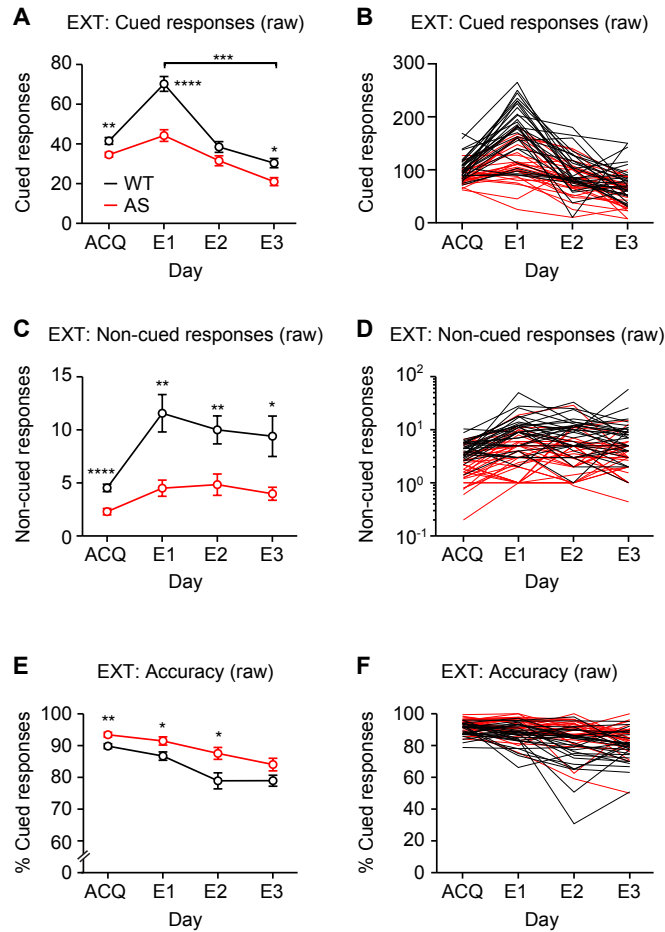


Supplementary Figures

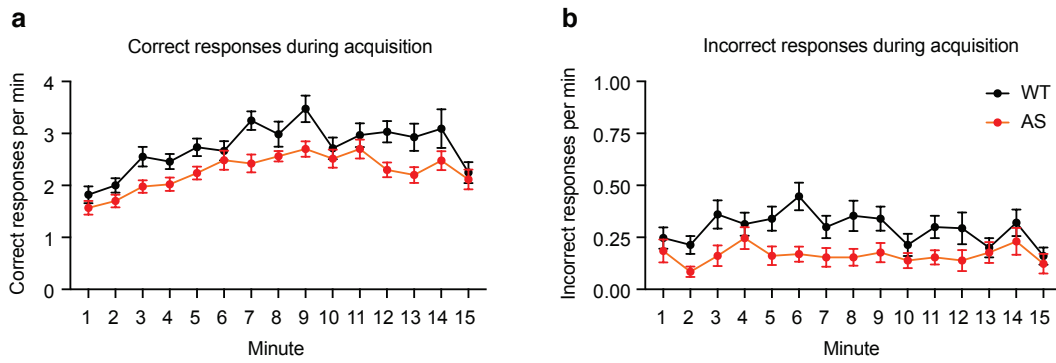
Manuscript Title: Operant behavior is reliably impaired in a mouse model of Angelman syndrome

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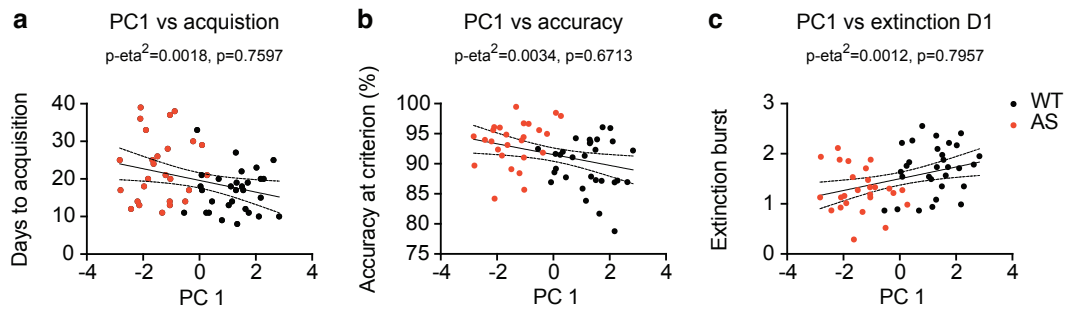


Supplementary Figure 1. Raw data during extinction. Data are associated with extinction reported as normalized to baseline in Figure 1. Black: WT, red: *Ube3a*^{m-/p+} (AS). (a) Cued responses during acquisition and extinction. *Ube3a*^{m-/p+} mice had fewer cued responses during the five days at criteria in the acquisition phase, represented as an average of five days in “ACQ” (as reported in Fig. 1g). During the extinction phase, analysis of raw responses revealed a main effect of genotype ($F_{(1,54)} = 25.00$, $p < 0.0001$) and a day X genotype interaction ($F_{(2,108)} = 9.292$, $p = 0.0002$). Bracket represents interaction and asterisks represent *post hoc* tests (E1 $p < 0.0001$, E2 $p = 0.1781$, E3 $p = 0.0117$). (b) Cued responses during extinction in individual mice. (c) Non-cued responses during acquisition and extinction. *Ube3a*^{m-/p+} had fewer non-cued responses during the five days at criteria in the acquisition phase, represented as an average of five days in “ACQ” (as reported in Fig. 1g). During the extinction phase, analysis of raw responses revealed a main effect of genotype ($F_{(1,58)} = 20.66$, $p < 0.0001$) but no day X genotype interaction ($F_{(2,116)} = 0.3888$, $p = 0.6788$). Asterisks represent *post hoc* tests (E1 $p = 0.0021$, E2 $p = 0.0091$, E3 $p = 0.0316$). (d) Non-cued responses during extinction in individual mice. (e) Accuracy [cued responses / (cued responses + non-cued responses)] during

acquisition and extinction. *Ube3a*^{m-/p+} mice had higher accuracy during the five days at criteria in the acquisition phase, represented as an average of five days in “ACQ” (as reported in Fig. 1h). During the extinction phase, analysis of accuracy revealed a main effect of genotype ($F_{(1,54)} = 9.046$, $p = 0.0040$) but no day X genotype interaction ($F_{(2,108)} = 1.128$, $p = 0.3276$). Asterisks represent *post hoc* tests (E1 $p = 0.0356$, E2 $p = 0.0247$, E3 $p = 0.1677$). (f) Accuracy during extinction in individual mice.



Supplementary Figure 2. Correct and incorrect responses per minute at the acquisition criteria. Data are additional analyses from Figures 1f and g. Correct and incorrect responses were measured in 1-minute bins and averaged across the 5 days of acquisition at criteria. (a) Correct responses per minute (main effect of genotype: $F(7.833, 423.0) = 10.28$, $p < 0.0001$; main effect of minute: $F(1, 54) = 10.36$, $p = 0.0022$; genotype $\times$ minute interaction: $F(7.833, 423.0) = 0.97$, $p = 0.4613$). (b) Incorrect responses per minute (main effect of genotype: $F(9.609, 518.9) = 1.85$, $p = 0.0520$; main effect of minute: $F(1, 54) = 16.10$, $p = 0.0002$; genotype $\times$ minute interaction: $F(9.609, 518.9) = 0.98$, $p = 0.4597$). WT: $n = 30$ mice, *Ube3a*^{m-/p+} (AS): $n = 26$ mice.



Supplementary Figure 3. Controlling for genotype, operant behaviors are independent of AS battery behaviors. Data are additional analyses from Figure 4. Using a mixed linear regression model with genotype as a covariate, we regressed each operant behavior of interest on PC1, controlling for genotype using R. (a) Days to acquisition does not correlate with PC1, controlling for genotype (Mixed linear model, main effect of PC1 controlling for genotype: $p = 0.7597$; main effect of genotype controlling for PC1: $p = 0.0599$). (b) Accuracy at criteria does not correlate with PC1, controlling for genotype (Mixed linear model, main effect of PC1 controlling for genotype: $p = 0.6713$; main effect of genotype controlling for PC1: $p = 0.0352$). (c) The extinction burst response does not correlate with PC1, controlling for genotype (Mixed linear model, main effect of PC1 controlling for genotype: $p = 0.7975$; main effect of genotype controlling for PC1: $p = 0.1301$). WT: $n = 30$ mice, *Ube3a*^{m-/p+} (AS): $n = 26$ mice.