Supplementary Materials for:

BICC1 expression is elevated in depressed subjects and contributes to depressive behavior in rodents

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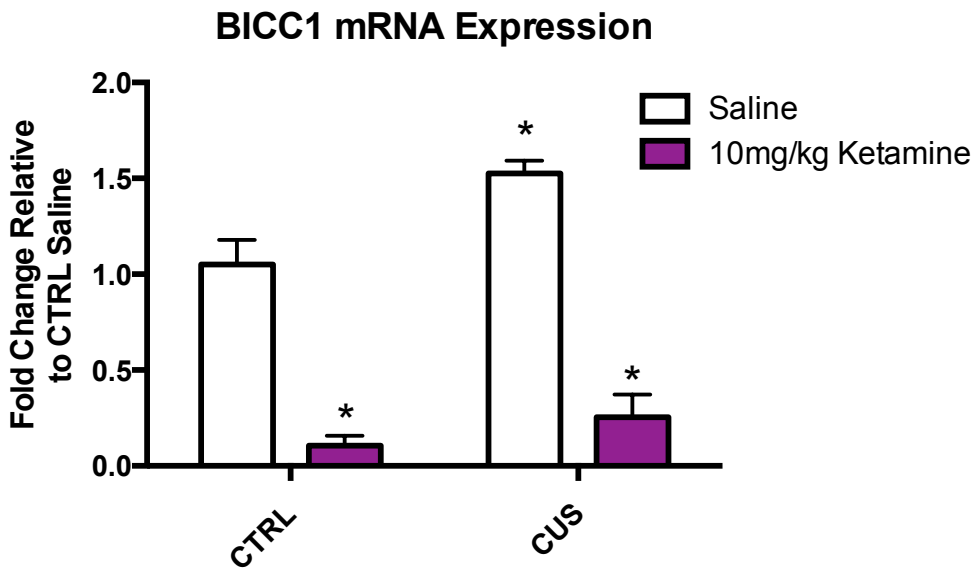
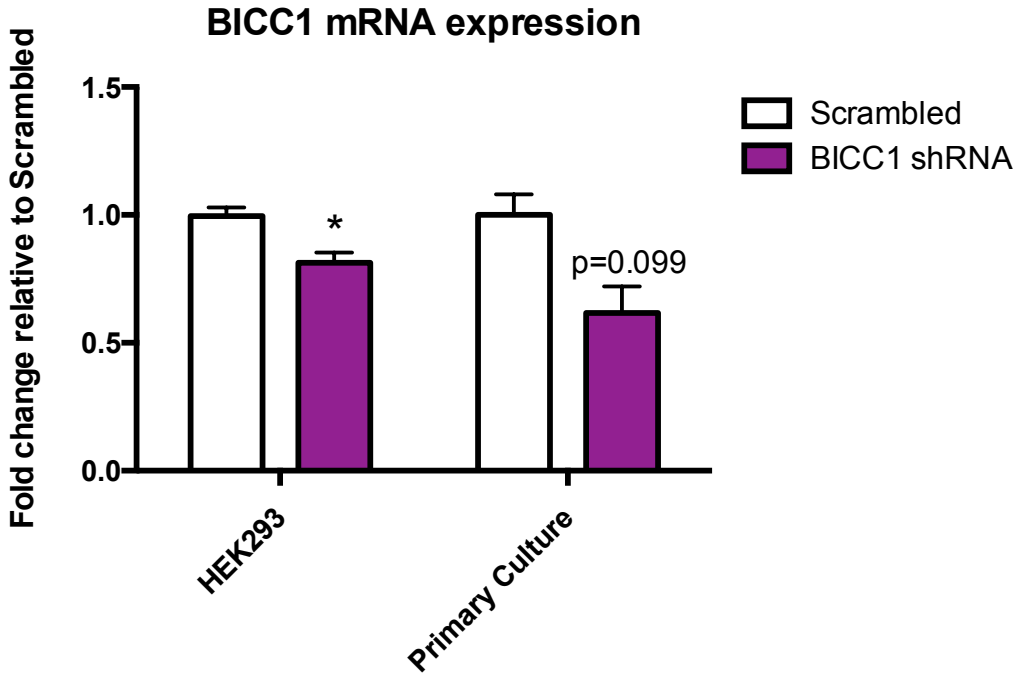
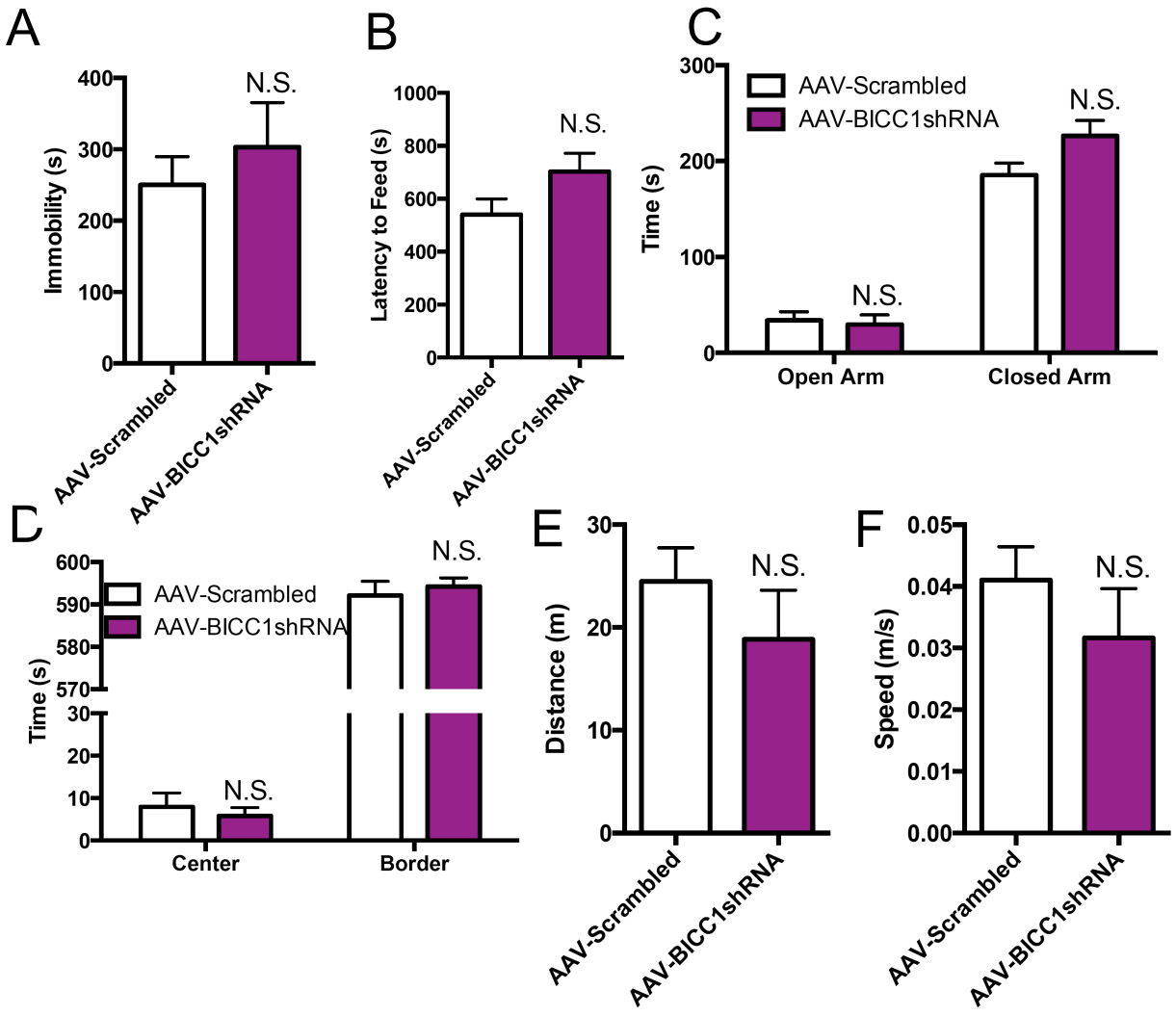


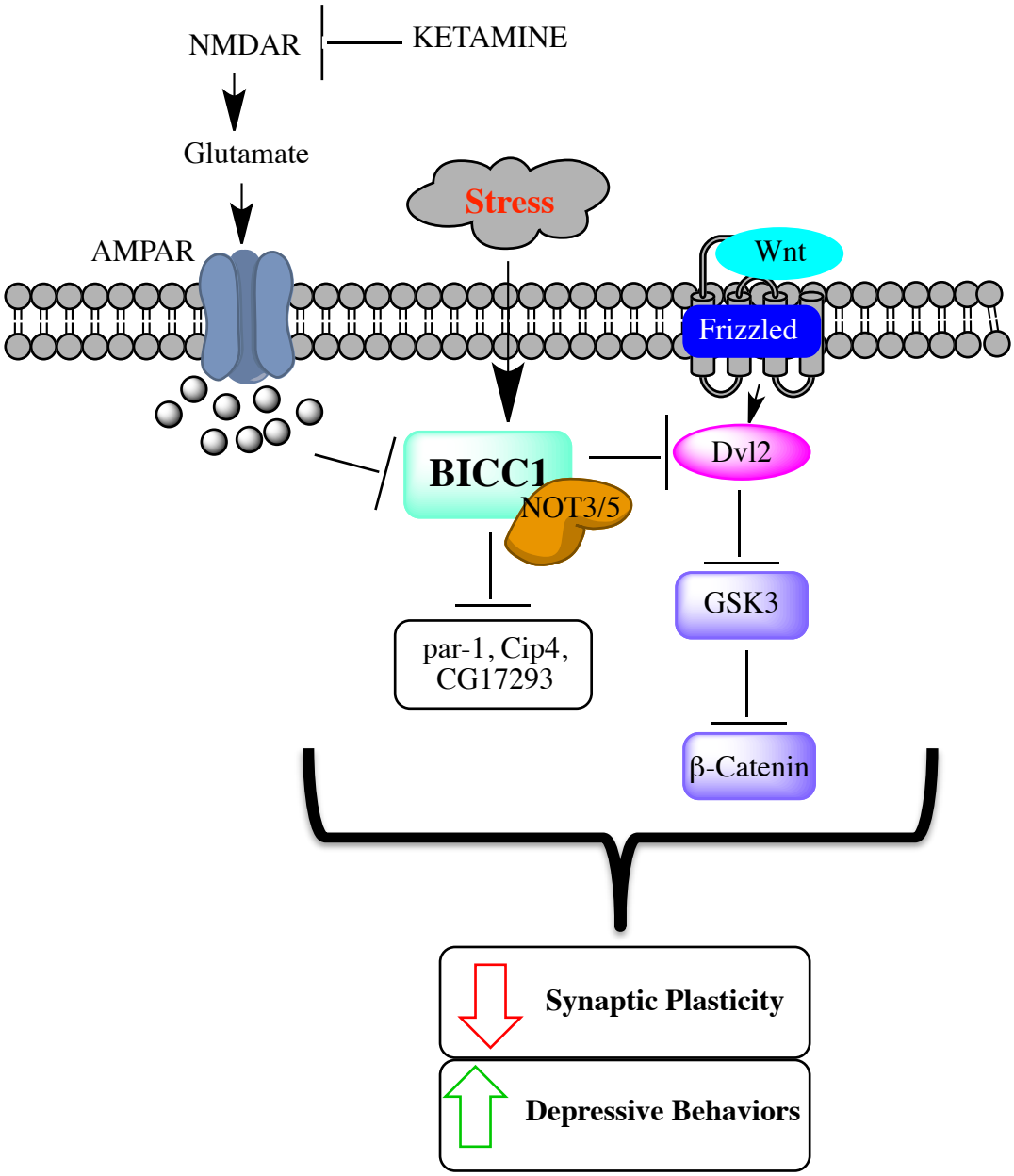
Supplementary Figure 1. BICC1 mRNA expression in the hippocampus is increased by CUS and decreased by ketamine treatment. Rats were subjected to 21 days of CUS or regular handling (Ctrl). Two hours following the final stressor, rats were injected with saline (Sal) or 10mg/kg of ketamine (Ket), then sacrificed 2 hours later. Results are mean (±SEM) fold change for BICC1 mRNA expression (n=7 per group) in the hippocampus. Two-factor ANOVA revealed a significant main effect of drug [$F(1,24)=131.2$; $p<0.0001$] and a significant main effect of stress [$F(1,24)=10.41$; $p<0.01$], but no significant drug x stress interaction ($p=0.104$). Post-hoc analysis showed that all pair-wise comparisons were significant ($p<0.05$), except for CTRL-KET vs. CUS-KET. (*) $p<0.05$ relative to Ctrl/Sal group.



Supplementary Figure 2. BICC1 mRNA expression in HEK293 cells and primary neuronal culture is decreased by BICC1 shRNA treatment. Left. HEK293 cells were treated with either Scrambled or BICC1 shRNA virus, and cells were collected 72 hours later for analysis. Results are mean (±SEM) fold change for BICC1 mRNA expression [AAV-Scrambled, n=4; AAV-BICC1shRNA, n=2]. *Right.* Primary neuronal culture was treated with either Scrambled or BICC1 shRNA virus, and cells were collected 21d later for analysis. Media was changed once per week. Results are mean (±SEM) fold change for BICC1 mRNA expression [n=2 per group]. (*) $p<0.05$ relative to Scrambled group.



Supplementary Figure 3. Knock down of BICC1 does not affect baseline depressive- or anxiety-like behavior or locomotor activity. (A) Results are mean (±SEM) immobility (seconds) in the forced swim test [AAV-Scrambled n=8; AAV-BICC1shRNA n=8]. (B) Results are mean (±SEM) latency to feed (seconds) in the novelty suppressed feeding test [AAV-Scrambled n=8; AAV-BICC1shRNA n=8]. (C) Results are mean (±SEM) time spent in open or closed arms (seconds) in the elevated plus maze test [AAV-Scrambled n=8; AAV-BICC1shRNA n=8]. (D) Results are mean (±SEM) center and border time (seconds) in the open field test [AAV-Scrambled n=8; AAV-BICC1shRNA n=7]. (E) Results are mean (±SEM) distance traveled (m) in the open field [AAV-Scrambled n=8; AAV-BICC1shRNA n=8]. (F) Results are mean (±SEM) mean speed (m/s) in the open field [AAV-Scrambled n=8; AAV-BICC1shRNA n=8].



Supplementary Figure 4. Hypothesized role for BICC1 in regulating synaptic plasticity and depressive behaviors. Ketamine increases glutamate and AMPA receptor activation, presumably via disinhibition of GABAergic interneurons. This leads to decreased levels of BICC1 expression. In contrast, stress increases levels of BICC1, which could influence several different signaling pathways. Notably, BICC1 negatively regulates Dvl2, a component of the Wnt signaling pathway, and could decrease par-1, Cip4, and CG17293, which are all targets associated with synaptic plasticity. We hypothesize that through these interactions and mechanisms, BICC1 regulates synaptic plasticity and depressive behaviors. Abbreviations: NMDA, N-methyl-D-aspartic acid; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid; Dvl2, Disheveled 2, BICC1, bicaudal C homolog1.

	AGE	GENDER	PMI	TISSUE pH	RIN	MEDICATION/ TOXICOLOGY	SUICIDE
	38	M	30	6.7	NA	ND	N
	33	M	23	6.9	NA	ND	N
	54	M	17	6.9	NA	ND	N
	50	F	27	6.7	NA	ND	N
	69	M	18	6.7	NA	ND	N
	54	M	26	6.5	NA	ND	N
	32	M	25	6.9	NA	ND	N
	39	M	21	6.7	NA	ND	N
	66	M	12	7.2	NA	ND	N
	50	M	22	6.8	NA	ND	N
	60	M	10	6.8	9.0	ND	N
	22	M	20	7.0	7.8	ND	N
	64	F	20	6.7	8.8	ND	N
	51	M	16	6.5	8.5	ND	N
	58	F	23	6.4	8.4	ND	N
	39	F	25	6.8	7.5	ND	N
	55	F	11	6.8	9.6	ND	N
	47	M	17	6.6	8.5	ND	N
	51	F	8	6.6	7.1	ND	N
	52	F	23	7.1	8.5	ND	N
	23	F	9	6.1	7.8	ND	N
	54	M	21	6.3	9.0	ND	N
	46	F	15	6.8	8.9	ND	N
	37	F	24	6.7	8.6	ND	N
	43	M	22	6.6	7.2	ND	N
	40	F	17	6.8	8.0	ND	N
	56	M	16	6.8	7.7	ND	N
	45	F	12	6.7	8.2	ND	N
	46	M	22	6.3	8.4	ND	N
	58	F	19	6.7	7.4	ND	N
	65	F	19	6.6	7.0	ND	N
	53	M	23	6.8	8.9	ND	N
	56	M	23	6.5	6.9	ND	N
	57	M	16	6.2	7.5	ND	N
	36	F	15	6.4	8.2	ND	N
	45	M	17	6.6	7.3	ND	N
	37	M	21	6.6	9.0	ND	N
AVG	**48.14**		**18.98**	**6.67**	**8.14**		
SEM	*1.86*		*0.86*	*0.04*	*0.12*		

Supplementary Table 1. Complete demographic information for control subjects from dlPFC study.

Demographic information (age, gender, PMI, tissue pH, RIN, medication/toxicology, and suicide) for control subjects in dlPFC study. PMI = post-mortem interval; RIN = RNA Integrity Number; NA = not available; ND = not detected.

	AGE	GENDER	PMI	TISSUE pH	RIN	MEDICATION/ TOXICOLOGY	SUICIDE
	33	M	18	6.8	NA	Y	N
	36	M	11	7.0	NA	ND	N
	54	M	23	6.2	NA	Y	N
	50	F	23	6.8	NA	Y	Y
	73	F	17	6.6	NA	Y	N
	52	M	17	6.5	NA	ND	Y
	34	F	24	6.3	NA	ND	Y
	42	F	24	6.6	NA	ND	Y
	65	M	30	6.2	NA	ND	Y
	50	F	28	6.5	NA	ND	N
	57	M	13	7.1	8.9	ND	Y
	24	M	13	6.9	9.0	ND	Y
	65	F	18	7.0	9.0	Y	N
	47	M	11	6.8	9.3	ND	N
	54	F	18	6.2	8.2	Y	N
	40	F	22	6.6	7.4	ND	N
	53	F	12	6.7	8.7	Y	N
	46	M	16	6.3	8.0	ND	Y
	52	F	10	6.5	8.4	Y	N
	49	F	23	6.4	8.1	Y	N
	26	F	13	6.4	7.8	Y	Y
	57	M	16	6.6	7.6	Y	N
	47	F	22	6.6	8.0	ND	Y
	28	F	25	6.6	7.2	ND	N
	44	M	19	6.5	7.5	ND	N
	40	F	11	6.5	9.0	Y	N
	58	M	13	6.8	8.1	Y	N
	39	F	13	6.4	9.0	Y	Y
	46	M	23	6.6	8.8	Y	N
	50	F	19	6.4	8.6	Y	N
	64	F	12	6.6	7.8	Y	N
	51	M	25	6.5	8.1	ND	N
	55	M	24	6.5	7.2	ND	N
	61	M	16	6.6	8.4	ND	N
	37	F	16	6.6	7.0	Y	N
	42	M	14	6.4	7.6	Y	Y
	36	M	20	6.8	8.9	Y	N
AVG	**47.49**		**18.16**	**6.56**	**8.21**		
SEM	*1.87*		*0.88*	*0.04*	*0.11*		

Supplementary Table 2. Complete demographic information for MDD subjects from dlPFC study. Demographic information (age, gender, PMI, tissue pH, RIN, medication/toxicology, and suicide) for MDD subjects in dlPFC study. PMI = post-mortem interval; RIN = RNA Integrity Number; NA = not available; ND = not detected.

	AGE	GENDER	PMI	TISSUE pH	RIN	MEDICATION/ TOXICOLOGY	SUICIDE
	56	M	25	6.14	5.6	ND	NO
	37	M	17	6.47	5.4	ND	NO
	80	F	21	6.78	5.8	ND	NO
	69	M	18	6.7	7.3	ND	NO
	77	M	24	6.56	5.5	ND	NO
	82	M	16	6.72	6.2	ND	NO
	66	M	12	7.17	7.5	ND	NO
AVG	**66.71**		**19.00**	**6.65**	**6.19**		
SEM	6.01		1.75	0.12	0.33		

	AGE	GENDER	PMI	TISSUE pH	RIN	MEDICATION/ TOXICOLOGY	SUICIDE
	54	M	23	6.24	4.6	Y	YES
	46	M	17	6.26	5.5	ND	NO
	77	F	32	6.79	5.8	Y	NO
	73	M	18	6.59	6.8	Y	YES
	77	M	26	6.74	4.7	Y	YES
	82	M	12	6.46	5.2	Y	YES
	68	M	4	6.21	5.7	Y	YES
AVG	**68.14**		**18.86**	**6.47**	**5.47**		
SEM	5.03		3.49	0.09	0.28		

Supplementary Table 3. Complete demographic information for postmortem subjects from DG study. Top: Demographic information (age, gender, PMI, tissue pH, RIN, medication/toxicology, and suicide) for control subjects in DG study. Bottom: Demographic information (age, gender, PMI, tissue pH, RIN, medication/toxicology, and suicide) for MDD subjects in DG study. PMI = post-mortem interval; RIN = RNA Integrity Number; NA = not available; ND = not detected.

	AGE	GENDER	PMI	TISSUE pH	RIN	MEDICATION/ TOXICOLOGY	SUICIDE
	37	M	17	6.47	6.4	ND	NO
	69	F	16	6.38	5.4	Y	NO
	26	M	13	6.66	NA	ND	NO
	47	M	25	6.1	5.9	Y	NO
	84	F	22	6.23	5.4	ND	NO
	82	M	16	6.72	2.9	ND	NO
	66	M	12	7.17	7.1	ND	NO
AVG	**58.71**		**17.29**	**6.53**	**5.52**		
SEM	8.48		1.77	0.13	0.54		

	AGE	GENDER	PMI	TISSUE pH	RIN	MEDICATION/ TOXICOLOGY	SUICIDE
	46	M	17	6.26	4.8	ND	NO
	67	F	17	6.68	6	Y	NO
	30	M	18	6.91	5.1	Y	YES
	42	M	20	6.8	6.1	ND	YES
	87	F	24	6.56	4.1	Y	NO
	82	M	12	6.46	6.4	Y	YES
	68	M	4	6.21	5.8	Y	YES
AVG	**60.29**		**16.00**	**6.55**	**5.47**		
SEM	8.09		2.42	0.10	0.31		

Supplementary Table 4. Complete demographic information for postmortem subjects from CA1 study. Top: Demographic information (age, gender, PMI, tissue pH, RIN, medication/toxicology, and suicide) for control subjects in CA1 study. Bottom: Demographic information (age, gender, PMI, tissue pH, RIN, medication/toxicology, and suicide) for MDD subjects in CA1 study. PMI = post-mortem interval; RIN = RNA Integrity Number; NA = not available; ND = not detected.