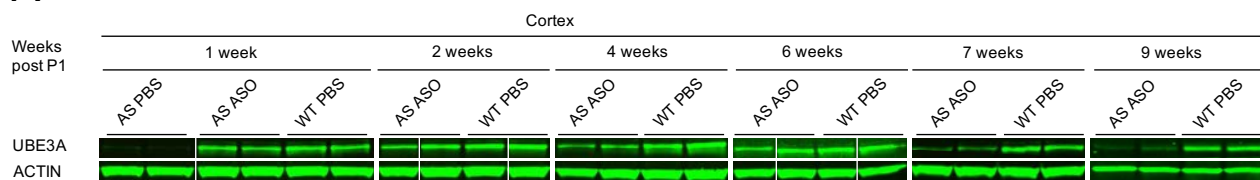
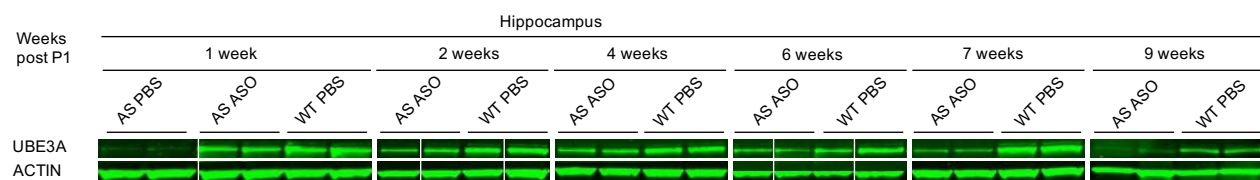


**Supplemental Figure 1: Reinstatement of UBE3A in AS mice injected with the ASO at P1 is not limited to glutamatergic neurons.** Four weeks post-P1 injection the brains (n=2) of WT-PBS, AS-ASO and AS-PBS injected mice were stained for UBE3A (green). (A) The brain of AS mice treated with ASO shows wide spread UBE3A reinstatement compared to the untreated AS brain. (B-D) the cortex (B) hippocampus (C) and cerebellum (D) of WT-PBS, AS-ASO and AS-PBS mice were stained for UBE3A (green), for parvalbumin (PV) (red) and counterstained for DAPI (blue). Scale bars, 2000  $\mu$ m (A), 200  $\mu$ m (B), top panel 200  $\mu$ m, lower two panels 100  $\mu$ m (C-D). Arrows point at cells positive for both parvalbumin and UBE3A.

**A**



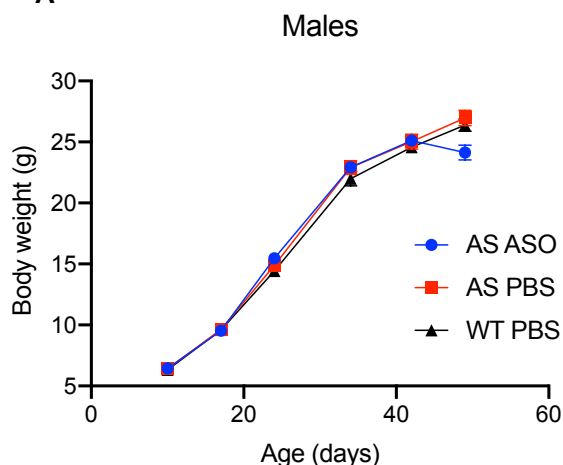
**B**



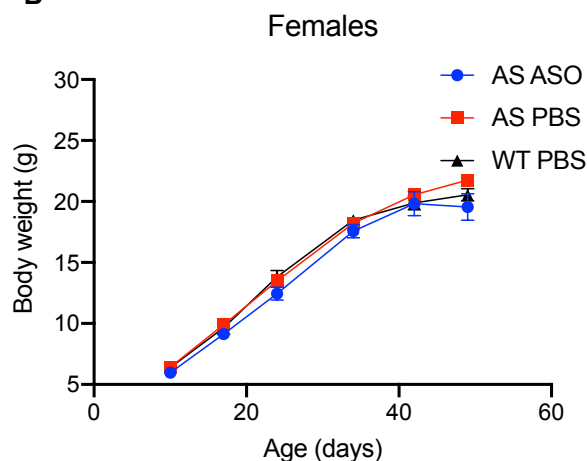
**Supplemental Figure 2: ASO successfully restores UBE3A in the brain of P1 injected AS mice.**

Brains of ASO treated AS mice were used for Western Blot analysis at different time points: 1 week after P1 injection (n=7), 2 (n=3), 4 (n=3), 6 (n=2) and 7 (n=4) weeks after P1 injection. AS-PBS (n=2) and WT (n=3) littermates were used as controls. The thin white vertical lines separating bands indicate noncontiguous lanes that were run on the same gel. UBE3A can be detected at 100kDa and actin, used as loading control, at 45kDa.

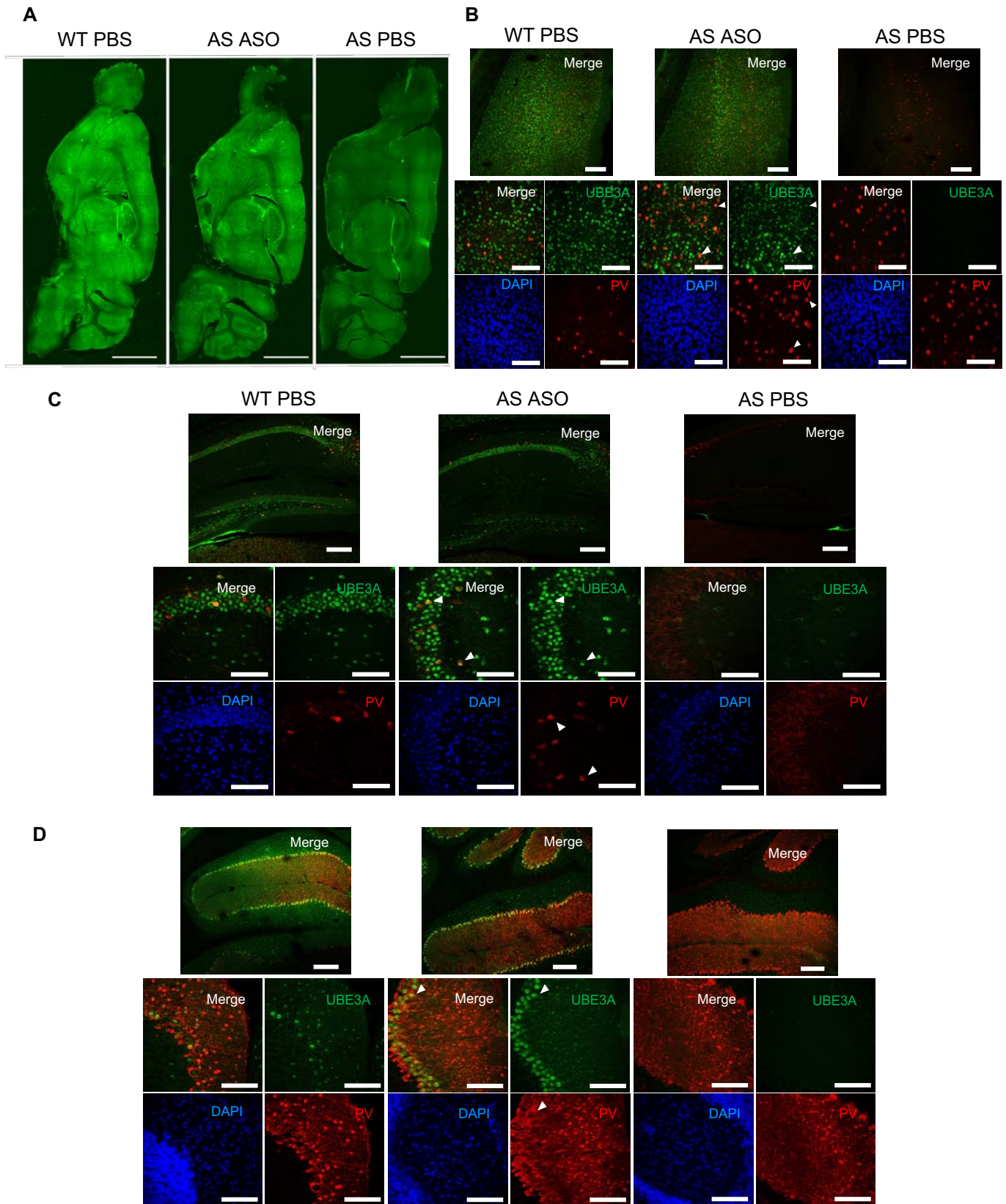
**A**



**B**



**Supplemental Figure 3: Body weight does not change among groups.** The body weight of AS ASO, WT PBS and AS PBS treated mice is noted at different ages, over the course of 49 days. A. Body weight of males only (AS ASO :10 and 17 days n=10; 24, 34 and 42 days n=9; 49d n= 4. WT PBS: 10, 24 and 42 days n=13; 17d n=12; 34 days n=10; 49d n= 4. AS PBS: 10, 24, and 42 days n=11; 17d n=7; 34d n=10; 49d n= 4). B. Body weight of females only (AS ASO: 10d n=9; 17, 24, 34, and 42 days n=10; 49d n=4. WT PBS: 10, 24 and 42 days n=7; 17d n=5; 34d n=4; 49d n=5. AS PBS:10, 24, and 42 days n=7;17 and 34 days n=4; 49d n=5). Data is represented as means  $\pm$  SEM.



**Supplemental Figure 4: Reinstatement of UBE3A in ASO treated AS mice at P21 is not limited to glutamatergic neurons.** Three weeks post-P21 injection the brains (n=2) of WT-PBS, AS-ASO and AS-PBS injected mice were stained for UBE3A (green). (A) The brain of AS mice treated with ASO shows wide spread UBE3A reinstatement compared to the untreated AS brain. (B-D) the cortex (B) hippocampus (C) and cerebellum (D) of WT-PBS, AS-ASO and AS-PBS mice were stained for UBE3A (green), for parvalbumin (PV) (red) and counterstained for DAPI (blue). Scale bars, 2000  $\mu$ m (A), top panel 200  $\mu$ m, lower two panels 100  $\mu$ m (B-D). Arrows point at cells positive for both parvalbumin and UBE3A.

**Supplemental Table 1: Summary of the statistical tests.**

	Behavioral test	Dependent variable	Normality Test	Sample N	Test statistic	p value	Test statistic	Directionality	Independent variable	Test statistic value (df)	p value F test	Post-hoc test	Comparison	Adjusted p-value
P1 injected mice	rotarod	latency to fall (s)	Shapiro-Wilk test	AS ASO =16	W: 0.950	0.735	2-way repeated measure ANOVA	2-sided	Genotype-Treatment	F (2,43)=14.339	<0.0001	Tukey	AS ASO vs. AS PBS	0.100
				AS PBS =16	W: 0.971	0.881		2-sided	Time	F (2,9, 124.7) = 0.799	0.49		AS ASO vs. WT PBS	0.005
				WT PBS =14	W: 0.946	0.708		2-sided	Genotype-Treatment*Time	F (5,8, 124.7) = 1.375	0.23		AS PBS vs. WT PBS	<0.0001
	open field	distance moved (cm)	D'Agostino & Pearson	AS ASO =16	K2: 2.893	0.235	Univariate ANOVA	2-sided	Genotype-Treatment	F (2, 43) = 8.824	<0.001	Bonferroni	AS ASO vs. AS PBS	0.003
				AS PBS =16	K2: 1.723	0.422							AS ASO vs. WT PBS	>0.999
				WT PBS =14	K2: 0.168	0.919							AS PBS vs. WT PBS	0.002
	marble burying	% buried marbles	D'Agostino & Pearson	AS ASO =16	K2: 3.519	0.172	Univariate ANOVA	2-sided	Genotype-Treatment	F (2, 42) = 24.05	<0.0001	Bonferroni	AS ASO vs. AS PBS	0.66
				AS PBS =16	K2: 4.971	0.083							AS ASO vs. WT PBS	<0.0001
				WT PBS =15	K2: 3.935	0.140							AS PBS vs. WT PBS	<0.0001
	nest building	used nesting material (%)	Shapiro-Wilk test	AS ASO =16	W: 0.966	p=0.85	2-way repeated measure ANOVA	2-sided	Genotype-Treatment	F (2, 42) = 16.64	<0.0001	Tukey	AS ASO vs. AS PBS	0.783
				AS PBS =16	W: 0.977	p=0.919		2-sided	Time	F (4, 168) = 150.4	<0.0001		AS ASO vs. WT PBS	<0.0001
				WT PBS =14	W: 0.981	p=0.939		2-sided	Genotype-Treatment*Time	F (8, 168) = 9.795	<0.0001		AS PBS vs. WT PBS	<0.0001
	forced swim test	floating time (%)	D'Agostino & Pearson	AS ASO =16	K2: 8.168	0.017	kruskal-wallis	2-sided	Genotype-Treatment	H(2,43)=15.94	0.0003	Dunn's	AS ASO vs. AS PBS	0.002
				AS PBS =16	K2: 31.86	<0.0001							AS ASO vs. WT PBS	>0.999
				WT PBS =14	K2: 3.393	0.183							AS PBS vs. WT PBS	0.002
	reverse rotarod	latency to fall (s)		AS ASO =17			2-way repeated measure ANOVA	2-sided	Genotype-Treatment	F (2, 63) = 15.48	<0.0001	Tukey	AS ASO vs. AS PBS	0.038
				AS PBS =30				2-sided	Time	F (4, 252) = 90.00	<0.0001		AS ASO vs. WT PBS	0.0321
				WT PBS =19				2-sided	Genotype-Treatment*Time	F (8, 252) = 3.826	0.0003		AS PBS vs. WT PBS	<0.0001
	brain weight	weight (g)	Shapiro-Wilk test	AS ASO =8	W: 0.902	0.3014	Univariate ANOVA	2-sided	Genotype-Treatment	F (2, 20) = 11.69	0.0004	Tukey	AS ASO vs. AS PBS	0.1062
				AS PBS =7	W: 0.918	0.4564							AS ASO vs. WT PBS	0.0311
				WT PBS =8	W: 0.942	0.6293							AS PBS vs. WT PBS	0.0003
	Induced Audiogenic Seizures	Seizures (%)		AS ASO =10			Fisher Test	2-sided	Treatment	AS PBS vs AS ASO	0.0001			
	AS PBS =6													
			WT PBS =7											
LTP	fEPSP slope (% of baseline)	-	AS ASO = 16/8 (slice per mouse)			Two-way ANOVA	2-sided	Genotype-Treatment	F (2, 39) = 3.56	0.038	Bonferroni	AS ASO vs. AS PBS	0.065	

				AS PBS = 13/16 (slice per mouse)								AS ASO vs. WT PBS	1.0
				WT PBS = 13/6 (slice per mouse)								AS PBS vs. WT PBS	0.089

P21 injected mice	Behavioral test	Dependent variable	Normality Test	Sample N	Test statistic	p value	Test statistic	Directionality	Independent variable	Test statistic value (df)	p value F test	Post-hoc test	Comparison	Adjusted p-value
	Induced Audiogenic Seizures	Seizures (%)		AS ASO =13 AS PBS =10 WT PBS =9			Fisher Test	2-sided	Treatment	AS PBS vs AS ASO	<0.0001			
	LTP	fEPSP slope (% of baseline)	-	AS ASO = 27/7 (slice per mouse) AS PBS = 26/5 (slice per mouse) WT PBS = 23/4 (slice per mouse)			Two-way ANOVA	2-sided	Genotype-Treatment	F (2, 73) = 3.56	0.018	Bonferroni	AS ASO vs. AS PBS	0.471
													AS ASO vs. WT PBS	0.371
													AS PBS vs. WT PBS	0.014
	Western Blot	Dependent variable	Normality Test	Sample N	Test statistic	Directionality	Independent variable	Test statistic value (df)	p value F test	Post-hoc test	Comparison	Adjusted p-value		
	Cortex	UBE3A (%)	N too small	AS ASO = 3	Univariate ANOVA	2-sided	Genotype-Treatment	F (2, 6) = 21.38	0.002	Tukey	AS ASO vs. AS PBS	0.028		
				AS PBS = 3							AS ASO vs. WT PBS	0.055		
				WT PBS = 3							AS PBS vs. WT PBS	0.002		
	Hippocampus			AS ASO = 3				F (2, 6) = 75.53	<0.0001	Tukey	AS ASO vs. AS PBS	0.003		
				AS PBS = 3							AS ASO vs. WT PBS	0.002		
				WT PBS = 3							AS PBS vs. WT PBS	<0.0001		
	Striatum			AS ASO = 3				F (2, 6) = 9.38	<0.0002	Tukey	AS ASO vs. AS PBS	0.024		
				AS PBS = 3							AS ASO vs. WT PBS	0.988		
				WT PBS = 3							AS PBS vs. WT PBS	0.020		
	Cerebellum			AS ASO = 2				F (2, 4) = 107.2	0.0003	Tukey	AS ASO vs. AS PBS	0.011		
				AS PBS = 2							AS ASO vs. WT PBS	0.001		
WT PBS = 2				AS PBS vs. WT PBS							0.0003			