

Supplementary Information –

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16p11.2 deletion mice exhibit compromised fronto-temporal connectivity, GABAergic dysfunction, and enhanced attentional ability

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Supplementary Table 1 - Statistical analysis details					
Figure	Paradigm	WT vs. 16p11 DUP (Effect of Genotype)	Genotype x sex	Effect of task stage	Effect of sex
1	2DG MS	F_(1,19)=13.64, p=0.002	F _(1,19) =0.33, p=0.574		F _(1,19) =0.22, p=0.647
1	2DG Piri	F_(1,19)=8.49, p=0.009	F _(1,19) =0.47, p=0.500		F _(1,19) =1.08, p=0.312
1	2DG AudC	F_(1,19)=7.34, p=0.014	F _(1,19) =0.78, p=0.389		F _(1,19) =0.01, p=0.977
1	2DG MB	F_(1,20)=5.81, p=0.026	F _(1,20) =0.03, p=0.873		F _(1,20) =3.61, p=0.072
1	2DG Sub	F _(1,19) =1.97, p=0.177	F_(1,19)=11.43, p=0.003		F_(1,19)=10.31, p=0.005
3	Pvalb PrL	F_(1,41)=33.69, p<0.001	F _(1,41) =4.33, p=0.050		F _(1,41) =59.24, p<0.001
3	Pvalb IL	F_(1,41)=26.04, p<0.001	F _(1,41) =0.21, p=0.650		F _(1,41) =45.41, p<0.001
3	Pvalb MO	F _(1,41) =6.02, p=0.023	F _(1,41) =0.69, p=0.416		F _(1,41) =0.81, p=0.378
3	Pvalb LO	F _(1,41) =1.49, p=0.236	F _(1,41) =0.21, p=0.650		F _(1,41) =0.86, p=0.365
3	Calb PrL	F_(1,47)=18.07, p<0.001	F_(1,47)=8.17, p=0.009		F _(1,47) =0.24, p=0.628
3	Calb IL	F_(1,47)=24.05, p<0.001	F_(1,47)=34.59, p<0.001		F _(1,47) =2.54, p=0.124
3	Calb MO	F _(1,47) =0.04, p=0.835	F_(1,47)=11.72, p=0.002		F _(1,47) =4.72, p=0.040
3	Calb LO	F _(1,47) =2.02, p=0.168	F _(1,47) =5.67, p=0.026		F _(1,47) =5.65, p=0.026
3	GAD1 PrL	F _(1,45) =0.03, p=0.854	F _(1,45) =5.35, p=0.027		F _(1,45) =0.04, p=0.839
3	GAD1 IL	F _(1,45) =0.37, p=0.547	F _(1,45) =2.20, p=0.148		F _(1,45) =1.53, p=0.226
4	Pvalb MS	F _(1,47) =2.58, p=0.117	F _(1,47) =5.67, p=0.023		F _(1,47) =3.29, p=0.078
4	Pvalb LS	F _(1,45) =0.94, p=0.339	F _(1,45) =0.10, p=0.759		F _(1,45) =0.95, p=0.338
4	Calret MS	F _(1,51) =2.85, p=0.100	F _(1,51) =1.60, p=0.213		F _(1,51) =1.09, p=0.304
4	Calret LS	F _(1,51) =0.00, p=0.956	F _(1,51) =0.06, p=0.813		F _(1,51) =0.42, p=0.520
4	GAD1 MS	F _(1,51) =3.87, p=0.057	F _(1,51) =2.00, p=0.166		F _(1,51) =2.84, p=0.100
4	GAD1 LS	F _(1,51) =1.42, p=0.241	F_(1,51)=7.62, p=0.009		F _(1,51) =1.15, p=0.290
4	SST INS	F _(1,47) =0.80, p=0.379	F _(1,47) =1.04, p=0.316		F _(1,47) =1.94, p=0.173
4	Pvalb INS	F _(1,45) =0.94, p=0.339	F _(1,45) =0.10, p=0.759		F _(1,45) =0.95, p=0.338
4	GAD1 INS	F _(1,47) =0.03, p=0.859	F _(1,47) =5.44, p=0.026		F _(1,47) =0.01, p=0.916
5	Pvalb CA1	F _(1,88) =9.08, p=0.004	F _(1,88) =0.83, p=0.365		F _(1,88) =4.30, p=0.042
5	Calb CA1	F _(1,92) =0.50, p=0.483	F _(1,92) =3.56, p=0.063		F _(1,92) =8.82, p=0.004
5	SST TRN	F_(1,70)=7.32, p=0.009	F _(1,70) =0.75, p=0.392		F _(1,70) =11.24, p=0.002
5	Pvalb TRN	F _(1,81) =2.17, p=0.147	F _(1,81) =1.21, p=0.277		F _(1,81) =0.02, p=0.901
5	GAD1 TRN	F _(1,98) =3.50, p=0.066	F _(1,98) =2.61, p=0.110		F _(1,98) =1.35, p=0.250
5	Pvalb ParCx	F _(1,51) =17.22, p<0.001	F _(1,51) =4.56, p=0.041		F _(1,51) =3.82, p=0.062
5	GAD1 ParCx	F _(1,47) =0.06, p=0.815	F _(1,47) =4.56, p=0.040		F _(1,47) =0.13, p=0.722
5	GAD1 PirCx	F _(1,51) =1.25, p=0.27	F _(1,51) =0.06, p=0.80		F _(1,51) =0.52, p=0.48

6	Startle			$F_{(9,252)} = 84.40$ $p = 0.0001$	
6	PPI (%)	$F_{(1,95)}=10.38, p=0.002$	$F_{(1,95)}=0.15, p=0.70$	$F_{(1,95)}=39.57, p<0.001$	
7	Stage 6 HR	CPT $F_{(1,263)}=46.95, p<0.001$	$F_{(1,263)}=75.87, p<0.001$ DEL M > WT M Tukey		$F_{(1,263)}=44.36, p<0.001$
7	Stage 6 FAR	$F_{(1,263)}=5.22, p=0.023$	ns $F_{(1,263)}=46.75, p<0.001$ DEL M > WT M Tukey		$F_{(1,263)}=77.08, p<0.001$
7	Stage 6 SI	$F_{(1,263)}=31.20, p<0.001$	0.01 $F_{(1,263)}=31.92, p<0.001$ DEL M > WT M Tukey		$F_{(1,263)}=99.31, p<0.001$
7	Stage 6 RI	$F_{(1,263)}=5.03, p=0.026$	0.001 $F_{(1,259)}=39.56, p<0.001$ WT M > WT F		ns $F_{(1,259)}=157.8, p<0.001$ M > F
7	Stage 6 d'	$F_{(1,259)}=47.29, p<0.001$			
8	VSD HR	$F_{(1,69)}=11.41, p=0.002$	$F_{(1,69)}=14.84, p<0.001$	$F_{(1,69)}=39.21, p<0.001$	$F_{(1,69)}=6.14, p=0.018$
8	VSD FAR	$F_{(1,69)}=3.56, p=0.067$	$F_{(1,69)}=0.42, ns$ $F_{(1,63)}=9.41, p=0.004$ DEL M > WT M Tukey	$F_{(1,69)}=4.47, p=0.018$	$F_{(1,69)}=9.20, p=0.004$
8	VSD SI	$F_{(1,63)}=31.82, p<0.001$	0.001	ns	ns
8	VSD RI	$F_{(1,71)}=4.55, p=0.039$	$F_{(1,71)}=7.98, p=0.007$ $F_{(1,71)}=11.07, p=0.002$ DEL M > WT M Tukey	$F_{(1,71)}=59.79, p<0.001$	ns
8	VSD d'	$F_{(1,71)}=13.39, p=0.001$	0.001	$F_{(1,71)}=36.64, p<0.001$	$F_{(1,71)}=8.10, p=0.007$

Supplementary Table 2: Reaction times in the rCPT (s)

Stage of task	WT females	WT males	DEL females	DEL males
<i>Stage 6</i>				
Correct Choice	0.74 +/- 0.03	0.74 +/- 0.05	0.79 +/- 0.02	0.76 +/- 0.04
Incorrect Choice	0.73 +/- 0.02	0.71 +/- 0.02	0.68 +/- 0.04	0.64 +/- 0.08
Reward collection	1.82 +/- 0.27	1.30 +/- 0.15	1.86 +/- 0.21	1.35 +/- 0.20
<i>Distractor</i>				
Correct Choice	1.04 +/- 0.09	0.98 +/- 0.10	0.86 +/- 0.14	0.73 +/- 0.18
Incorrect Choice	1.15 +/- 0.05	1.22 +/- 0.10	1.08 +/- 0.04	1.13 +/- 0.11
Reward collection	2.10 +/- 0.32	1.31 +/- 0.14	1.66 +/- 0.19	0.98 +/- 0.21
<i>vSD</i>				
Correct Choice	0.64 +/- 0.02	0.60 +/- 0.03	0.66 +/- 0.02	0.63 +/- 0.04
Incorrect Choice	0.56 +/- 0.04	0.49 +/- 0.03	0.50 +/- 0.02	0.44 +/- 0.07
Reward collection	2.03 +/- 0.39	1.37 +/- 0.18	1.44 +/- 0.18	1.21 +/- 0.14

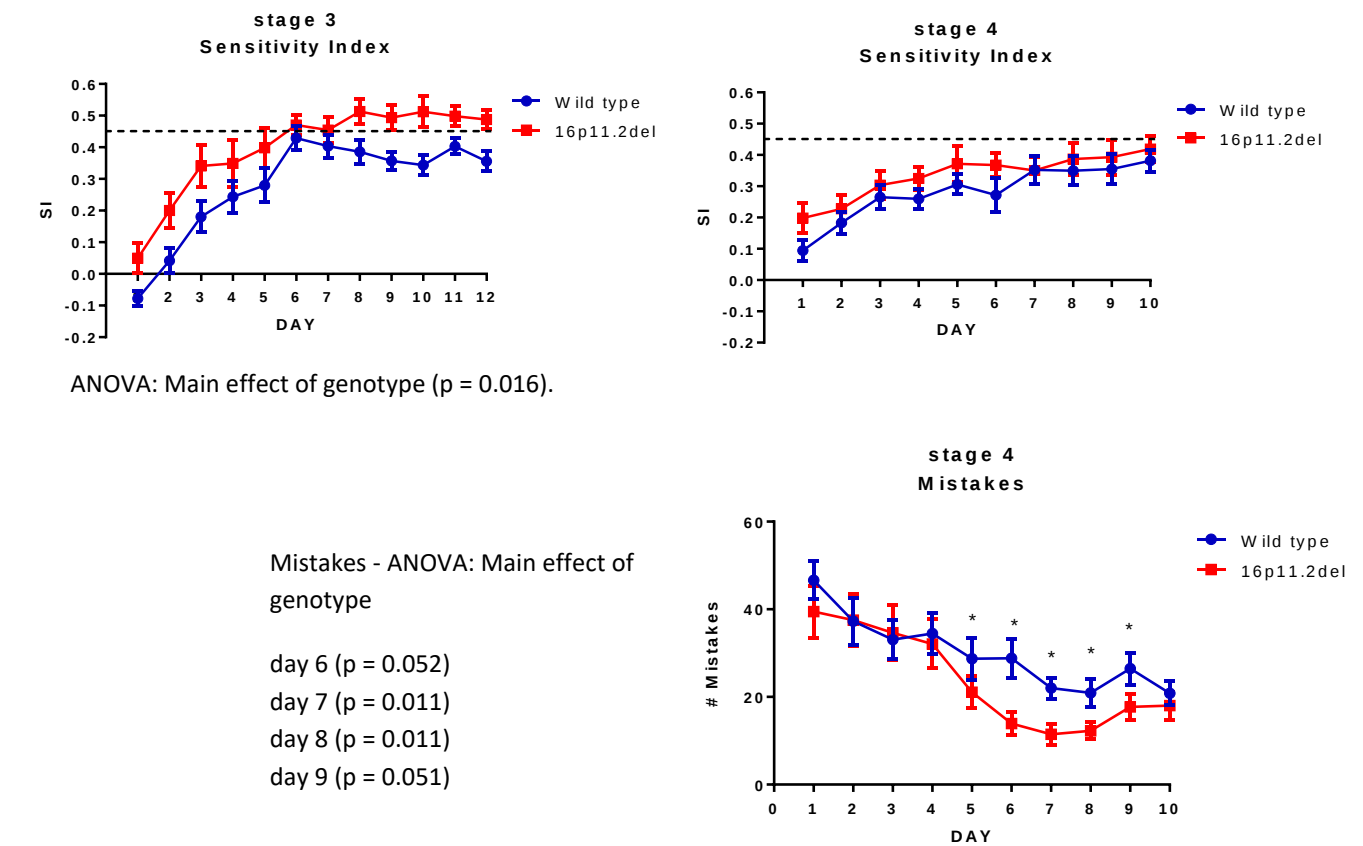
Supplementary Table 3: Brain region abbreviations

Prefrontal Cortex	Mesolimbic	Olfactory
Anterior Prelimbic Cortex (aPrL)	Nucleus Accumbens Core (AcbC)	Olfactory Bulb (OB)
Frontal Association Area (FRA)	Nucleus Accumbens Shell (AcbSh)	Neuromodulatory
Dorsolateral Orbital Cortex (DLO)	Ventral Tegmental Area (VTA)	Dorsal Raphe (DR)
Medial Orbital Cortex (MO)	Basal Ganglia	Median Raphe (MR)
Lateral Orbital Cortex (LO)	Dorsolateral Striatum (DLST)	Hippocampus
Medial Prelimbic Cortex (mPrL)	Ventromedial Striatum (VMST)	Dorsal Subiculum (DSub)
Infralimbic Cortex (IL)	Globus Pallidus (GP)	Dorsal Cornu Ammonis 1 (DH CA1)
Cingulate Cortex (Cg1)	Substantia Nigra pars Compacta (SNC)	Dorsal Cornu Ammonis 2 (DH CA2)
Cortex	Substantia Nigra pars Reticulata (SNR)	Dorsal Molecular Layer (DH Mol)
Insular Cortex (Ins)	Amygdala	Dorsal Dentate Gyrus (DH DG)
Piriform Cortex (Piri)	Basolateral Amygdala (BLA)	Ventral Cornu Ammonis 1 (VH CA1)
Retrosplenial Cortex (RSC)	Central Amygdala (CeA)	Ventral Cornu Ammonis 3 (VH CA3)
Somatosensory Cortex (S1)	Medial Amygdala (MeA)	Ventral Molecular Layer (VH Mol)
Thalamus	Auditory	Ventral Dentate Gyrus (VH DG)
Anteromedial Thalamus (AM)	Inferior Colliculus (IC)	Entorhinal Cortex (ENT)
Thalamic Reticular Nucleus (TRN)	Medial Geniculate (MG)	Perirhinal Cortex (PRh)
Anterior Reticular Thalamus (aRT)	Septum/Diagonal Band of Broca (DB)	Multimodal
Anteroventral Thalamus (AV)	Lateral Septum (LS)	Habenula (Hab)
Mediodorsal Thalamus (MD)	Medial Septum (MS)	Mamillary Body (MB)
Ventrolateral Thalamus (VL)	Horizontal Limb of DB (HDB)	Corpus Callosum (CC)
Ventromedial Thalamus (VM)	Vertical Limb of DB (VDB)	

Supplementary Table 4: Oligonucleotide sequences

Gene	Methodology	Sequence
Pvalb	In situ hybridisation	AGTGGAGAATTCTTCAACCCCAATCTTGCCGTCCCCATCCTTGTC
Calb1	In situ hybridisation	AATTCCTATTTTTCCATCATCTCTCTGTCCATATTGATCCACAAA
Calb2	In situ hybridisation	CTGTTGGATGTTTCATCTCCTTCTTGTTCCTTCATACAGATCCTT
SST	In situ hybridisation	CAAATCCTCGGGCTCCAGGGCATCATTCTCTGTCTGGTTGGGCTC
Gad1	In situ hybridisation	CCTGCACACATCTGGTTGCATCCTTGGAGTATACCCTTTTCCTTG
16p11 wt	Genotyping (fwd)	TACCTCACACCTCAGTTCCAAGTGG
16p11 wt	Genotyping (rev)	GGGTGGGAGTTCTCGCCTATCACAG
16p11 mutant	Genotyping (fwd)	GGTAGAATTTGAGGTCGCTAG
16p11 mutant	Genotyping (rev)	CAA GCT GAT CCG GAA CCC

Supplementary Figure 1: d' data at stages 3 and 4 of training for rCPT, plus no. of mistakes at stage 4. Data shown as mean +/-standard error of the mean



Supplementary Figure 2: Summary of the core limbic circuitry affected in male 16p11.2DEL mice. PFC/OFC: prefrontal /orbitofrontal cortex; Aud, Piri, Ins: auditory, piriform and Insular cortex; MS: medial septum; MB: mammillary bodies; Sub: subiculum; Amyg: basolateral amygdala; Acc: nucleus accumbens shell. Gray region names indicate unaltered metabolism. Red arrows indicate unaltered connectivity. Green arrows indicate unaltered connectivity.

