct nature of the cerebellum is easily apparent, as is the relative similarity of neocortical regions, with V1C, A1C, and STC the most distinct of those regions. Other non-neocortical regions cluster separately both from the NCX and CBC. (d) Column graph representing the proportions of genomic features of all CpG sites assayed and the proportion of assayed CpG sites exhibiting various levels of methylation (Beta-value ranges from 0 to 0.2, 0.2 to 0.4, 0.4 to 0.6, 0.6 to 0.8, and 0.8 to 1.0). GENCODE v21 annotation was used to define genomic regions, with TSS defined for this figure as the region within 1 kb of the known transcription start site. (e,f) Distribution of the DNA methylation signal near transcription start sites (e) and relative to gene bodies (f), as related to gene expression as indicated by RPKM. Genes were grouped by expression level calculated from RNA-seq data in the BrainSpan resource.

**EDF 4: Basic characterics of key histone modifications in the human brain.** (a,f,k,p) Pie chart representing the proportions of genomic features where the histone modifications H3K4me3, H3K27me3, H3K27ac, and CTCF binding sites are present. (b-s) Distribution of the respective histone modification or CTCF binding signals relative to transcription start sites, gene bodies, and transcription end sites as these data relate to gene expression. (rest) Relationships between regional enrichment of histone modification and gene expression. Regional enrichment values were calculated by subtracting the signal for each mark in the CBC from the signal observed in DFC, divided by the total signal in DFC + CBC + 1. (last) Heatmap showing regional enrichment of expression as it relates to all histone marks observed. Genes were ordered by the regional enrichment of expression, with the expected positive trends observed for H3K4me3 and H3K27ac and the expected inverse trend for H3K27me3.

**EDF 5: Multidimensional scaling suggests samples fall into two broad clusters, with perinatal samples bridging the divide.** (a) Samples collected during each window (w1-w9) are colored by their brain region of origin. A sample from any given region is more similar to any other sample within the same developmental cluster than it is to a sample from the same region across the perinatal divide. For example, DFC and CBC samples collected during w3 are more similar to each other than DFC from w3 is to DFC from w8 or CBC from w3 is to CBC from w8. (b) MDS plot showing relationships between prenatal (w1-4), perinatal (w5), and postnatal (w6-9) samples, following the coloring scheme first described in Figure 2. Perinatal samples (w5) tend to cluster either between other prenatal and postnatal samples or towards the greater postnatal cluster.

**EDF 6: Brain regions rely on temporal-DEX gene expression across the perinatal transition.** a) Of protein-coding genes, a total of 10,825 were differentially expressed between at least two brain regions (spatial-DEX), 13,485 were differentially expressed within at least one brain region across any two time points (temporal-DEX), and 10,371 were both temporally and spatially regulated in the BrainSpan dataset. Here the presence of temporal-DEX (orange), spatial-DEX (blue), and both temporal and spatial-DEX genes (green) are plotted for each brain region and developmental window. Each cell includes the number of temporal-DEX genes as compared to any cell for that brain region/neocortical area and the number of spatial-DEX genes as compared to any region/area for that developmental window. B) Distribution of temporal-DEX genes across brain regions and neocortical areas. C) Distribution of spatial-DEX genes across developmental time.

**EDF 7: Whole genome co-expression network analysis (WGCNA) identified 73 co-expression modules.** WGCNA identified 73 modules of co-expressed genes, with regional eigengenes plotted for each modules using the color scheme present in Figure 2. Blue = NCX, light blue = HIP, green = AMY, purple = STR, orange = MD, and red = CBC. Time from conception, in days, is plotted using a log2 scale on the X-axis, with the solid vertical line showing birth. The Y-axis shows gene expression in arbitrary units.

EDF 8: a/b) Identification of cell-type specific genes. c/d) WGCNA modules enriched for assorted cell-type specific genes.