

PSYCHEDELICS REOPEN THE SOCIAL REWARD LEARNING CRITICAL PERIOD

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CNS Journal Club

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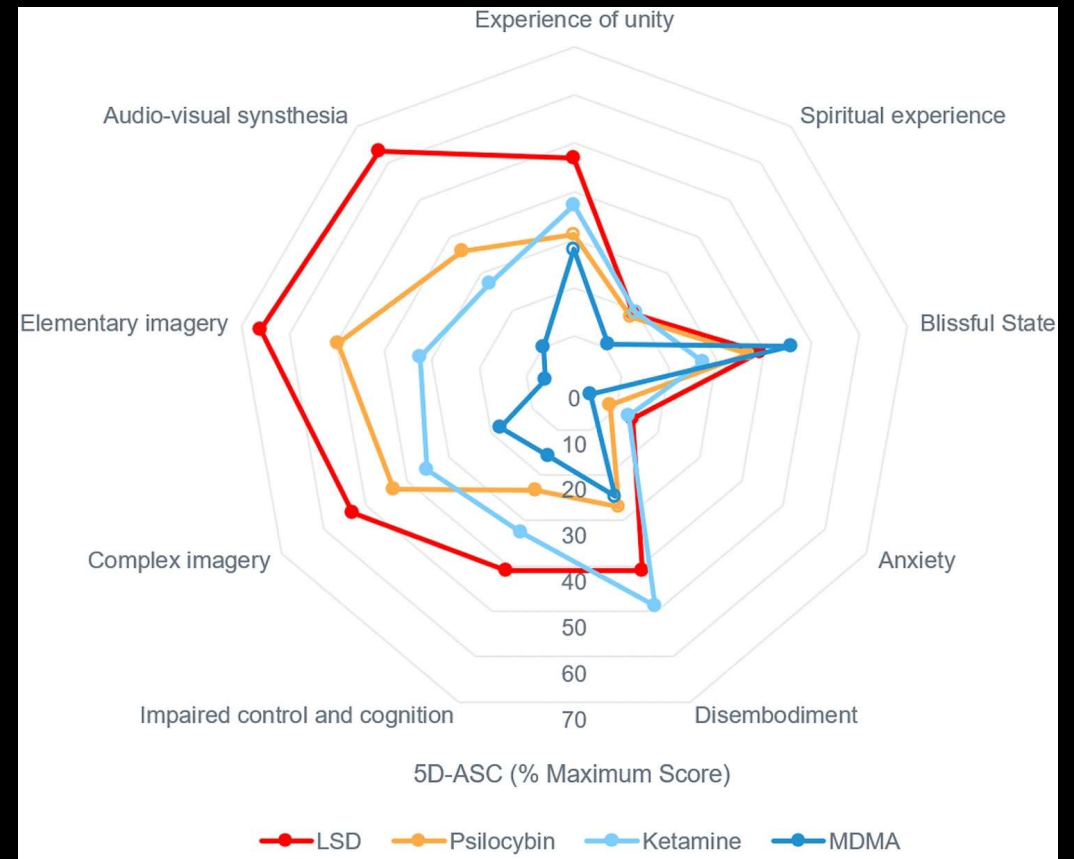
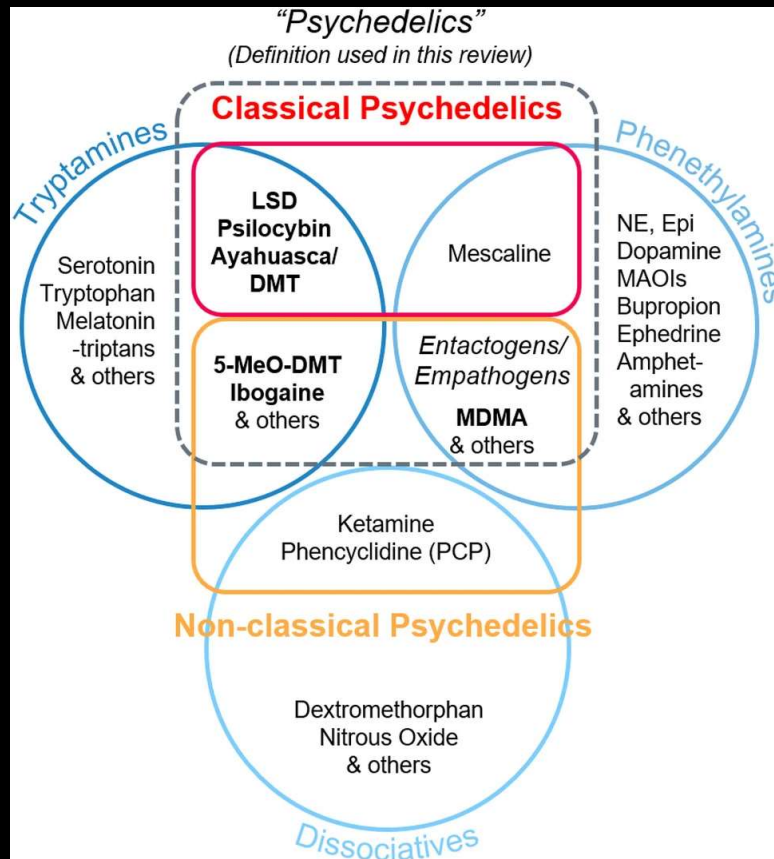
Uris 205



HOW PSYCHEDELIC DRUGS COULD BE USED TO TREAT DEPRESSION, ANXIETY, PTSD



PSYCHEDELICS ENCOMPASS A WIDE ARRAY OF SUBSTANCES WITH VARYING MECHANISMS AND SUBJECTIVE EFFECTS

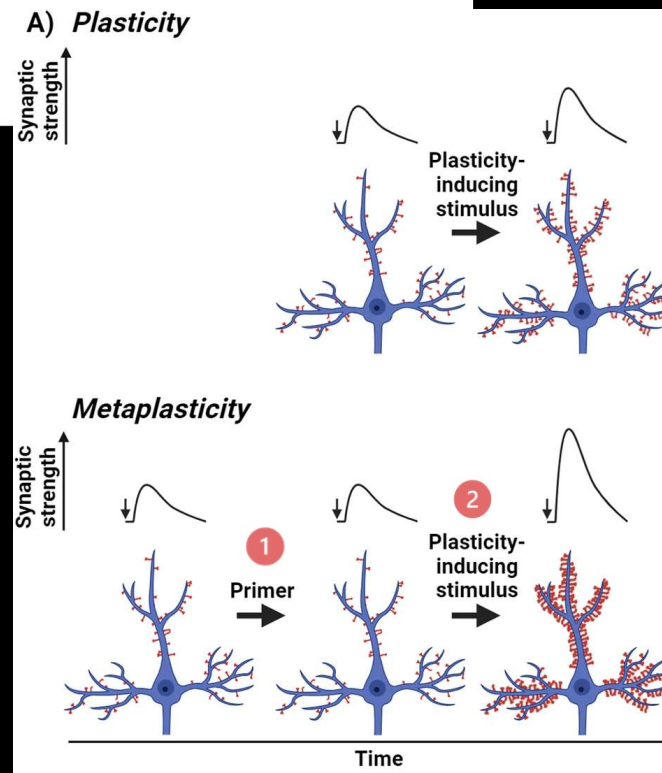


Metaplasticity: the plasticity of synaptic plasticity

Wickliffe C. Abraham¹, Mark F. Bear¹

Synaptic plasticity = adaptive changes that occur at the synapse, resulting in the strengthening or weakening of synaptic connections

Results in enhanced excitatory synaptic transmission and structural plasticity.



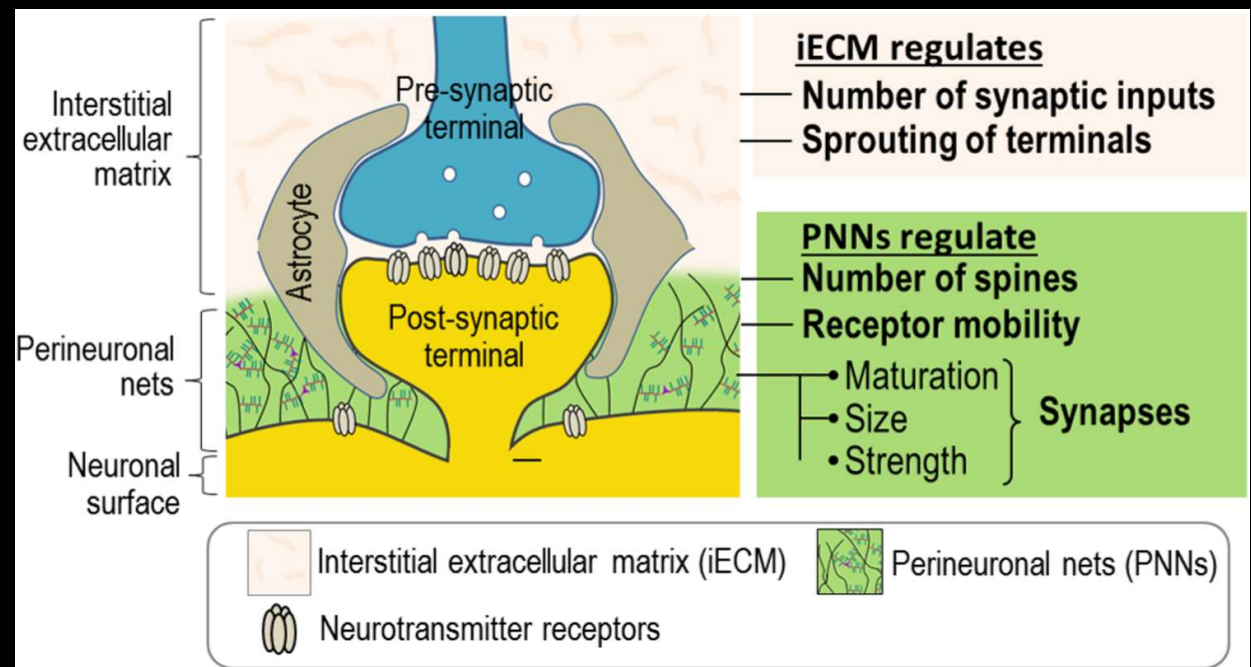
Metaplasticity is a higher-order mechanism where the history of neural activity changes the future capability for plasticity.

A metaplastic stimulation acts as a primer (1), shifting the threshold for altering synaptic efficacy by a successive stimulus.

Leading to the same plasticity induction event (2) eliciting a quantitatively greater evoked EPSP response and augmented structural plasticity

EXTRACELLULAR MATRIX (ECM) REFERS TO A COLLECTION OF EXTRACELLULAR MOLECULES THAT PROVIDES PHYSICAL AND BIOCHEMICAL SUPPORT TO CELLS

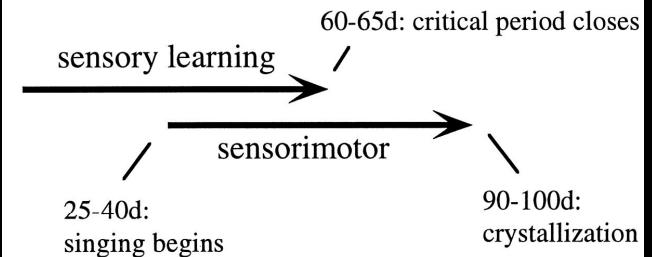
- The ECM in the CNS is mainly composed of fibrous proteins, proteoglycans, and glycoproteins.
- All synapses are embedded in the ECM, either the general interstitial ECM (iECM) found throughout the CNS or the specialized ECM of perineuronal nets (PNNs).
- Diffusion of molecules such as neurotransmitters, ions, guidance molecules, and metabolites are tightly regulated by this 3D structural network.
 - Crucial for synaptic plasticity
- Changes with age by becoming stiffer, more brittle, and less elastic



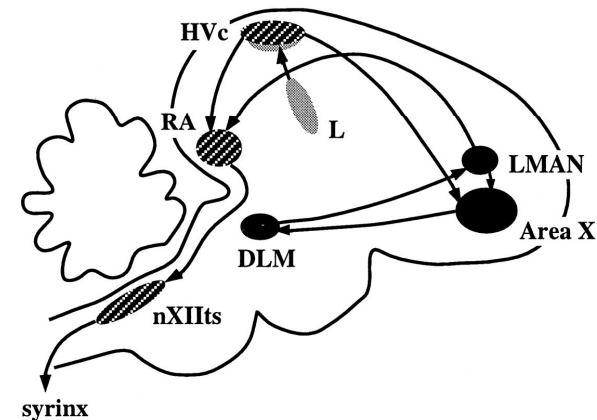
THE EXTRACELLULAR MATRIX (ECM) ACTS AS A "MOLECULAR BRAKE" THAT TERMINATES VARIOUS CRITICAL PERIODS

- **Vocal learning/sensorimotor period:** In songbirds, PNNs in the song nucleus HVC correlates with the end of the sensitive period for learning.

a. Song learning in zebra finches

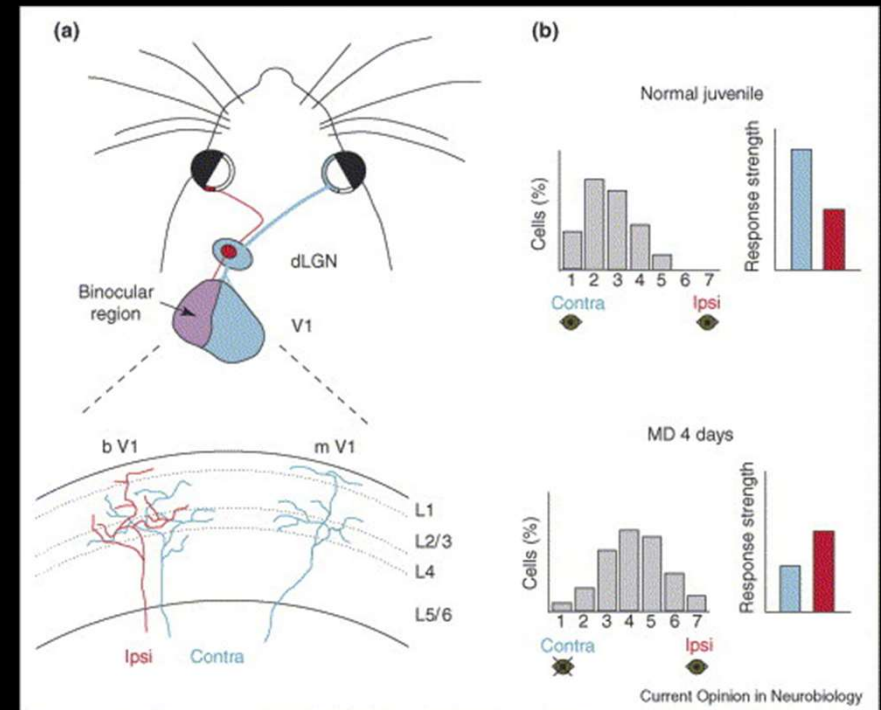


b. The song system

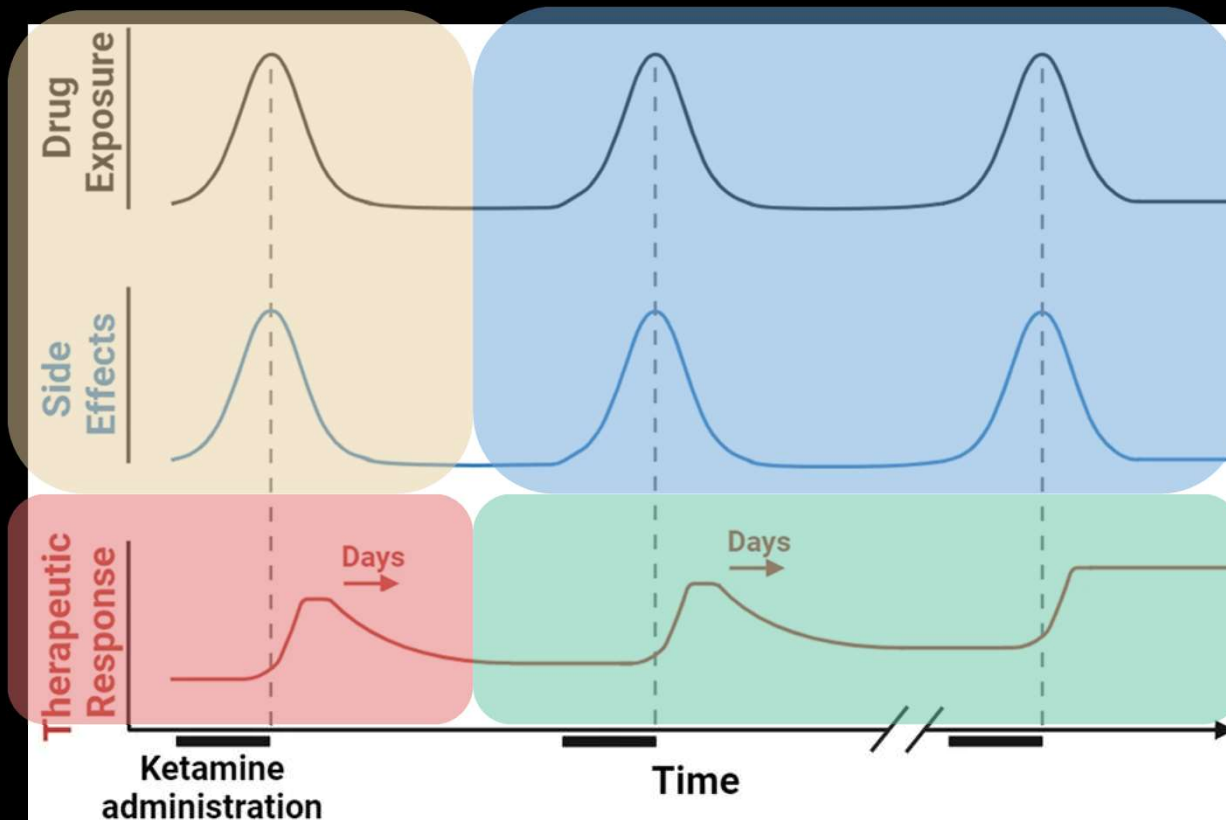


THE EXTRACELLULAR MATRIX (ECM) ACTS AS A "MOLECULAR BRAKE" THAT TERMINATES VARIOUS CRITICAL PERIODS

- **Vocal learning/sensorimotor period:** In songbirds, PNNs in the song nucleus HVC correlates with the end of the sensitive period for learning.
- **Visual system development (Ocular Dominance):** PNNs mature around PV+ neurons in the visual cortex as the critical period for plastic changes to ocular dominance ends.
- **Fear conditioning and memory consolidation:** PNNs are involved in memory consolidation by organizing neuronal oscillations (theta & gamma) and regulating synaptic plasticity in the cortex and hippocampus.



TARGETING METAPLASTIC MECHANISMS TO YIELD PERSISTENT ANTIDEPRESSANT EFFECTS



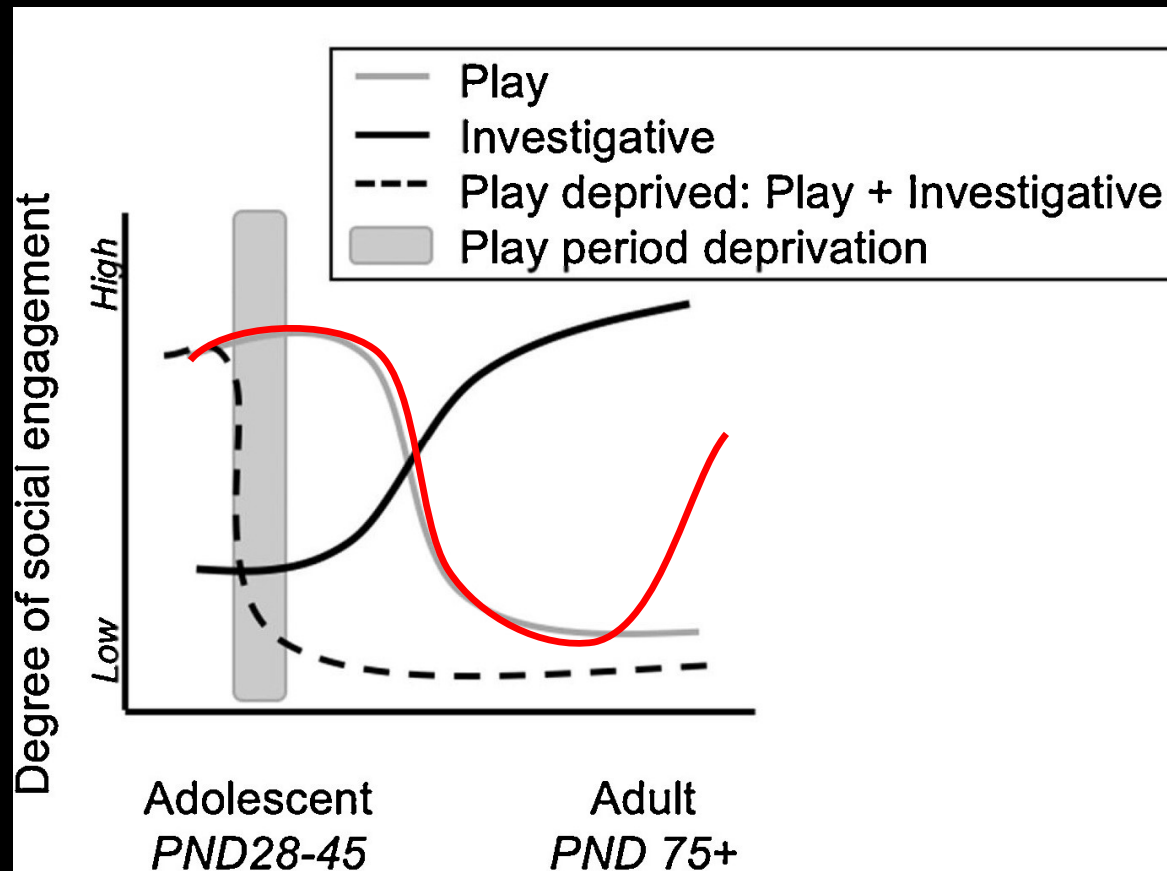
Following intravenous administration, ketamine is rapidly eliminated and side effects generally follow these pharmacokinetics.

Acute antidepressant effects are typically observed after exposure and can extend for hours or days.

Repeated ketamine administration elicits greater antidepressant effects, and these effects typically persist longer than after a single administration.

Reduces dosing frequency and adverse responses because the necessity for the drug to be continuously present is eliminated.

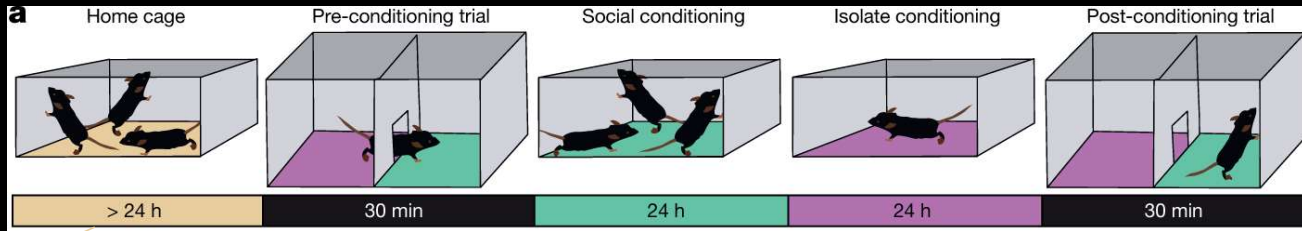
SOCIAL REWARD LEARNING CRITICAL PERIOD IS A TIME IN DEVELOPMENT WHEN THE BRAIN IS RECEPTIVE TO LEARNING THAT SOCIAL INTERACTIONS ARE REWARDING



Can psychedelics reopen this critical period in adulthood?



SOCIAL CONDITIONED PLACE PREFERENCE (SOCIAL CPP = SCPP) ASSAY



After weaning, 4-5 same sex cage mates are socially housed

Corn cob bedding

Each subject used at only one behavioral time point

Subjects placed in a partitioned open field with two equally sized zones (clear plexiglass)

Each zone contained one type of novel bedding

Establish preference for the two sets of bedding cues



Subjects assigned to receive social conditioning with cage mates on one type of bedding

Subjects assigned to experience isolation conditioning with the other type of bedding

Subjects returned to the partitioned open field to establish preference for the two conditioned cues

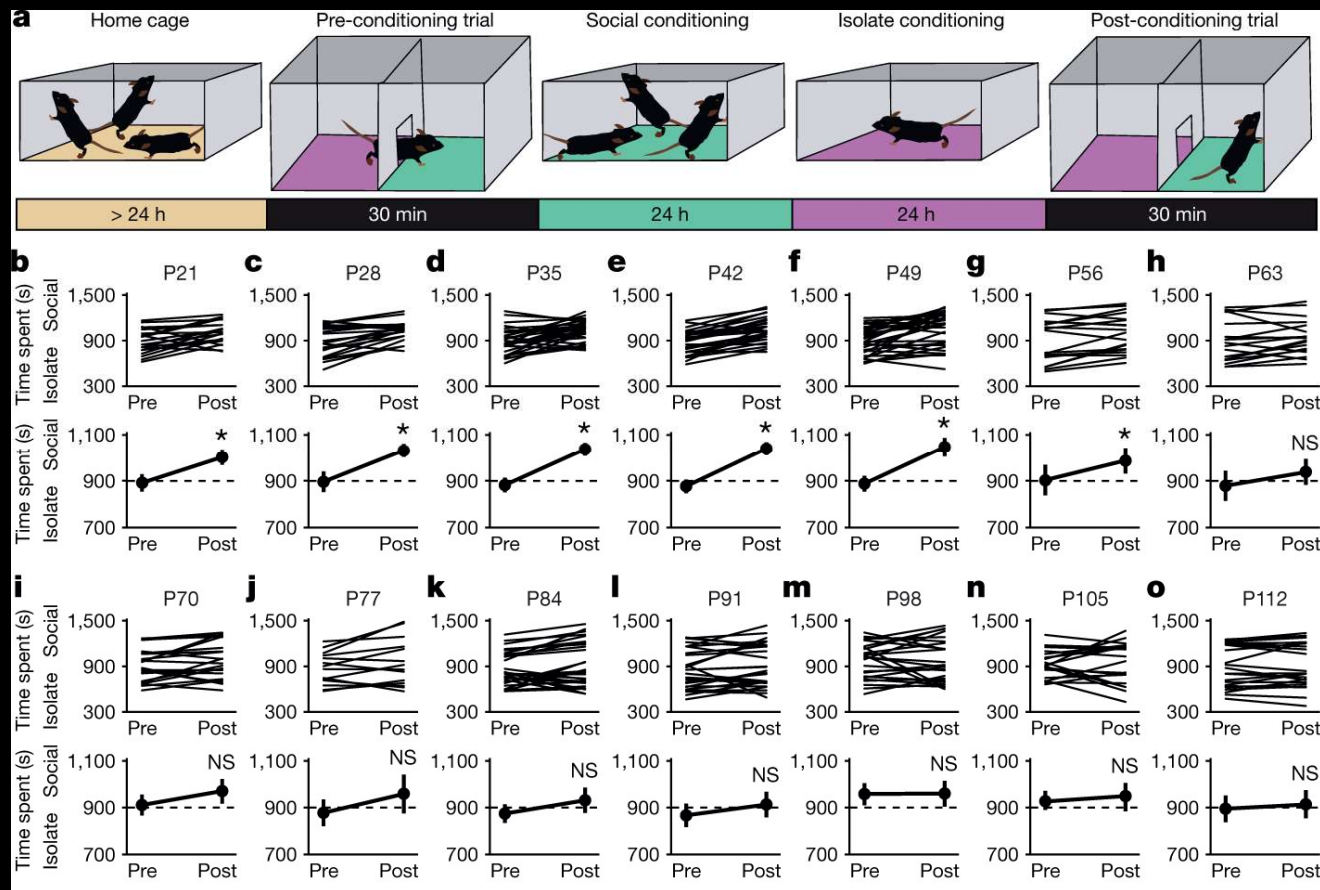
- CPP is a learned association between condition (social or drug) and a cue (bedding or light/dark).
- Does not require scent from other mice.
- Does not measure the quality of social interactions. Subjects never excluded based on the quality of their social interactions.
- The magnitude of the reward learning is almost certainly linked to changes in the types of social interactions animals engage in as they mature (↓ play behavior = ↑ agonistic behavior).

Figure 1 from Nardou *et al.*, 2019 *Nature*

RESPONSES OF MALE MICE FROM P21 TO P112 REVEAL A SIGNIFICANT DEVELOPMENTAL DECLINE IN THE MAGNITUDE OF SOCIAL CPP

Ages were chosen to span milestones in brain development:

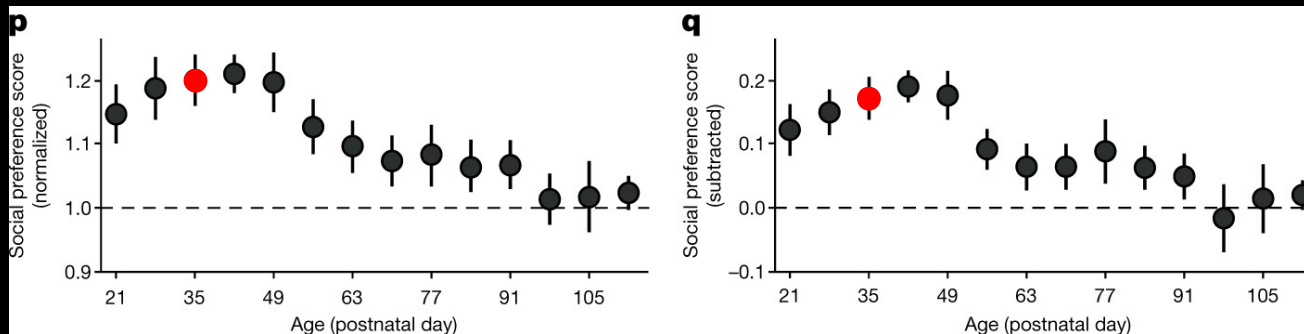
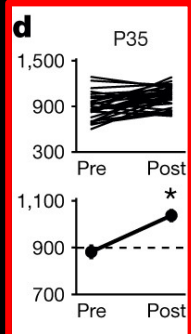
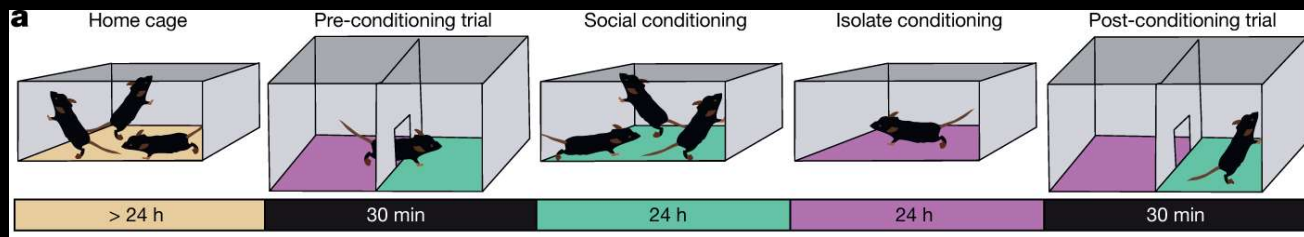
- weaning (P21)
- onset of puberty (P28)
- sexual maturity (P42)
- early adulthood (P63)
- mature adulthood (P90)



- A score of 900 = mouse spent exactly 50% of its time on each of the two beddings
- A score of 1,800 = mouse spent the full 30 min in the bedding that would be subsequently assigned as the social conditioning cue

Figure 1 from Nardou *et al.*, 2019 *Nature*

SOCIAL CPP PEAKS AT P42 AND THEN DECLINES UNTIL THE CLOSURE OF THE CRITICAL PERIOD AT P98

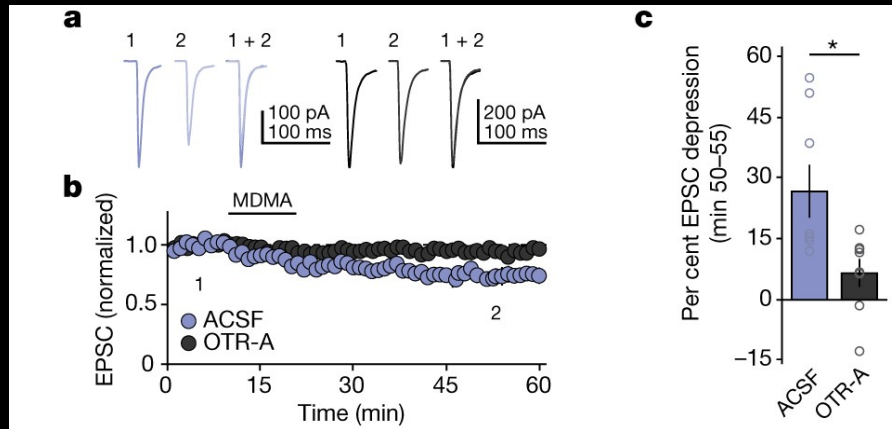


Normalized social preference score = time spent in social zone post-treatment divided by pre-treatment

Subtracted social preference score = time spent in social zone post-treatment minus pre-treatment

Figure 1 from Nardou *et al.*, 2019 *Nature*

OXYTOCIN-DEPENDENT REOPENING OF A SOCIAL REWARD LEARNING CRITICAL PERIOD WITH MDMA



Recorded EPSCs from MSNs in acute slices to characterize the synaptic effects of MDMA in the NAc.

Administered a single intraperitoneal dose of MDMA to adult mice (P96) and assessed the magnitude of SCPP 48 h later.

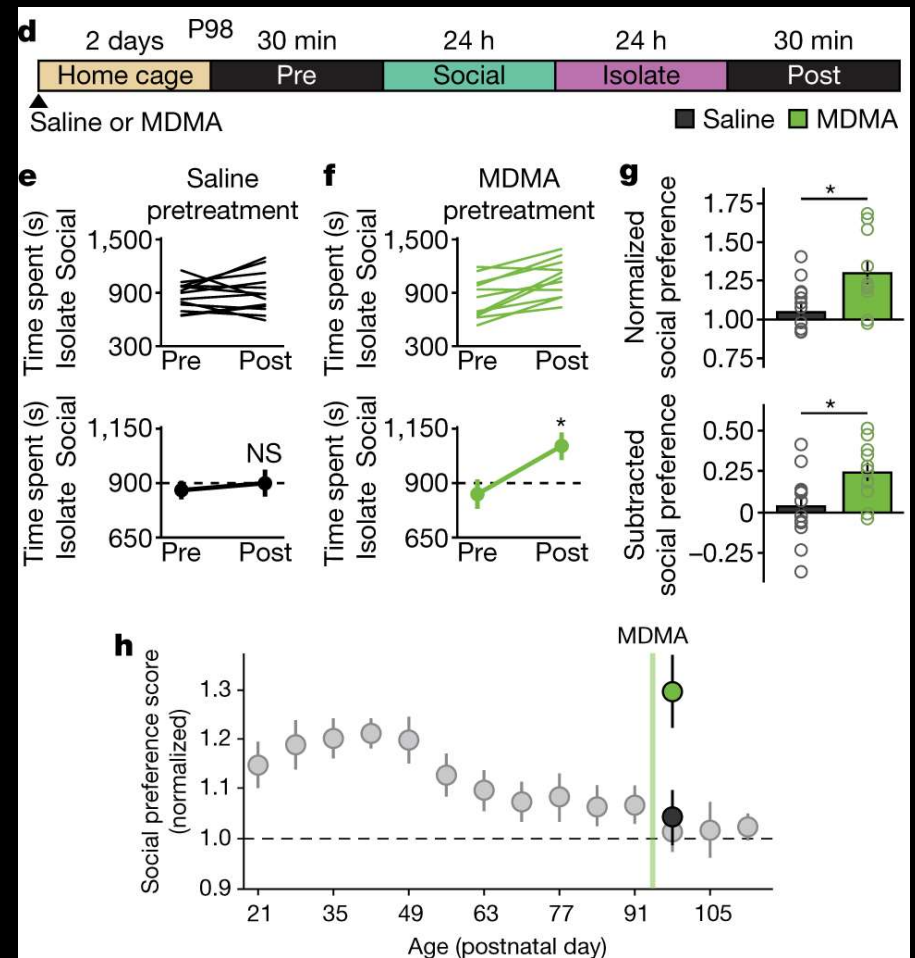
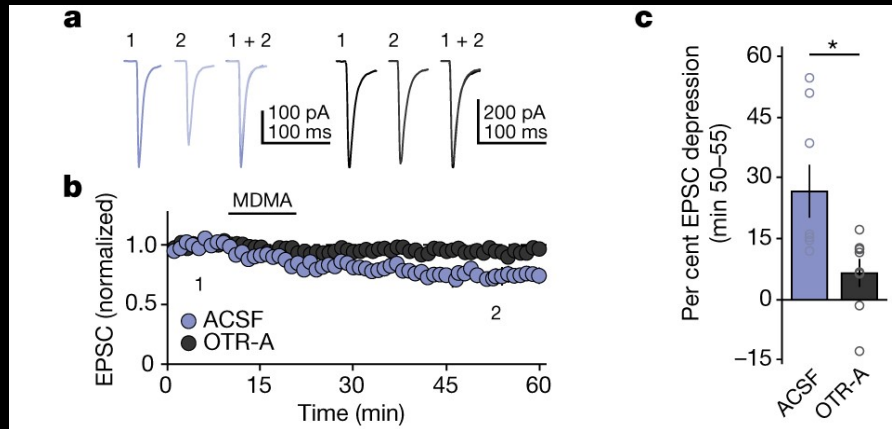


Figure 3 from Nardou *et al.*, 2019 *Nature*

OXYTOCIN-DEPENDENT REOPENING OF A SOCIAL REWARD LEARNING CRITICAL PERIOD WITH MDMA



Delivered MDMA directly into the NAc of adult mice (P96) and assessed the magnitude of SCPP 48 h later.

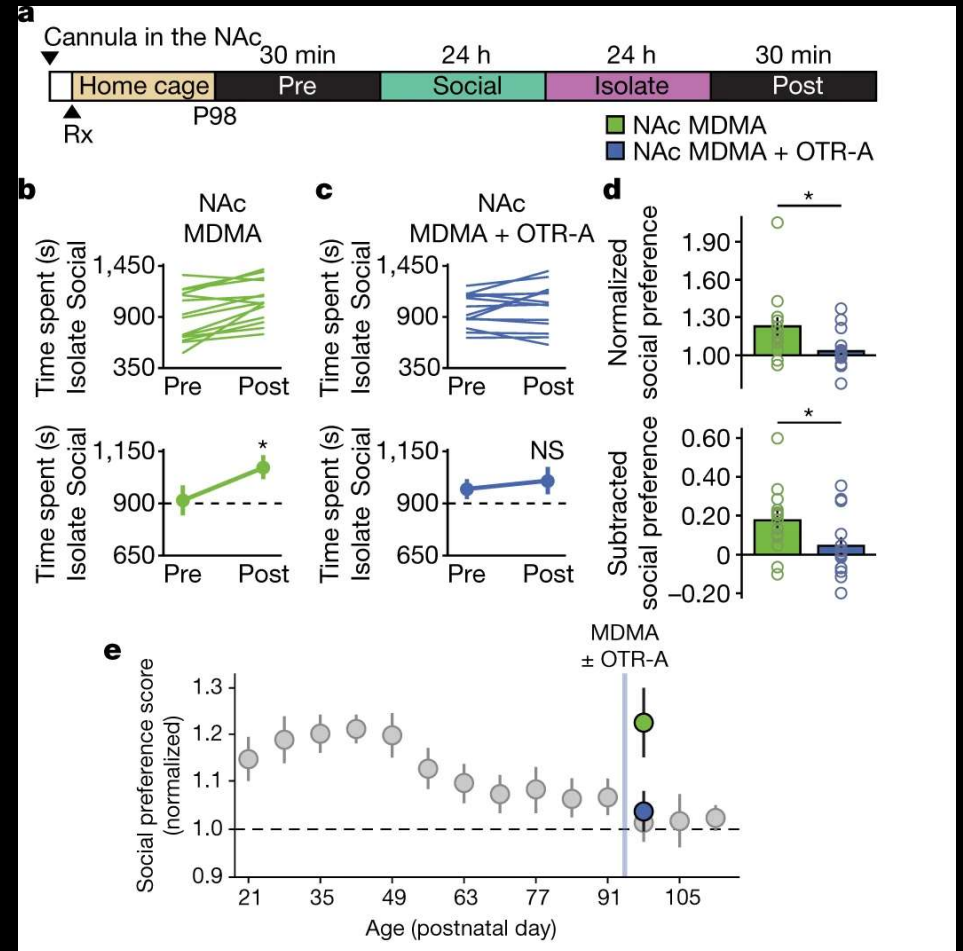
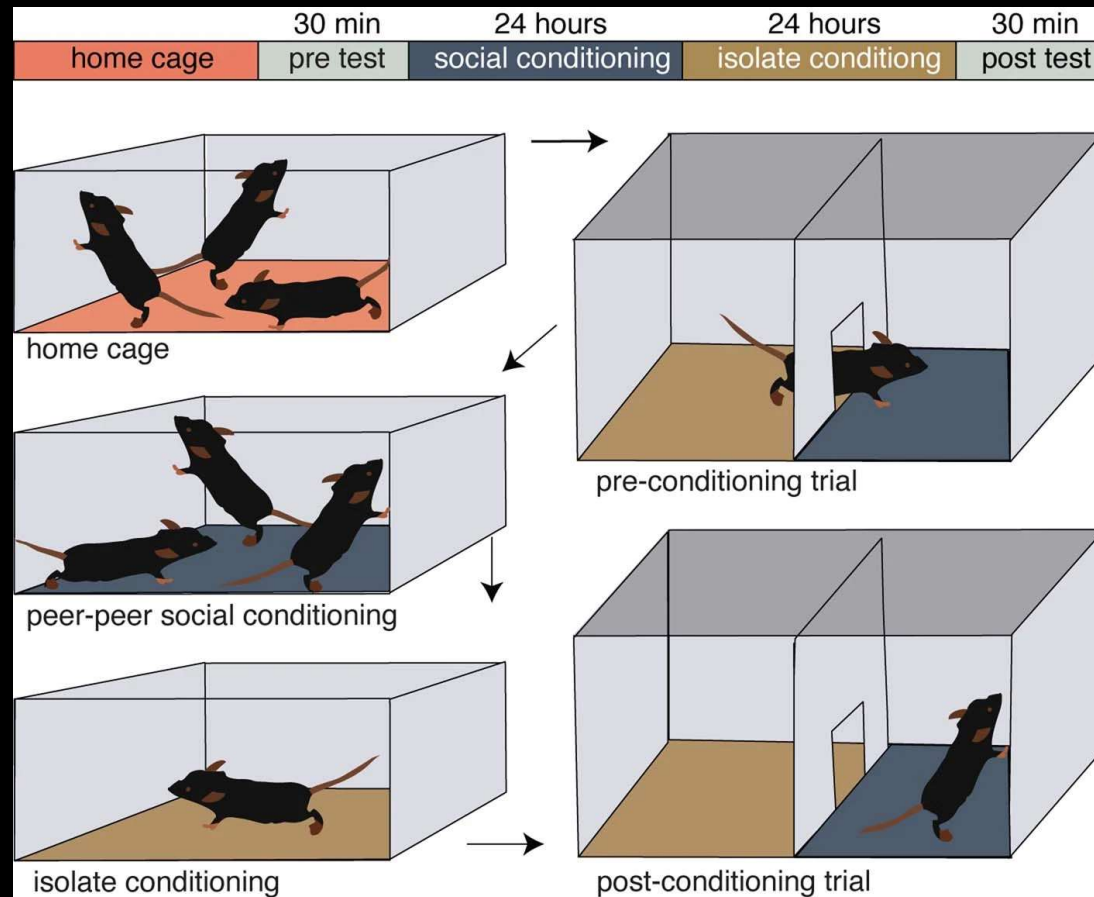


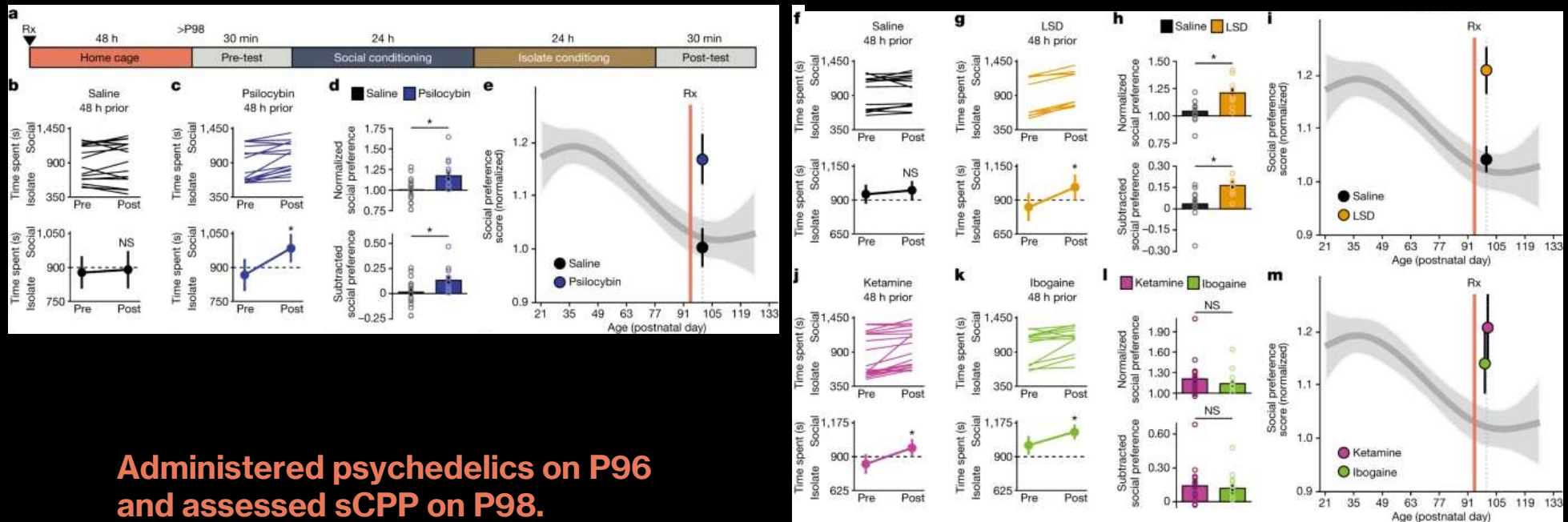
Figure 3 & 4 from Nardou *et al.*, 2019 *Nature*

SOCIAL CONDITIONED PLACE PREFERENCE (SOCIAL CPP = SCPP) ASSAY



Extended Data Figure 1

PSYCHEDELICS REOPEN THE SOCIAL REWARD LEARNING CRITICAL PERIOD

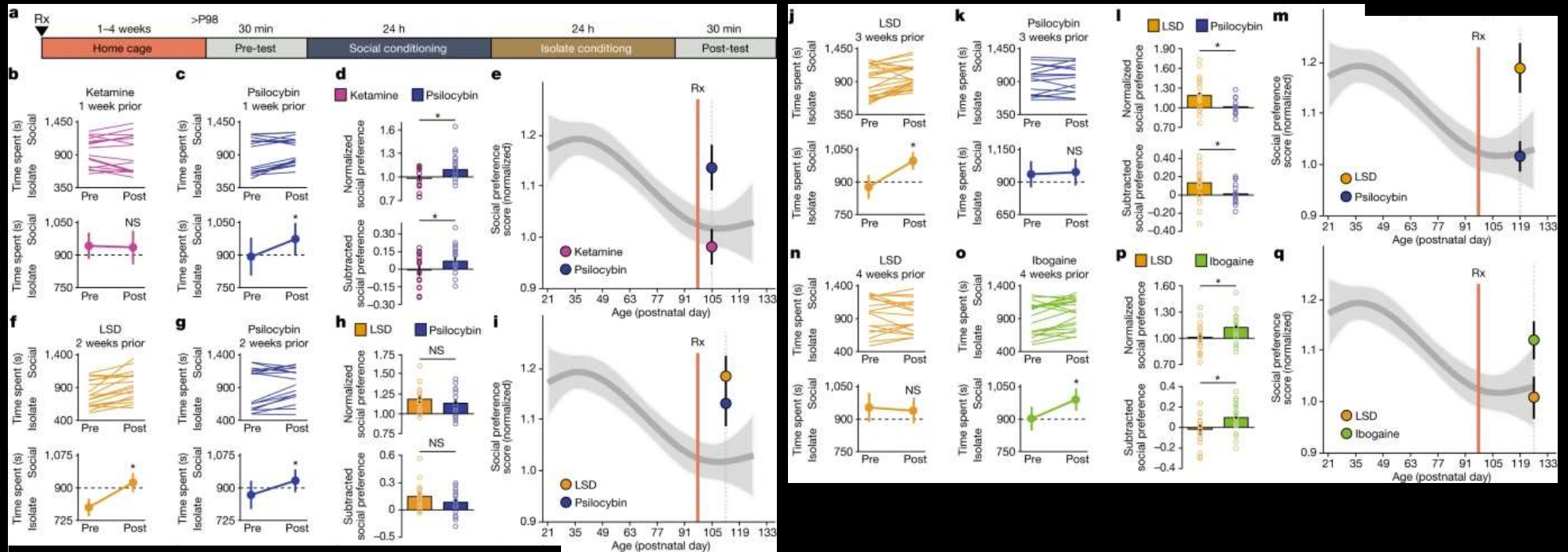


**Administered psychedelics on P96
and assessed sCPP on P98.**

- Psilocybin (i.p. 0.3 mg/kg)
- LSD (i.p. 1 ug/kg)
- Ketamine (i.p. 3 mg/kg)
- Ibogaine (i.p. 40 mg/kg)

Figure 1

THE DURATION OF THE OPEN STATE INDUCED BY PSYCHEDELICS IS VARIABLE



Injected psychedelics on P96 and assessed sCPP at >3 different time points to probe the time course of the critical period open state induced by each psychedelic.

- Psilocybin (i.p. 0.3 mg/kg) → 1, 2, and 3 weeks
- LSD (i.p. 1 ug/kg) → 2, 3, and 4 weeks
- Ketamine (i.p. 3 mg/kg) → 1 week
- Ibogaine (i.p. 40 mg/kg) → 4 weeks

Figure 2

THE DURATIONS OF ACUTE SUBJECTIVE EFFECTS IN HUMANS ARE PROPORTIONAL TO THE DURATIONS OF THE CRITICAL PERIOD OPEN STATE IN MICE

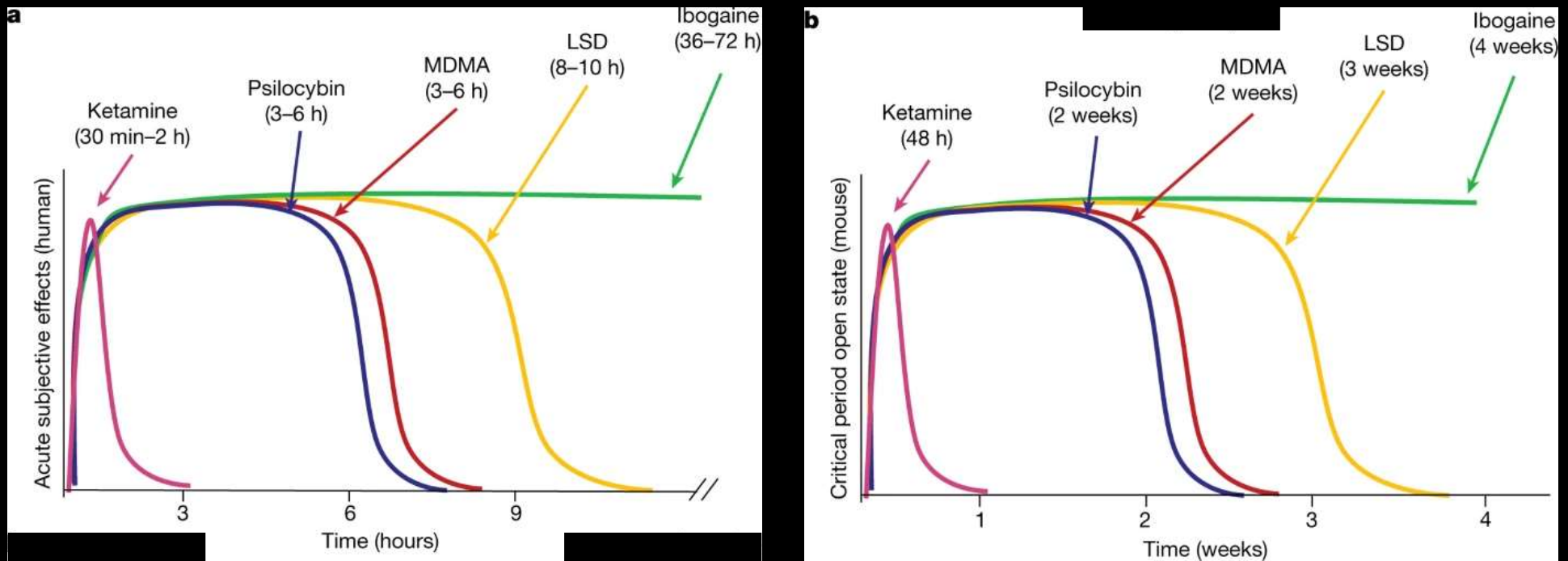
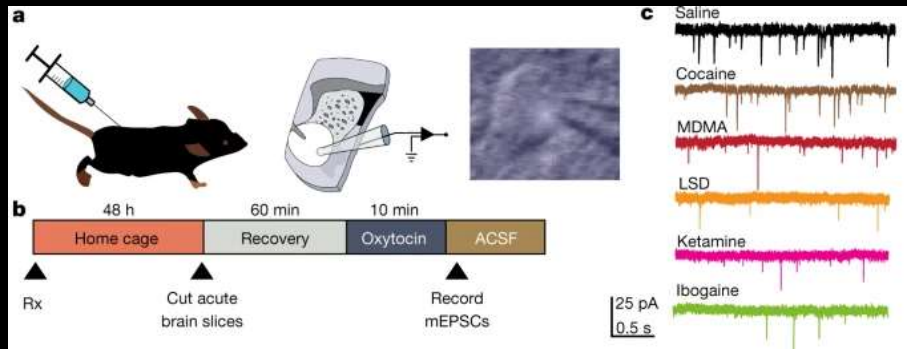


Figure 3

PSYCHEDELICS INDUCE METAPLASTICITY



To determine whether the ability to induce metaplastic upregulation of oxytocin plasticity generalizes across psychedelics, adult mice were pretreated with either saline, cocaine or psychedelics.

48 hours or 2 weeks later *ex vivo* acute slices containing the nucleus accumbens (NAc) were prepared and whole-cell voltage-clamp recordings were conducted from MSNs.

“...psychedelics induce metaplasticity rather than hyperplasticity...”

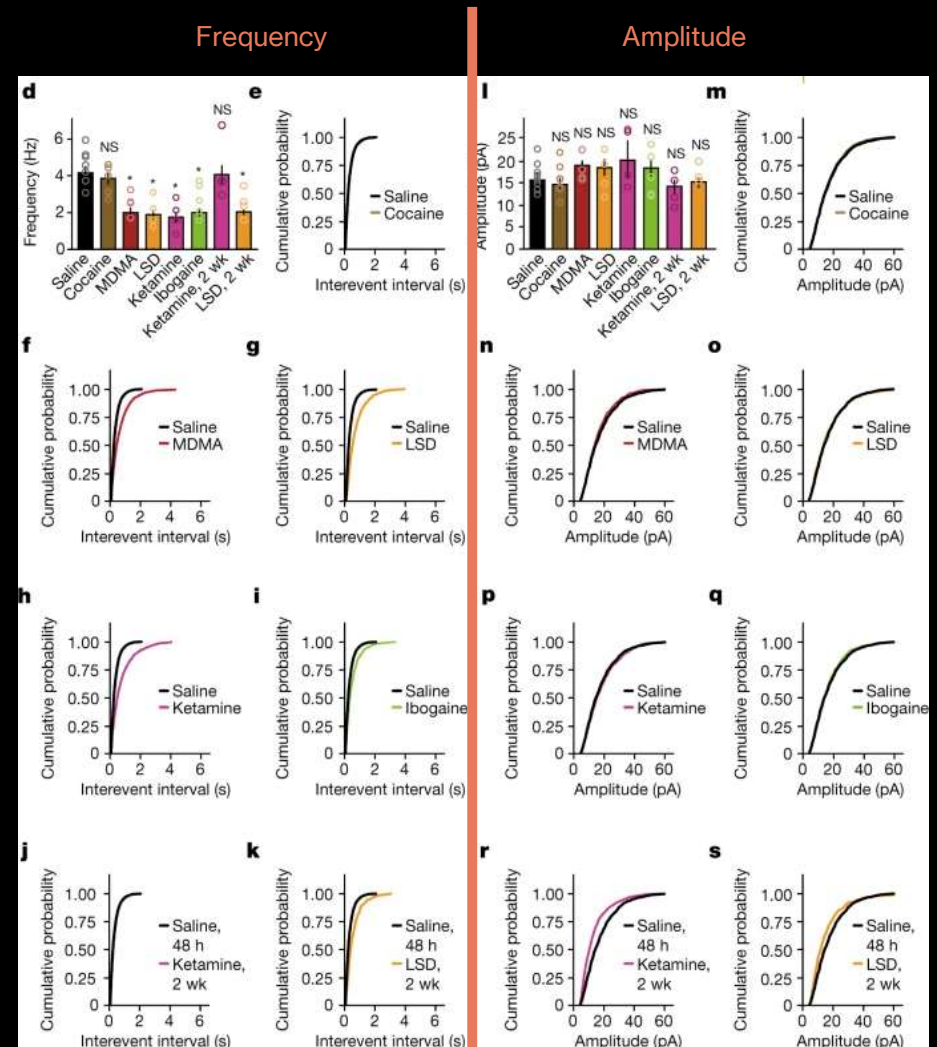
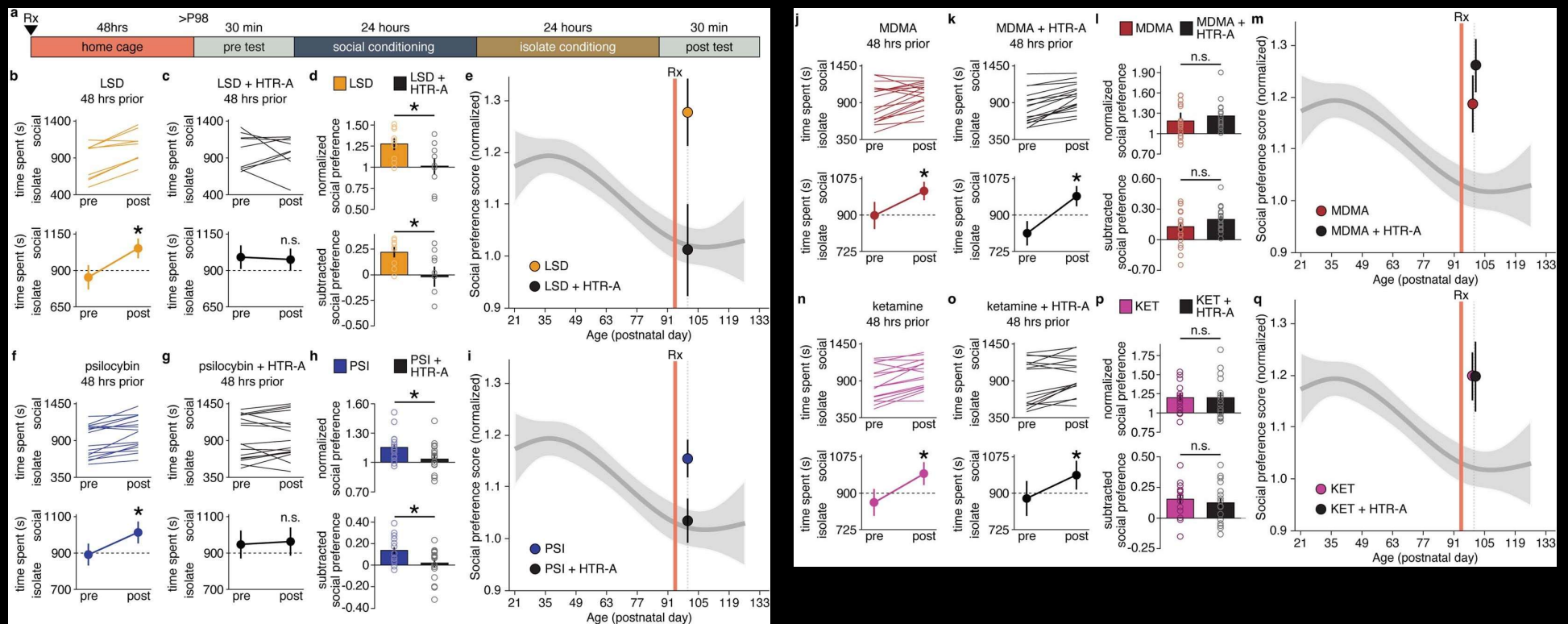


Figure 4

SEROTONIN 2A RECEPTORS (5-HT_{2A}R) ARE NOT UNIVERSALLY REQUIRED FOR CRITICAL PERIOD REOPENING

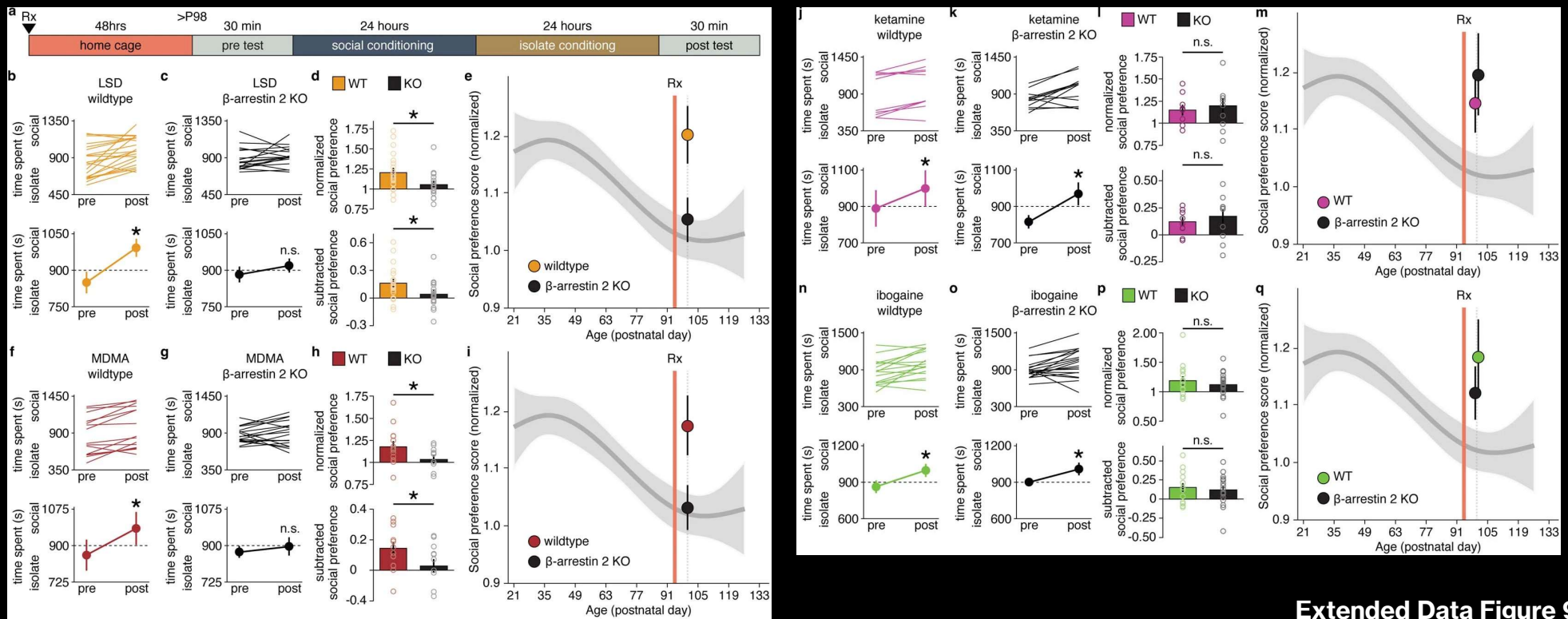
- 5-HT_{2A}R mediates alterations of perception and cognition induced by 'serotonergic psychedelics.'
- MDMA triggers synaptic efflux of serotonin through its binding at the serotonin transporter SERT.
- Some of the effects of ketamine are reportedly mediated by 5-HT_{2A}R.



Extended Data Figure 7

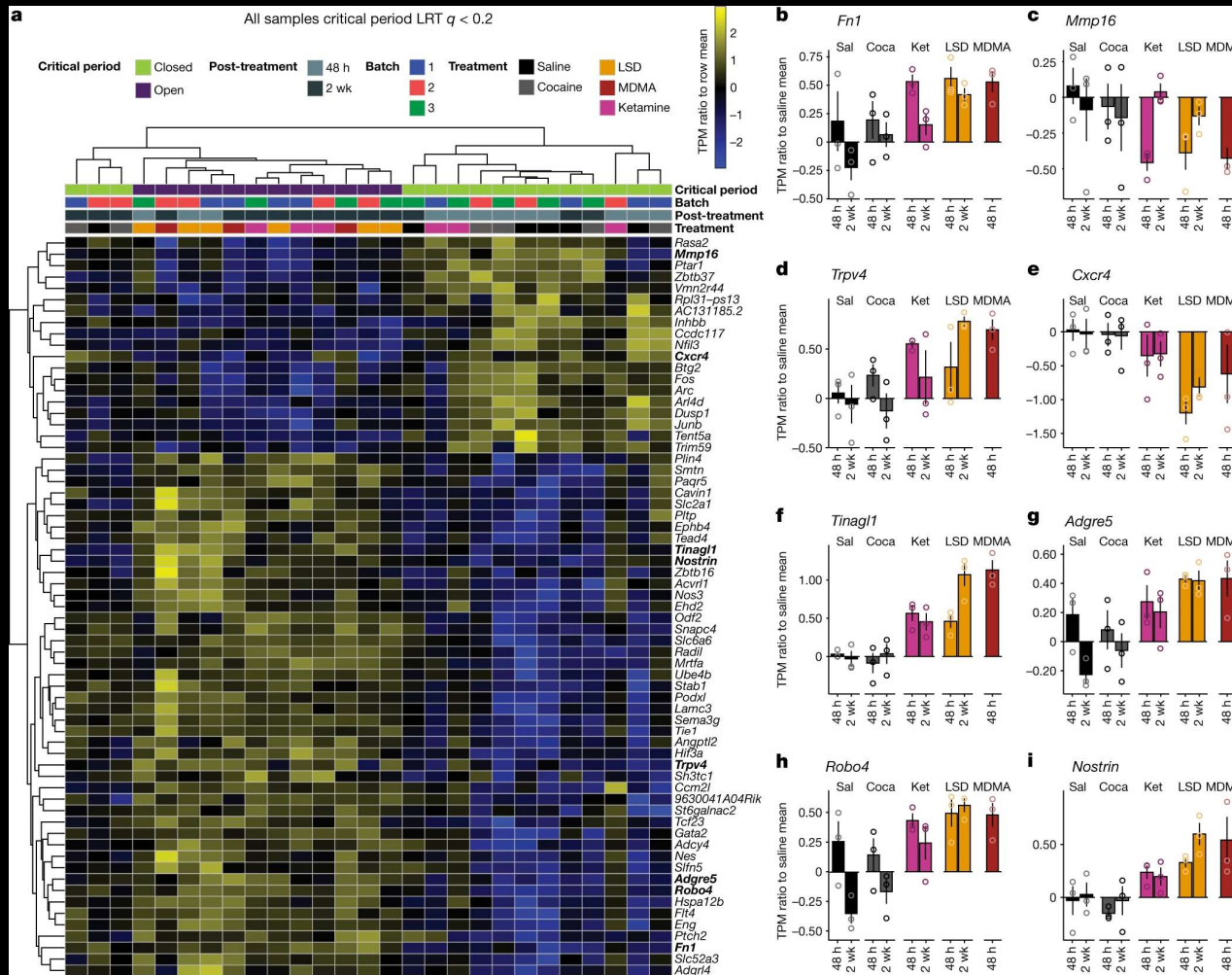
B-ARRESTIN-2 IS NOT UNIVERSALLY REQUIRED FOR CRITICAL PERIOD REOPENING

- Prolonged LSD binding to 5-HT_{2A}R triggers β -arrestin-2-biased signaling over canonical G-protein signaling.
- The effects of MDMA and ibogaine are mediated by metabotropic G-protein-coupled receptors (GPCRs).
- Although the therapeutic effects of ketamine are thought to be mediated by ionotropic NMDA receptors, the metabotropic glutamate receptor 5 has also been implicated.
- **Juvenile and adult β -arr2-KO mice exhibit the normal maturational profile of social reward learning**



Extended Data Figure 9

THE SHARED ABILITY OF PSYCHEDELICS TO REOPEN THE SOCIAL REWARD LEARNING CRITICAL PERIOD CONVERGES AT TRANSCRIPTIONAL REGULATION OF THE ECM



65 DEGs (open vs closed state)

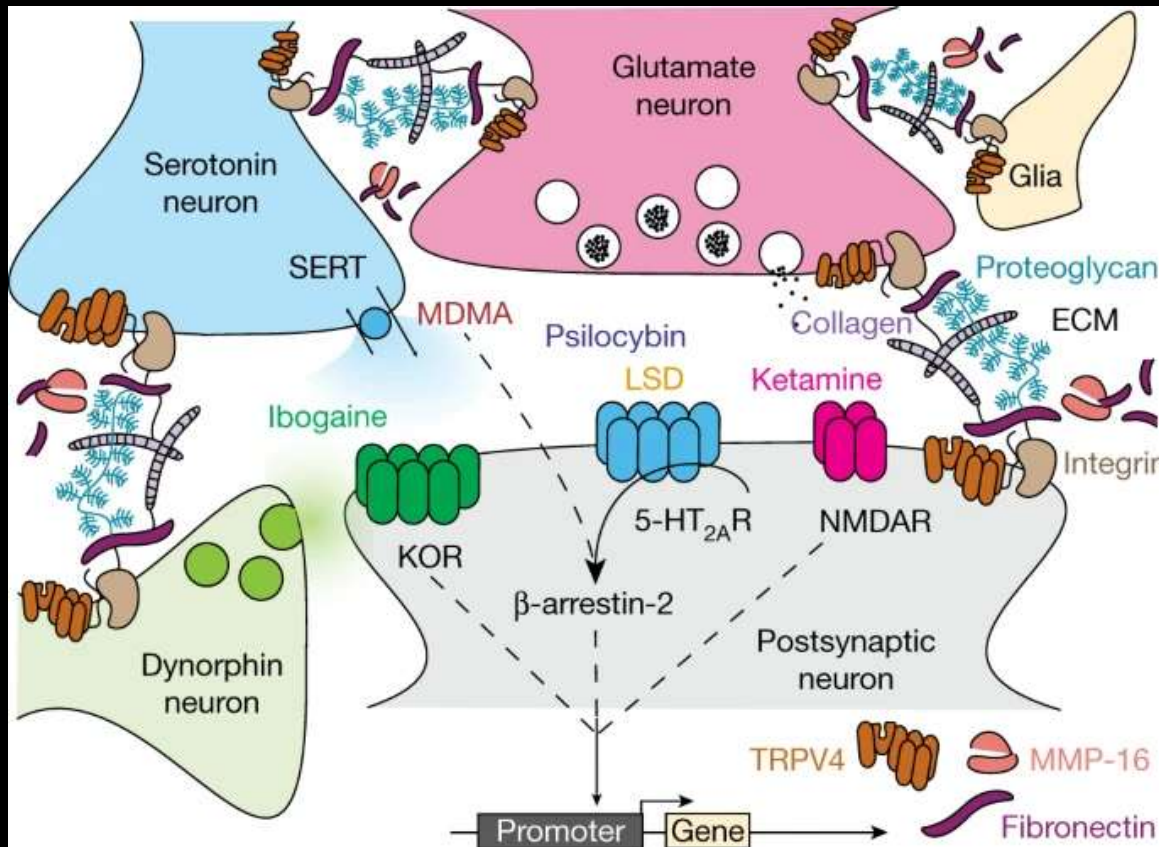
- Gene set enrichment analysis: significant enrichment of ontologies associated with endothelial development, regulation of angiogenesis, vascular development and tissue morphogenesis.
- Many of the top scoring genes are components of the extracellular matrix (ECM) or have been implicated in its remodeling
- Includes the immediate early genes (IEGs) *Fos*, *Junb*, *Arc* and *Dusp*

39 DEGs (saline vs all drugs)

- Enrichment analysis identified no significant ontologies

Figure 5

WORKING MODEL OF CONVERGENT CELLULAR MECHANISMS OF PSYCHEDELICS



Psychedelics act at a diverse array of binding targets (SERT, 5-HT_{2A}R, NMDAR and KOR), to trigger a downstream signaling response that leads to activity-dependent (perhaps via IEG-mediated coincidence detection) degradation of the ECM.

In turn, it is the permissive event that enables metaplasticity.

In this model, transcriptional upregulation of ECM components (FN1) and downregulation of ECM proteolytic enzymes (MMP-16), reflects the homeostatic response to these long-lasting cellular changes.

Figure 6

THIS IS ALL THEORY...BUT WHY IS IT IMPORTANT?

- We might be able to "reset" the clock, allowing adults to develop social intuition or communication skills that they missed out on earlier in life.
- Instead of "numbing" the brain indefinitely, a clinician might use a psychedelic to "open the window" briefly and provide intensive therapy to "rewire" the brain.
- If we can reopen the period for motor learning, we might be able to help stroke victims regain movement in limbs that were previously thought to be permanently paralyzed.

