Table S1. Statistical analyses. Related to Figures 1 and 2.

Figure 1	Textured NORT	1 Hour Ret.	tPPI	Air Puff Alone	Open Field Time in Center	EPM Time in Open Arms	EPM Total Arm Crosses	Habituation to Startle Noise	Marble Burying	Sociability	Social Novelty Preference	Grooming
$Shank3B^{+/+}$ (control) vs $ShankB^{+/-}$	N = 17, 16	N = 17, 17	N = 31, 37	N = 31, 37	N = 14, 10	N = 11, 12	N = 11, 12	N = 31, 37	N = 8, 10	N = 18, 14	N = 18, 14	N = 8, 10
	p = 0.0190	p = 0.0486	p = 0.0029	p = 0.0083	p = 0.0091	p = 0.0125	p = 0.9477	p = 0.0068	p < 0.0001	p = 0.0237	p = 0.0110	p = 0.0016
$Shank3^{f/+}$ (control) vs $Cdx2^{Cre}$; $Shank3^{f/+}$	N = 13, 13	N = 11, 13	N = 11, 13	N = 11, 13	N = 11, 13	N = 11, 13	N = 11, 13	N = 11, 13	N = 13, 12	N = 13, 13	N = 13, 13	N = 11, 11
	p = 0.0437	p = 0.7919	p = 0.0145	p = 0.0172	p = 0.0286	p = 0.0174	p = 0.2810	p = 0.0327	p = 0.0471	p = 0.0447	p = 0.0458	p = 0.1925
$Shank3^{f/+}$ (control) vs $Advillin^{Cre}$; $Shank3^{f/+}$ vs $Advillin^{Cre}$; $Shank3^{f/f}$	N = 37, 20, 9	N = 34, 26, 9	N = 30, 25, 9	N = 30, 25, 9	N = 38, 25, 9	N = 34, 20, 9	N = 34, 20, 9	N = 30, 25, 9	N = 34, 21, 9	N = 36, 26, 9	N = 36, 26, 9	N = 8, ---, 9
	F(2,63)=5.826	F(2,66)=0.3597	F(2,61)=6.812	F(2,61)=5.44	F(2,69)=8.502	F(2,60)=8.807	F(2,60)=0.153	F(2,61)=9.049	F(2,61)=4.324	F(2,68)=16.36	F(2,68)=12.11	p = 0.3436
	P = 0.0048	P = 0.6993	P = 0.0021	P = 0.0067	P = 0.0005	P = 0.0004	P = 0.8583	P = 0.0004	P = 0.0165	P < 0.0001	P < 0.0001	
$Mecp2^{f/+ \text{ or } f/y}$ (control) vs $Advillin^{Cre}$; $Mecp2^{f/+}$ vs $Advillin^{Cre}$; $Mecp2^{f/y}$	N = 35, 20, 18	N = 33, 17, 18	N = 41, 24, 20	N = 41, 24, 20	N = 38, 20, 20	N = 32,13,11	N = 32,13,11	N = 41, 24, 20	N = 26, 11, 16	N = 33, 24, 20	N = 33, 24, 20	N = 9, ---, 7
	F(2,70)=5.996	F(2,65)=0.4695	F(2,82)=5.104	F(2,82)=6.226	F(2,75))=16.5	F(2,53)=12.02	F(2,53)=0.214	F(2,82)=6.391	F(2,50)=4.219	F(2,62)=11.73	F(2,62)=18.8	p = 0.4667
	P = 0.0039	P = 0.6274	P = 0.0081	P = 0.0030	P < 0.0001	P < 0.0001	P = 0.8083	P = 0.0026	P = 0.0203	P < 0.0001	P < 0.0001	
$Shank3^{+/+}$ (control) vs $Shank3^{FX/+}$ vs $Cdx2^{Cre}$; $Shank3^{FX/+}$	N = 22, 24, 23	N = 24, 24, 29	N = 22, 21, 26	N = 22, 21, 26	N = 21, 24, 22	N = 22, 23, 22	N = 22, 23, 22	N = 22, 21, 26	N = 21, 18, 21	N = 21, 25, 29	N = 21, 25, 29	N =21, 26, 29
	F(2,66)=4.231	F(2,74)=3.924	F(2,66)=6.496	F(2,66)=4.316	F(2,64)=5.694	F(2,64)=6.679	F(2,64)=0.914	F(2,66)=3.488	F(2,57)=10.4	F(2,72)=10.25	F(2,72)=5.61	F(2,73)=7.824
	P = 0.0187	P = 0.0240	P = 0.0027	P = 0.0173	P = 0.0053	P = 0.0023	P = 0.4061	P = 0.0363	P = 0.0001	P = 0.0001	P = 0.0055	P = 0.0008
$Shank3^{+/+}$ (control) vs $Shank3^{FX/+}$ vs $Advillin^{Cre}$; $Shank3^{FX/+}$	N = 25, 26, 22	N = 26, 25, 25	N = 26, 29, 25	N = 26, 29, 25	N = 26, 28, 26	N = 21, 22, 16	N = 21, 22, 16	N = 26, 29, 25	N = 22, 25, 19	N = 26, 29, 24	N = 26, 29, 24	N = 24, 28, 19
	F(2,70)=4.589	F(2,73)=1.631	F(2,77)=7.408	F(2,77)=7.184	F(2,77)=4.49	F(2,56)=5.105	F(2,56)=1.861	F(2,77)=3.19	F(2,63)=11.83	F(2,75)=4.385	F(2,75)=5.208	F(2,68)=4.709
	P = 0.0134	P = 0.2027	P = 0.0011	P = 0.0014	P = 0.0143	P = 0.0092	P = 0.1649	P = 0.0466	P < 0.0001	P = 0.0158	P = 0.0076	P = 0.0122
$HCN1^{+/+}$ (control) vs $HCN1^{+/-}$ vs $HCN1^{-/-}$	N = 16, 14, 6	N = 16, 14, 6	N = 16, 14, 6	N = 16, 14, 6	not determined (n.d.)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	F(2,33)=7.604	F(2,33)=6.308	F(2,33)=7.064	F(2,33)=0.2048	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	P = 0.0028	P = 0.0048	P = 0.0028	P = 0.8158	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

Figures 2D-F and R-V	PV+ Neuron #, S1	PV+ Neuron #, V1	PV+ Neuron #, BLA	E/I Ratio (S1 and V1)	Event Frequency, S1	Event Frequency, V1	Event Amplitude, S1	Event Amplitude, V1	**Figures 2I-K**	PV+ Neuron #, S1	PV+ Neuron #, V1	PV+ Neuron #, BLA
$Shank3^{f/+}$ (control) vs $Advillin^{Cre}$; $Shank3^{f/+}$	N = 6, 6	N = 6, 6	N = 6, 6	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	$Shank3^{+/+}$ (control) vs $Shank3^{FX/+}$ vs $Advillin^{Cre}$; $Shank3^{FX/+}$	N = 4, 4, 4	N = 4, 4, 4	N = 4, 4, 4
	p = 0.0115	p = 0.5561	p = 0.0012	F(1,12)=6.254	F(1,12) = 4.698	F(1,12)=0.0030	F(1,12)=9.572	F(1,12)=0.0739		F(2,9)=6.206	F(2,9)=5.794	F(2,9)=6.945
				P = 0.0254	P = 0.0459	P = 0.9569	P = 0.0093	P = 0.7904		P = 0.0202	P = 0.0241	P = 0.0150
$Mecp2^{f/+ \text{ or } f/y}$ (control) vs $Advillin^{Cre}$; $Mecp2^{f/y}$	N = 5, 4	N = 5, 4	N = 5, 4	N = 5, 4	N = 5, 4	N = 5, 4	N = 5, 4	N = 5, 4	$Mecp2^{f/y}$ (control) vs $Mecp2^{STOP/y}$ vs $Advillin^{Cre}$; $Mecp2^{STOP/y}$	N = 4, 5, 4	N = 4, 5, 4	N = 4, 5, 4
	p = 0.0380	p = 0.5726	p = 0.0108	N(1,14)=5.776	F(1,14) = 6.822	F(1,14)=0.3446	F(1,14)=1.736	F(1,14)=0.3476		F(2,10)=30.95	F(2,10)=4.833	F(2,10)=7.180
				P = 0.0296	P = 0.0205	P = 0.5654	P = 0.2088	P = 0.5648		P < 0.0001	P = 0.0340	P = 0.0117

Table S2. Time spent per compartment in the three chamber social interaction test (seconds). Related to Figure 1.

	Novel Mouse	Novel Object	Center	Pref. for novel mouse	Novel Mouse	Familiar Mouse	Center	Pref. for novel mouse
Control (n = 18)	298.27 +/-15.70	232.95 +/- 13.01	68.76 +/- 8.26	Yes p = 0.0044	301.41 +/- 16.63	220.12 +/- 17.69	78.43 +/- 9.72	Yes p = 0.0010
$Shank3B^{+/-}$ (n=14)	259.26 +/- 18.38	272.32 +/- 18.32	68.38 +/- 17.16	No p = 0.8332	262.77 +/- 24.67	258.38 +/- 23.28	78.81 +/- 17.39	No p = 0.9839
Control (n=13)	320.14 +/- 20.70	229.85 +/- 16.07	50.01 +/- 5.52	Yes p = 0.0002	302.08 +/- 22.70	225.07 +/- 20.20	72.85 +/- 8.79	Yes p = 0.0093
$Cdx2^{Cre}$; $Shank3^{f/+}$ (n = 13)	296.29 +/- 19.2	249.12 +/- 16.43	54.56 +/- 7.80	No p = 0.0826	283.41 +/- 15.03	250.77 +/- 16.05	65.82 +/- 6.72	No p = 0.4217
Control (n = 36)	318.59 +/- 7.61	229.55 +/- 7.95	51.83 +/- 3.51	Yes p < 0.0001	302.31 +/- 10.59	233.82 +/- 10.46	63.87 +/- 4.38	Yes p < 0.0001
$Advillin^{Cre}$; $Shank3^{f/+}$ (n = 26)	286.31 +/- 13.00	258.17 +/- 12.72	55.51 +/- 3.75	No p = 0.0957	275.71 +/- 17.50	258.88 +/- 18.17	65.37 +/- 7.11	No p = 0.6429
$Advillin^{Cre}$; $Shank3^{f/f}$ (n = 9)	271.12 +/- 21.95	248.43 +/- 23.47	80.40 +- 12.17	No p = 0.5463	250.53 +/- 24.67	277.25 +/- 29.16	72.22 +/- 16.79	No p = 0.6647
Control (n = 33)	292.60 +/- 9.63	219.51 +/- 8.59	87.79 +/- 6.22	Yes p < 0.0001	300.86 +/- 13.57	220.08 +/- 10.79	79.05 +/- 4.45	Yes p < 0.0001
$Advillin^{Cre}$; $Mecp2^{f/+}$ (n = 24)	264.45 +/- 12.41	243.93 +/- 12.20	90.95 +/- 9.22	No p = 0.5892	260.96 +/- 9.83	244.33 +/- 10.15	94.69 +/- 7.15	No p = 0.5861
$Advillin^{Cre}$; $Mecp2^{f/y}$ (n = 20)	265.88 +/- 9.71	270.10 +/- 8.46	64.02 +/- 10.94	No p = 0.9517	236.62 +/- 16.53	264.85 +/- 21.73	98.53 +/- 14.45	No p = 0.3159
Control (n = 21)	315.54 +/- 10.12	233.93 +/- 10.08	50.53 +/- 5.27	Yes p < 0.0001	299.85 +/- 16.41	233.89 +/- 16.86	66.26 +/- 8.22	Yes p = 0.0102
$Shank3^{FX/+}$ (n = 25)	267.10 +/- 15.00	275.67 +/- 15.30	57.22 +/- 4.28	No p = 0.8334	264.64 +/- 15.83	253.43 +/- 12.56	81.89 +/- 7.41	No p = 0.8429
$Cdx2^{Cre}$; $Shank3^{FX/+}$ (n = 29)	304.00 +/- 10.74	243.52 +/- 11.61	52.48 +/- 3.85	Yes p < 0.0001	278.90 +/- 17.34	249.11 +/- 19.26	71.98 +/- 7.43	No p = 0.2631
Control (n = 26)	308.01 +/- 11.38	253.89 +/- 11.24	38.10 +/- 4.87	Yes p = 0.0043	307.56 +/- 15.49	234.56 +/- 15.06	57.87 +/- 5.50	Yes p = 0.0007
$Shank3^{FX/+}$ (n = 29)	279.66 +/- 17.66	276.31 +/- 18.40	44.03 +/- 3.72	No p = 0.9761	275.36 +/- 17.66	260.55 +/- 17.30	64.08 +/- 7.82	No p = 0.7030
$Advillin^{Cre}$; $Shank3^{FX/+}$ (n = 24)	304.88 +/- 10.25	250.61 +/- 10.03	44.51 +/- 4.01	Yes p = 0.0064	294.60 +/- 14.00	244.51 +/- 14.63	60.88 +/- 7.86	Yes p = 0.0380

Table S3. Time spent per compartment in the three chamber social interaction test (seconds). Related to Figure 3.

	Novel Mouse	Novel Object	Center	Pref. for novel mouse	Novel Mouse	Familiar Mouse	Center	Pref. for novel mouse
Control (TAM P5, n = 13)	349.62 +/- 16.86	206.53 +/- 14.34	43.80 +/- 5.79	Yes $p < 0.0001$	322.74 +/- 15.59	230.75 +/- 12.99	46.51 +/- 5.33	Yes $p < 0.0001$
$Advillin^{CreERT2}$; $Shank3^{f/+}$ (TAM P5, n = 15)	286.43 +/- 19.87	249.20 +/- 19.90	64.37 +/- 9.48	No $p = 0.1944$	275.27 +/- 19.37	257.81 +/- 20.95	66.92 +/- 7.10	No $p = 0.6809$
Control (TAM P10, n = 21)	303.06 +/- 10.55	226.48 +/- 8.99	70.46 +/- 5.79	Yes $p < 0.0001$	289.51 +/- 10.38	222.13 +/- 9.50	88.36 +/- 6.40	Yes $p < 0.0001$
$Advillin^{CreERT2}$; $Shank3^{f/+}$ (TAM P10, n = 15)	271.91 +/- 16.14	239.42 +/- 16.49	88.67 +/- 8.89	No $p = 0.1413$	250.75 +/- 16.59	247.23 +/- 16.91	102.02 +/- 9.15	No $p = 0.9782$
Control (TAM P28, n = 19)	344.57 +/- 14.61	200.88 +/- 12.22	54.54 +/- 5.06	Yes $p < 0.0001$	307.33 +/- 14.13	221.20 +/- 13.32	71.47 +/- 6.20	Yes $p < 0.0001$
$Advillin^{CreERT2}$; $Shank3^{f/+}$ (TAM P28, n = 11)	282.90 +/- 16.43	228.27 +/- 19.03	88.83 +/- 8.00	Yes $p = 0.0321$	268.47 +/- 21.98	255.38 +/- 18.22	76.14 +/- 8.23	No $p = 0.8342$
Control (TAM P5, n =14)	340.81 +/- 6.10	217.48 +/- 8.16	41.71 +/- 10.47	Yes $p < 0.0001$	347.97 +/- 24.46	182.43 +/- 20.13	69.59 +/- 6.94	Yes $p < 0.0001$
$Advillin^{CreERT2}$; $Mecp2^{f/y}$ (TAM P5, n = 10)	265.07 +/- 10.00	254.04 +/- 15.60	80.89 +/- 8.90	No $p = 0.7007$	271.75 +/- 14.27	232.13 +/- 15.78	96.12 +/- 2.59	No $p = 0.3015$
Control (TAM P10, n = 28)	315.17 +/- 12.39	215.41 +/- 11.61	69.43 +/- 8.84	Yes $p < 0.0001$	295.56 +/- 11.41	233.80 +/- 12.50	70.64 +/- 6.46	Yes $p = 0.0004$
$Advillin^{CreERT2}$; $Mecp2^{f/y}$ (TAM P10, n = 19)	293.58 +/- 12.40	239.46 +/- 13.44	66.95 +/- 9.35	Yes $p = 0.0108$	243.66 +/- 15.43	279.71 +/-17.94	76.64 +/- 6.13	No $p = 0.9980$
Control (TAM P28, n = 19)	294.83 +/- 7.72	221.32 +/- 8.27	83.85 +/- 6.45	Yes $p < 0.0001$	278.09 +/- 9.62	218.26 +/- 9.30	103.65 +/- 7.45	Yes $p = 0.0029$
$Advillin^{CreERT2}$; $Mecp2^{f/y}$ (TAM P28, n = 15)	271.80 +/- 13.30	233.79 +/- 11.70	94.41 +/- 13.82	Yes $P = 0.0355$	258.26 +/- 19.11	250.20 +/- 22.49	91.54 +/- 9.97	No $p = 0.9133$
Control (TAM P28, n = 27)	311.54 +/- 8.03	228.78 +/- 7.46	59.66 +/- 5.10	Yes $p < 0.0001$	321.87 +/- 12.15	200.02 +/- 9.20	78.10 +/- 6.71	Yes $p < 0.0001$
$Shank3^{FX/+}$ (TAM P28, n = 16)	288.40 +/- 23.65	261.07 +/- 21.29	50.52 +/- 5.20	No $p = 0.3343$	269.44 +/- 25.01	242.85 +/- 21.55	87.70 +/- 22.80	No $p = 0.5104$
$Advillin^{CreERT2}$; $Shank3^{FX/+}$ (TAM P28, n = 10)	322.14 +/- 18.54	209.10 +/- 24.33	68.76 +/- 8.48	Yes $p < 0.0001$	261.30 +/- 24.87	238.59 +/- 22.72	100.11 +/- 12.60	No $p = 0.7423$
Control (TAM P28, n = 23)	306.43 +/- 12.56	195.60 +/- 12.48	97.97 +/- 8.83	Yes $p < 0.0001$	287.16 +/- 18.43	220.98 +/- 15.86	91.86 +/- 7.81	Yes $p < 0.0014$
$Mecp2^{STOP/y}$ (TAM P28, n = 13)	266.50 +/- 20.00	241.09 +/- 17.69	92.41 +/- 11.19	No $p = 0.5220$	225.78 +/- 25.47	256.42 +/- 32.13	117.78 +/- 30.65	No $p = 0.6635$
$Advillin^{CreERT2}$; $Mecp2^{STOP/y}$ (TAM P28, n = 10)	330.98 +/- 20.74	203.65 +/- 21.45	65.38 +/- 21.45	Yes $p < 0.0001$	267.65 +/- 37.29	239.57 +/- 36.78	92.78 +/- 37.43	No $p = 0.7678$

Table S4. Statistical analyses. Related to Figures 3 and S3

	Textured NORT	1 Hour Ret.	tPPI	Air Puff Alone	Open Field Time in Center	EPM Time in Open Arms	EPM Total Arm Crosses	Habituation to Startle Noise	Marble Burying	Sociability	Social Novelty Preference
$Shank3^{f/+}$ (control) vs $Advillin^{CreERT2}$; $Shank3^{f/+}$ (TAM P5)	N = 8, 15	N = 8, 15	N = 10, 15	N = 10, 15	N = 8, 14	N = 13, 15	N = 13, 15	N = 13, 15	N = 12, 15	N = 13, 15	N = 13, 15
	p = 0.0319	p = 0.9657	p = 0.0126	p = 0.0306	p = 0.0024	p = 0.0007	p = 0.6128	p = 0.0057	p = 0.0483	p = 0.0004	p = 0.0007
$Shank3^{f/+}$ (control) vs $Advillin^{CreERT2}$; $Shank3^{f/+}$ (TAM P10)	N = 20, 14	N = 17, 14	N = 20, 14	N = 20, 14	N = 25, 14	N = 17, 11	N = 17, 11	N = 23, 14	N = 23, 14	N = 21, 15	N = 21, 15
	p = 0.0128	p = 0.9789	p = 0.0294	p = 0.0362	p = 0.0489	p = 0.0189	p = 0.6092	p = 0.5227	p = 0.0070	p = 0.0219	p = 0.0013
$Shank3^{f/+}$ (control) vs $Advillin^{CreERT2}$; $Shank3^{f/+}$ (TAM P28)	N = 20, 14	N = 17, 14	N = 20, 14	N = 20, 14	N = 21, 14	N = 21, 11	N = 21, 11	N = 19, 11	N = 18, 11	N = 19, 11	N = 19, 11
	p = 0.0292	p = 0.9122	p = 0.0126	p = 0.0115	p = 0.1732	p = 0.1144	p = 0.2031	p = 0.8368	p = 0.6816	p = 0.1592	p < 0.0001
$Mecp2^{f/y}$ (control) vs $Advillin^{CreERT2}$; $Mecp2^{f/y}$ (TAM P5)	N = 14, 10	N = 14, 10	N = 14, 10	N = 14, 10	N = 14, 10	N = 14, 10	N = 14, 10	N = 14, 10	N = 14, 10	N = 14, 10	N = 14, 10
	p = 0.0074	p = 0.7196	p = 0.0021	p = 0.0010	p = 0.0026	p < 0.0001	p = 0.3922	p = 0.0012	p = 0.0010	p = 0.0004	p < 0.0001
$Mecp2^{f/y}$ (control) vs $Advillin^{CreERT2}$; $Mecp2^{f/y}$ (TAM P10)	N = 27, 29	N = 27, 28	N = 16, 22	N = 16, 22	N = 22, 20	N = 28, 29	N = 28, 29	N = 27, 25	N = 20, 15	N = 28, 19	N = 28, 19
	p = 0.0355	p = 0.6588	p = 0.0120	p = 0.0124	p = 0.0398	p = 0.0026	p = 0.1291	p = 0.1242	p = 0.0269	p = 0.0064	p = 0.0003
$Mecp2^{f/y}$ (control) vs $Advillin^{CreERT2}$; $Mecp2^{f/y}$ (TAM P28)	N = 25, 13	N = 22, 12	N = 22, 12	N = 22, 12	N = 22, 12	N = 22, 12	N = 22, 12	N = 19, 15	N = 17, 15	N = 19, 15	N = 19, 15
	p = 0.0051	p = 0.8460	p = 0.0338	p = 0.0005	p = 0.8042	p = 0.5364	P = 0.9674	p = 0.8970	p = 0.6079	p = 0.0272	p = 0.0024
$Shank3^{+/+}$ (control) vs $Shank3^{FX/+}$ vs $Advillin^{CreERT2}$; $Shank3^{FX/+}$ (TAM P28)	N = 27, 16, 10	N = 27, 16, 10	N = 27, 18, 14	N = 27, 18, 14	N = 25, 15, 10	N = 29, 16, 10	N = 29, 16, 10	N = 27, 16, 10	N = 27, 16, 10	N = 27, 16, 10	N = 27, 16, 10
	F(2,50)=3.648	F(2,50)=6.130	F(2,56)=4.193	F(2,56)=4.318	F(2,47)=6.597	F(2,52)=7.242	F(2,52)=1.758	F(2,50)=8.214	F(2,50)=8.548	F(2,50)=8.028	F(2,50)=13.87
	P = 0.0332	P = 0.0042	P = 0.0201	P = 0.0180	P = 0.0030	P = 0.0017	P = 0.1825	P = 0.0008	P = 0.0006	P = 0.0009	p < 0.0001
$Mecp2^{+/y}$ (control) vs $Mecp2^{STOP/y}$ vs $Advillin^{CreERT2}$; $Mecp2^{STOP/y}$ (TAM P28)	N = 24, 14, 11	N = 25, 15, 11	N = 25, 18, 12	N = 25, 18, 12	N = 32, 22, 12	N = 25, 14, 14	N = 25, 14, 14	N = 25, 18, 11	N = 19, 15, 10	N = 23, 13, 10	N = 23, 13, 10
	F(2,46)=3.970	F(2,48)=4.783	F(2,52)=5.151	F(2,52)=8.054	F(2,63)=10.84	F(2,50)=7.014	F(2,50)=0.243	F(2,54)=4.480	F(2,41)=17.17	F(2,43)=10.42	F(2,43)=8.417
	P = 0.0257	P = 0.0128	P = 0.0091	P = 0.0009	P < 0.0001	P = 0.0021	P = 0.7856	P = 0.0158	P < 0.0001	P = 0.0002	P = 0.0008

Table S5. Statistical analyses. Related to Figures 4, 5 and S5

Figures 4 and S5	GABRB3/ vGLUT1 coloc.	Textured NORT	1 Hour Ret.	tPPI	Air Puff Alone	Open Field Time in Center	EPM Time in Open Arms	EPM Total Arm Crosses	Habituation to Startle Noise	Sociability	Social Novelty Preference	PV+ Neuron #, S1	PV+ Neuron #, V1	PV+ Neuron #, BLA
$Mecp2^{R/y}$ (control) vs $Mecp2^{C/y}$ vs $Advillin^{Cre}$; $Mecp2^{C/y}$		N = 30, 22, 10	N = 32, 21, 10	N = 30, 16, 8	N = 30, 16, 8	N = 31, 22, 12	N = 31, 16, 8	N = 31, 16, 8	N = 30, 22, 10	N = 26, 15, 10	N = 26, 15, 10	N = 6, 6, 6	N = 6, 6, 6	N = 6, 6, 6
	N = 5, 5, 19	F(2,59)=4.671	F(2,60)=5.974	F(2,51)=21.42	F(2,51)=25.90	F(2,55)=14.53	F(2,52)=6.615	F(2,52)=0.729	F(2,59)=4.689	F(2,48)=9.428	F(2,48)=6.188	F(2,15)=40.32	F(2,15)=8.162	F(2,15)=21.18
	F(2,26)=14.88	P = 0.0131	P = 0.0043	P < 0.0001	P < 0.0001	P < 0.0001	P = 0.0028	P = 0.4872	P = 0.0129	P = 0.0004	P = 0.0041	P < 0.0001	P = 0.0040	P < 0.0001
$Mecp2^{R/R}$ (control) vs $Mecp2^{R/C}$ vs $Advillin^{Cre}$; $Mecp2^{R/C}$		N = 25, 14, 12	N = 26, 14, 8	N = 29, 15, 8	N = 29, 15, 8	N = 28, 15, 8	N = 22, 14, 8	N = 22, 14, 8	N = 29, 15, 8	N = 26, 13, 8	N = 26, 13, 8	N = 7, 7, 6	N = 7, 7, 6	N = 6, 6, 6
	not determined (n.d.)	F(2,48)=4.234	F(2,45)=4.803	F(2,49)=13.74	F(2,49)=16.24	F(2,48)=5.746	F(2,41)=4.664	F(2,41)=0.113	F(2,48)=5.544	F(2,44)=9.207	F(2,44)=9.962	F(2,17)=5.977	F(2,17)=7.372	F(2,15)=8.452
		P = 0.0202	P = 0.0129	P < 0.0001	P < 0.0001	P = 0.0058	P = 0.0150	P = 0.8936	P = 0.0068	P = 0.0005	P = 0.0003	P = 0.0108	P = 0.0050	P = 0.0035

Figure 5A-D	tPPI	Air Puff Alone	Startle Amplitude	Startle Amplitude (compare to iso)
$Mecp2^{f/y}$ (control) vs. $Advillin^{Cre}$; $Mecp2^{f/y}$	N = 18, 9	N = 18, 9	N = 18, 9	N = 31
	F(1,50)=38.66	F(1,50)=8.531	F(1,50)=14.03	F(2,90)=3.908
	P < 0.0001	P = 0.0047	P = 0.0004	P = 0.0236

Table S6. Statistical analyses. Related to Figures 7 and S7

	Textured NORT	1 Hour Ret.	tPPI	Air Puff Alone	Open Field Time in Center	EPM Time in Open Arms	EPM Total Arm Crosses	Habituation to Startle Noise	Sociability	Social Novelty Preference	Marble Burying	Grooming
Saline-treated: $Shank3B^{+/+}$ (control) vs $Shank3B^{+/-}$	N = 12, 16	N = 12, 17	N = 12, 17	N = 12, 17	N = 14, 15	N = 12, 17	N = 12, 17	N = 12, 17	N = 12, 17	N = 12, 17	N = 12, 17	N = 7, 7
	p = 0.0040	p = 0.0349	p = 0.0214	p = 0.0332	p = 0.0038	p = 0.0025	p = 0.8292	p = 0.3355	p = 0.0026	p < 0.0001	p = 0.0004	p = 0.0320
Isoguvacine-treated: $Shank3B^{+/+}$ (control) vs $Shank3B^{+/-}$	N = 19, 21	N = 19, 21	N = 19, 21	N = 19, 21	N = 19, 21	N = 19, 21	N = 19, 21	N = 19, 21	N = 19, 21	N = 19, 21	N = 19, 21	N = 10, 11
	p = 0.0447	p = 0.0458	p = 0.8862	p = 0.1553	p = 0.0750	p = 0.9697	p = 0.8744	p = 0.3633	p = 0.3855	p = 0.0220	p = 0.7603	p = 0.0192
Saline-treated: $Mecp2^{R/y\ or\ R/R}$ (control) vs $Mecp2^{R/C}$ vs $Mecp2^{C/y}$	N = 34, 11, 10	N = 34, 11, 10	N = 35, 14, 11	N = 35, 14, 11	N = 34, 16, 11	N = 35, 11, 10	N = 35, 11, 10	N = 35, 11, 10	N = 29, 10, 8	N = 29, 10, 8	N = 29, 9, 9	N = 8, ---, 7
	F(2,52)=8.116	F(2,52)=4.440	F(2,57)=9.182	F(2,57)=18.61	F(2,58)=8.146	F(2,53)=14.55	F(2,53)=0.255	F(2,46)=0.462	F(2,44)=6.203	F(2,45)=14.03	F(2,44)=16.14	p = 0.4319
	P = 0.0009	P = 0.0166	P = 0.0003	P < 0.0001	P = 0.0008	P < 0.0001	P = 0.7756	P = 0.6328	P = 0.0042	p < 0.0001	P < 0.0001	
Isoguvacine-treated: $Mecp2^{R/y\ or\ R/R}$ (control) vs $Mecp2^{R/C}$ vs $Mecp2^{C/y}$	N=30, 14, 8	N = 30, 14, 8	N = 31, 15, 8	N = 31, 15, 8	N = 30, 15, 8	N = 28, 15, 8	N = 28, 15, 8	N = 28, 15, 8	N = 28, 8, 8	N = 28, 8, 8	N = 25, 14, 8	N = 7, ---, 7
	F(2,49)=3.708	F(2,49)=3.251	F(2,51)=0.719	F(2,51)=2.671	F(2,50)=0.376	F(2,48)=0.765	F(2,48)=0.175	F(2,39)=0.206	F(2,41)=0.975	F(2,41)=0.337	F(2,44)=14.53	p = 0.4002
	P = 0.0335	P=0.0472	P = 0.4920	P = 0.0789	P = 0.6886	P = 0.4708	P = 0.8484	P = 0.8144	P = 0.3858	P = 0.7162	P < 0.0001	

	PV+ Neuron #, S1	PV+ Neuron #, V1	PV+ Neuron #, BLA	E/I Balance, S1	E/I Balance, V1	Event Amplitude, S1	Event Frequency, S1	Event Amplitude, V1	Event Frequency, V1
Saline-treated: $Shank3B^{+/+}$ (control) vs $Shank3B^{+/-}$	N = 4, 5	N = 4, 5	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4
	p = 0.0100	p = 0.0012	p = 0.0154	p < 0.0001	p = 0.0011	F(1,12)=17.52 ; P=0.0013	F(1,12)=4.949 ; P=0.0461	F(1,12)=21.75 ; P=0.0005	F(1,12)=10.07 ; P=0.0080
Isoguvacine-treated: $Shank3B^{+/+}$ (control) vs $Shank3B^{+/-}$	N = 6, 4	N = 6, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4
	p = 0.0582	p = 0.0023	p = 0.0066	p = 0.1086	p = 0.0003	F(1,12)=0.205 8; P=0.6582	F(1,12)=6.922 ; P=0.0219	F(1,12)=17.78 ; P=0.0012	F(1,12)=19.09 ; P=0.0009
Saline-treated: $Mecp2^{R/y}$ (control) vs $Mecp2^{C/y}$	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4
	p = 0.0384	p = 0.0146	p = 0.0012	p = 0.0006	p = 0.0016	F(1,12)=0.208 4; P=0.6562	F(1,12)=15.94 ; P=0.0018	F(1,12)=2.551 ; P=0.1362	F(1,12)=9.131 ; P=0.0106
Isoguvacine-treated: $Mecp2^{R/y}$ (control) vs $Mecp2^{C/y}$	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4	N = 4, 4
	p = 0.1504	p = 0.0089	p = 0.0194	p = 0.3652	p = 0.0117	F(1,12)=1.740 ; P=0.2118	F(1,12)=0.226 4; P=0.6428	F(1,12)=1.155 ; P=0.3036	F(1,12)=4.863 ; P=0.0477

Table S7. Summary of findings. Related to all figures.

	Hairy Skin Sensitivity	Texture Discrimination	Anxiety-like Behaviors	Sociability	Social Novelty	Marble Burying	Grooming	PV+ Neuron #, S1	PV+ Neuron #, BLA	PV+ Neuron #, V1	E/I Balance S1	E/I Balance V1
Germline Mutants												
Shank3B$^{+/-}$	↑	↓	↑	↓	↓	↓	↑	↓	↓	↓	↓	↓
Shank3$^{FX/+}$	↑	↓	↑	↓	↓	↓	↑	↓	↓	↓	n.d.	n.d.
Mecp2$^{STOP/y}$	↑	↓	↑	↓	↓	↓	---	↑	↓	↑	n.d.	n.d.
Mecp2$^{R/C\ or\ C/y}$	↑	↓	↑	↓	↓	↓	---	↑	↓	↑	↓	↓
Conditional Deletions												
Cdx2^{Cre}; Shank3$^{f/+}$	↑	↓	↑	↓	↓	↓	---	n.d.	n.d.	n.d.	n.d.	n.d.
Advillin^{Cre}; Shank3$^{f/+}$	↑	↓	↑	↓	↓	↓	n.d.	↓	↓	---	↓	---
Advillin^{Cre}; Shank3$^{f/f}$	↑	↓	↑	↓	↓	↓	---	n.d.	n.d.	n.d.	n.d.	n.d.
Advillin^{CreERT2}; Shank3$^{f/+}$ (TAM P5)	↑	↓	↑	↓	↓	↓	n.d.	↓	↓	---	n.d.	n.d.
Advillin^{CreERT2}; Shank3$^{f/+}$ (TAM P10)	↑	↓	↓	↓	↓	↑	n.d.	↓	↑	---	n.d.	n.d.
Advillin^{CreERT2}; Shank3$^{f/+}$ (TAM P28)	↑	↓	---	---	↓	---	n.d.	↓	---	---	n.d.	n.d.
Advillin^{Cre}; Mecp2$^{f/+}$	↑	↓	↑	↓	↓	---	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Advillin^{Cre}; Mecp2$^{f/y}$	↑	↓	↑	↓	↓	↓	---	↑	↓	---	↓	---
Advillin^{CreERT2}; Mecp2$^{f/y}$ (TAM P5)	↑	↓	↑	↓	↓	↓	n.d.	↑	↓	---	n.d.	n.d.
Advillin^{CreERT2}; Mecp2$^{f/y}$ (TAM P10)	↑	↓	↓	+/-	↓	↑	n.d.	↓	↑	---	n.d.	n.d.
Advillin^{CreERT2}; Mecp2$^{f/y}$ (TAM P28)	↑	↓	---	---	↓	---	n.d.	↓	---	---	n.d.	n.d.
Genetic Rescues												
Shank3$^{FX/+}$	↑	↓	↑	↓	↓	↓	↑	↓	↓	↓	↓	↓
Cdx2^{Cre}; Shank3$^{FX/+}$	---	---	---	---	+/-	+/-	↑	n.d.	n.d.	n.d.	n.d.	n.d.
Advillin^{Cre}; Shank3$^{FX/+}$	---	---	---	---	+/-	+/-	↑	---	---	↓	n.d.	n.d.
Advillin^{CreERT2}; Shank3$^{FX/+}$ (TAM P28)	---	↓	↑	---	↓	↓	n.d.	---	↓	↓	n.d.	n.d.
Mecp2$^{STOP/y}$	↑	↓	↑	↓	↓	↓	---	↑	↓	↑	↓	↓
Advillin^{Cre} Mecp2$^{STOP/y}$	---*	---*	---*	---*	---*	n.d.	n.d.	+/-	---	↑	n.d.	n.d.
Advillin^{CreERT2}; Mecp2$^{STOP/y}$ (TAM P28)	---	↓	↑	---	↓	↓	n.d.	+/-	↓	↑	n.d.	n.d.
Viral Rescues												
Mecp2$^{R/C\ or\ C/y}$	↑	↓	↑	↓	↓	↓	---	↑	↑	↑	n.d.	n.d.
Advillin^{Cre}; Mecp2$^{R/C}$	---	---	---	---	---	n.d.	n.d.	---	---	↑	n.d.	n.d.
Advillin^{Cre}; Mecp2$^{C/y}$	---	---	---	---	+/-	n.d.	n.d.	+/-	+/-	↑	n.d.	n.d.
Pharmacological Rescues												
Shank3B$^{+/-}$ + saline	↑	↓	↑	↓	↓	↓	↑	↓	↓	↓	↓	↓
Shank3B$^{+/-}$ + iso	---	↓	---	---	---	---	---	---	---	↓	---	↓
Mecp2$^{R/C\ or\ C/y}$ + saline	↑	↓	↑	↓	↓	↓	---	↑	↑	↑	↓	↓
Mecp2$^{R/C\ or\ C/y}$ + iso	---	↓	---	---	---	↓	---	---	---	↑	---	↓

(↑, increased; ↓, decreased; +/-, intermediate phenotype; ---, not different than control littermates; n.d., not determined; *, findings observed in Orefice et al., 2016)

Table S8. Oligonucleotide List. Related to Key Resources Table.

Mouse Line	Oligo	Sequence (5' to 3')
Advillin^{Cre}	transgene forward	CCC TGT TCA CTG TGA GTA GG
	transgene reverse	AGT ATC TGG TAG GTG CTT CCA G
	internal control	GCG ATC CCT GAA CAT GTC CAT C
Advillin^{CreERT2}	AdvilCreERT2_1	CCC TGT TCA CTG TGA GTA GG
	AdvilCreERT2_2	AGT ATC TGG TAG GTG CTT CCA G
	AdvilCreERT2_3	GCG ATC CCT GAA CAT GTC CAT C
Cdx2^{Cre}	forward	CTC GAC GTC TCC AAC CAT TG
	reverse	ATC TTC AGG TTC TGC GGG AA
Cntnap2 null	wild type forward	TGC CCT CCT AGA AAG TAA ATG C T
	mutant forward	GCC AGA GGC CAC TTG TGT AG
	common reverse	TCC TCT CTT CAT GCA CAC TAT GA
Fmr1 null	mutant forward	CAC GAG ACT AGT GAG ACG TG
	wild type forward	TGT GAT AGA ATA TGC AGC ATG TGA
	common reverse	CTT CTG GCA CCT CCA GCT T
Gabrb3^{floxed}	forward	ATT CGC CTG AGA CCC GAC T
	reverse	GTT CAT CCC CAC GCA GAC
Hcn1 null	mutant forward	AGA GAA ATC ATT CCC CGT GA
	wild type forward	CAC CTG CTA CGC AAT GTT TG
	common reverse	ATT GGG CAC TAC ACG CTA GG
Mecp2^{floxed}	forward	TGG TAA AGA CCC ATG TGA CCC AAG
	reverse	GGC TTG CCA CAT GAC AAG AC
	post-Cre excision	TCC ACC TAG CCT GCC TGT ACT TTG
Mecp2^{R306C}	forward	GGA TTG TGG AAA AGC CAG
	reverse	ATG ACC TGG GCA GAT GTG GTA G
Mecp2^{STOP}	forward common	AAC AGT GCC AGC TGC TCT TC
	wild type reverse	CTG TAT CCT TGG GTC AAG CTG
	mutant reverse	GCC AGA GGC CAC TTG TGT AG
Shank3^{floxed}	pFW (Sh3cKO) Gen 1a	CAGCATTTATACCTGACTGTGAAGC
	pRV (Sh3cKO) Gen 3b	GGGAGTAGAGCTCAGATAACC
Shank3B null	common forward	GAG ACT GAT CAG CGC AGT TG
	wild type reverse	TGA CAT AAT CGC TGG CAA AG
	mutant reverse	GCT ATA CGA AGT TAT GTC GAC TAG G
Shank3$^{\Delta ex4-9}$	common forward	TGG GAT GTG AGA GTG ACC AG
	wild type reverse	AGG AGG TCA GTG GCG TTG T
	mutant reverse	AAT TCT GTT CAG TCC ACA CAG G
Shank3^{FX}	common forward	CGT TTG ACA CAC ATA AGC ACC
	wild type reverse	CTC CAC CTA GCT GAA TTT CCC

Table S8. Oligonucleotide List. Related to Key Resources Table.

	FX mutant reverse	GCT GAC ATC ACA TTG CTG CC
	FX rescue forward	CGT TTG ACA CAC ATA AGC ACC
	FX rescue reverse (wildtype rvs)	CTC CAC CTA GCT GAA TTT CCC
16$^{p11.2df}$ null	mutant forward	ACC TGG TAT TGA ATG CTT GC
	wild type forward	CCT GAG CCT CTT GAG TGT CC
	mutant reverse	TGG TAT CTC CAT AAG ACA GAA TGC
	wild type reverse	GTC GGT TCA GGT GGT AGA CG