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Synaptic Mechanisms Regulating Mood State Transitions in Depression
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Supplemental Materials

Supplemental Table 1. **Antidepressants reverse the effects of stress on structural and functional properties of neurons in multiple brain regions.** A selection of studies assessing antidepressant effects on structural (green) and functional (blue) endpoints in stress and depression models. CA3, cornu Ammonis subfield 3; DG, dentate gyrus; mPFC, medial prefrontal cortex; PL, prelimbic cortex; Cg, cingulate cortex; NAc, nucleus accumbens; D1, dopamine receptor 1; LHb, lateral habenula; vHb, ventral habenula (homolog of LHb); CRS, chronic restraint stress; CORT, chronic corticosterone administration; CMS, chronic mild stress; UMS, unpredictable mild stress; CUS, chronic unpredictable stress; cLH, congenital learned helplessness; TBG, tabernanthalog

Study	Stressor	Brain region	Antidepressant	Endpoint	Effect direction	
					Stress	Antidepressant
Watanabe et al. 1992	CORT	Hippocampus, CA3	Tianeptine	Dendrite length	↓	↑
				Dendrite complexity	↓	↑
	CRS			Dendrite length	↓	↑
				Dendrite complexity	↓	↑
Bessa et al. 2009	CMS	Hippocampus, CA3	Fluoxetine	Dendrite length	↓	↑
				Spine density	↓	↑
			Imipramine	Dendrite length	↓	↑
				Spine density	↓	↑
		Hippocampus, DG	Fluoxetine	Dendrite length	↓	↑
				Spine density	↔	↔
			Imipramine	Dendrite length	↓	↑
				Spine density	↔	↔

		PL	Fluoxetine	Dendrite length	↓	↑
				Spine density	↓	↑
			Imipramine	Dendrite length	↓	↑
				Spine density	↓	↑
Moda-Sava, Murdock, Parekh, et al. 2019	CORT	mPFC	Ketamine	Spine formation	↓	↑
				Multicell. ensembles (Ca2+)	↓	↑
Li et al. 2011	CUS	Cg/PL	Ketamine	Spine density	↓	↑
				Spine diameter	↓	↑
				Spine length	↑	↓
				Synaptic proteins	↓	↑
				5-HT/Hypocretin EPSCs	↓	↑
Lu et al. 2021	UMS	Barrel cortex	TBG	Synch. Firing (Ca2+)	↑	↓
				PV neuron excitability	↓	↑
Berton et al. 2006	CSDS	NAc	Fluoxetine	BDNF signaling genes	↑	↓
LeGates et al. 2018	CMS	NAc D1 MSN	Fluoxetine	AMPA/NMDA ratio	↓	↑
Andalman et al. 2019	Shock	vHb (LHb)	Ketamine	Ca2+ activity	↑	↓
Yang et al. 2018	cLH strain	LHb	Ketamine	Bursting activity	↑	↓
			Fluoxetine	Bursting activity	↑	↔
	CRS	LHb	Ketamine	Bursting activity	↑	↓

Supplemental Discussion: Common Preclinical Stress Models

- **Corticosterone (CORT) administration:** CORT can be administered to animals in drinking water or through implanted pellets. Endogenous corticosterone synthesis and release varies with the circadian cycle and therefore, timed administration is ideal to modulate the naturally occurring circadian rhythm in glucocorticoid activity (Liston et al. 2013).

- **Unpredictable Chronic Mild Stress (UCMS):** The UCMS paradigm and related variants include randomized, daily exposures to various mild stressors over the course of several weeks. Stressed animals develop reward consumption deficits and despair-like behavioral profiles which can be reversed with classic antidepressants including fluoxetine (Frisbee et al. 2015, Willner 1997).

- **Chronic Social Defeat Stress (CSDS):** CSDS is an ethologically relevant paradigm that exploits the natural tendency of rodents to form social dominance hierarchies (Golden et al. 2011, Krishnan et al. 2007, Kudryavtseva et al. 1991). Repeated subordination results in elevated corticosterone, social avoidance, consummatory anhedonia and structural changes in the hippocampus of susceptible animals (Magariños et al. 1996). The basis for resilience to social stress is under active investigation (Cathomas et al. 2019, Wang et al. 2018). Importantly, efforts have been made to adapt the protocol for female rodents, as sex is a significant risk factor for depression (Harris et al. 2018, Yohn et al. 2019).

- **Learned Helplessness (LH)**: Animals exposed to uncontrollable aversive events display maladaptive passive behaviors (Overmier & Seligman 1967). In this paradigm, rodents are tested for active avoidance following inescapable foot-shocks. The increased latency to escape is rescued by classic antidepressants, lending predictive validity to this model. Limitations include questions about its relevance for identifying antidepressant compounds that do not target monoamines and caveats about anthropomorphizing rodent behavior (Nestler & Hyman 2010).

- **Early Life (ELS) and 2-Hit Stress:** Early childhood and adolescence are sensitive periods for long-lasting deleterious effects of stress on brain function and the development of affective disorders (Sánchez et al. 2001). Limited bedding environment paired with maternal separation early in life may increase susceptibility to chronic stress effects on social interaction and reward-seeking behavior in adulthood (Fenoglio et al. 2006, Peña et al. 2019).

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