Supplementary Figure 1

Effects of nicotine exposure from birth to 3 weeks of age on dendritic complexity across cortical regions assessed at 3 months of age.

(a-c) Sholl analysis of the apical dendritic tree in frontal (F), parietal (P) and occipital (O) regions of cortex. Exposure to nicotine in the postnatal period significantly increased dendritic complexity across cortical regions. (a) $F(1,80)=6.901$, $p=0.010321$. (b) $F(1,30)=16.525$, $p=0.0000001$. (c) $F(1,65)=32.586$, $p=0.000319$. (d-f) Layer-specific effects of postnatal-only nicotine exposure on dendritic complexity in superficial (1/2), intermediate (3/4) and deep (5/6) layers of cortex. (d) $F(1,20)=5.625$, $p=0.027854$. (e) $F(1,46)=13.719$, $p=0.000565$. (f) $F(1,23)=10.746$, $p=0.003299$, * $p<0.05$. F: Sac, n=28; Nic, n=54; P: Sac, n=36; Nic, n=31; O: Sac, n=20; Nic, n=12; 1/2: Sac, n=9; Nic, n=13; 3/4: Sac, n=18, Nic, n=30; 5/6: Sac, n=10. Nic, n=15.
Supplementary Figure 2

Volcano plot showing all probe sets evaluated in the microarray study.

(a) Genes whose expression levels were significantly different between developmentally nicotine exposed animals and controls are shown as red dots. (b) 6 of 15 probe sets were significantly altered in independent samples at 3 months of age following nicotine treatment throughout the pre- and postnatal period compared to the control group: $F(1,8)=7.77$ for Ash2l, $p=0.02365035$; $F(1,8)=6.797$ for Chsy3, $p=0.03127061$; $F(1,8)=0.64$ for Zfp91, $p=0.44681333$; $F(1,8)=0.41$ for Cllar, $p=0.5987164$; $F(1,8)=26.538$ for Zcchc11, $p=0.00087271$; $F(1,8)=5.18$ for Cep192, $p=0.05240060$; $F(1,8)=1.24$ for Alkbh1, $p=0.29780695$; $F(1,8)=0.72$ for Gmeb1, $p=0.42080639$; $F(1,8)=0.36$ for Unc13b, $p=0.56511006$; $F(1,8)=0.035$ for Duox1, $p=0.85625319$; $F(1,8)=8.82$ for Scula2, $p=0.01787528$; $F(1,8)=1.84$ for Zip597, $p=0.21198878$; $F(1,8)=1.18$ for Ctnnal1, $p=0.30899997$; $F(1,8)=0.65$ for Ntrk, $p=0.44341660$; $F(1,8)=7.397$ for Tmem107, $p=0.02625917$. (* $p<0.05$, ** $p<0.01$ with Sidak’s test; # $p<0.05$ with LSD test for multiple comparisons). 2 to 4 animals were pooled for each biological replicate. Five Biological replicates were used for each condition (Sac: $n=5$; Nic: $n=5$). A total of 26 animals were used (Sac: $n=14$; Nic: $n=12$).
Changes in H3K4me3 associated with the promoter sites of multiple gene loci following developmental nicotine exposure.

(a) Gene ontology (GO) analysis identified significantly regulated gene groups, all of which are related to glutamatergic synaptic function. (b) Gene structure and coordination of Ank1 loci associated with H3K4me3 depicted in Fig. 3c. (c) Whisker plot showing verification of changes in histone H3Me3K4 levels associated with gene loci identified in the ChIP-seq analysis by ChIP-PCR in independent samples from subjects treated with nicotine from birth to 21 days (postnatal-only) and evaluated at 3 months of age: F(1,8) = 11.02 for Eif4a, p = 0.01054575; F(1,8) = 6.028 for Izumo1, p = 0.03961426; F(1,8) = 1.406 for Gpr19, p = 0.26974334; F(1,8) = 21.7 for Litaf, p = 0.00162698; F(1,8) = 15.839 for kcnq1, p = 0.00406270; F(1,8) = 19.147 for Lage3, p = 0.00236227; F(1,8) = 17.512 for Fbxw4, p = 0.00305973; F(1,8) = 16.594 for Fgfl2, p = 0.00356573; F(1,8) = 77.18 for Sepsec, p = 0.00002212; F(1,8) = 9.979 for Rin2, p = 0.01341607; F(1,8) = 64.634 for Rabbgp1l, p = 0.00004215; F(1,8) = 81.61 for Apc, p = 0.0001803; F(1,8) = 17.505 for Apol, p = 0.00306323; F(1,8) = 99.602 for Lpc, p = 0.00000862; F(1,8) = 45.502 for Cdk5rap2, p = 0.0014572; F(1,8) = 565.869 for Ing4, p = 0.00000091; F(1,8) = 118.256 for Ank3, p = 0.00000452; F(1,8) = 43.276 for Ntm, p = 0.00017324; F(1,8) = 487.52 for Zfp658, p = 0.00000002; F(1,8) = 8.77 for Ybx3, p = 0.01810693; F(1,7) = 41.57 for Sorcs1, p = 0.00019884; F(1,8) = 153.564 for Lar2, p = 0.00000168; F(1,8) = 50.843 for Ank1, p = 0.00009898; F(1,8) = 242.093 for Acacb, p = 0.00000092; F(1,8) = 223.283 for Mdaa2, p = 0.00000040; F(1,8) = 110.84 for Chl1, p = 0.00000592; F(1,8) = 23.981 for Autos2, p = 0.00119824; F(1,8) = 483 for Mbn1, p = 0.50674655; F(1,8) = 10.846 for Cpeb1, p = 0.01096747; F(1,8) = 15.121 for Zfp65, p = 0.00461852; F(1,8) = 5.928 for Chd9, p = 0.0489817; F(1,8) = 24.034 for Syl1, p = 0.00119008; F(1,8) = 7.836 for Sp110, p = 0.02322340; F(1,8) = 51.276 for Sorbs2, p = 0.00009607; F(1,8) = 24.889 for Slc35a2, p = 0.00106755; F(1,8) = 19.501 for Met2c, p = 0.00238483 (*p < 0.05 with LSD test for multiple comparisons). Each replicate was a pool of 2-4 brain samples and 5 replicates were used for each condition (Sac: n = 5 pools from 14 animals; Nic: n = 5 pools from 12 animals). (d) Ash2l and Met2c binding sites overlap with sites of H3K4me3 enrichment. Among these, GO analysis of 106 genomic sites identified as differentially enriched following nicotine exposure reveals that overlapped genomic sites are associated with synapse related functions.
Supplementary Figure 4

Regulation of Mef2c locus by nicotine treatment in vivo.

(a) Mef2c mRNA levels were significantly elevated at 21 days of age, immediately after nicotine exposure was completed $F(1,8)=19.237, p=0.00232999$. 5 Biological replicates per each condition from pooled female animals; Nic = 11 Sac = 15. (b) Histone H3 acetylation associated with the Mef2c locus was significantly increased as a result of nicotine exposure during development $F(1,8)=118.802, p=0.00000445$. 5 Biological replicates per each condition from pooled female animals; Nic = 12 Sac = 12. (c) Nicotine exposure during development significantly increased the level of H3K4me3 associated with the Mef2c locus ($F(5,24)=10.403, p=0.000021$) with Tukey’s multiple comparison test. Frontal sac vs Frontal nic, $p=0.001277$; Parietal sac vs Parietal nic, $p=0.005846$; Occipital sac vs Occipital nic, $p=0.011952$. 5 Biological replicates per each condition from pooled female animals; Nic = 12 Sac = 12.

* $p < 0.05$, *** $p < 0.001$ with dk’s test.
Supplementary Figure 5

Evaluation of shRNA-mediated knock down of Ash2l and Mef2c protein levels in neural progenitor cells.

a) shRNA targeting Ash2l. b) shRNA targeting Mef2c. Original Western blots presented in Supplementary Figure 7.
Supplementary Figure 6

Spread following in utero electroporation.

Example of the extent of shRNA spread and of GFP expression in a layer 6 cortical pyramidal neuron following in utero electroporation of shRNAs.
Supplementary Figure 7

Original images of representative western blot images in Figure 4 and Supplementary Figure 5.

(a-d) indicate uncropped LICOR machine scanned gel image with annotation. (e) Scanned film image of Figure 4 immunoprecipitation experiment. (f-g) Nicotine induced Wdr5 and Rbbp5 expression blot: original scanned image from LICOR machine. (i-j) Scanned images from LICOR machine for shRNA knockdown efficiency experiment presented in Supplementary Figure 5.
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Nature Neuroscience: doi:10.1038/nn.4315
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Supplementary Table 1. 39 common gene loci identified from pre & postnatal nicotine and postnatal nicotine treated group (adj.p<0.05)
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**Supplementary Table 2.** 73 common gene loci identified from pre & postnatal nicotine and postnatal nicotine treated group (adj.p<0.05)

*Nature Neuroscience: doi:10.1038/nn.4315*
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<th>GO:0044456~synapse part</th>
<th>GO:0014069~postsynaptic density</th>
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Supplementary Table 3. Significant Gene Ontology Groups for H3MeK4 sequencing data of tissue from pre- and postnatal nicotine treated subjects.
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Supplementary Table 4. Significant Gene Ontology Groups for H3MeK4 sequencing data of tissue from postnatal-only nicotine treated subjects.

Nature Neuroscience: doi:10.1038/nn.4315
### ChIP-PCR primers (H3K4me3)

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### ChIP-PCR primers (Control GAPDH H3K4me3)

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ChIP-PCR primers (Acetylation)

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qRT-PCR primer list

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pAAV-shRNA cloning primer

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<tbody>
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Supplementary Table 5. Primer list used in ChIP-PCR, qRT-PCR, and cloning