Psychedelics enhance the effects of brain stimulation in rodents

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Abstract

Background: Psychedelics have resurged in neuroscience and psychiatry with promising success in psychedelic-assisted therapy for the treatment of anxiety, depression, and addiction. At the cellular level, psychedelics elicit neuroplastic processes 24 hours after administration, priming neural circuits for change. The acute effects of psychedelics are well characterized with functional imaging and neural oscillations showing an increase in the entropy of spontaneous cortical activity.

Hypotheses: We hypothesized that cortical-striatal oscillations recorded in rats would confirm the effects of psychedelics. We also hypothesized that brain stimulation delivered 24 hours after LSD administration would lead to different effects than brain stimulation alone.

Methods: We recorded local field potential (LFP) oscillations from rats following lysergic acid diethylamide (LSD) or saline administration and determined if exposure to these treatments altered the effect of a targeted intervention (brain stimulation) 24 hours later.

Results: We confirmed acutely decreased low frequency power across the brain when rats are given LSD. We also demonstrated these altered states return to baseline after 24 hours. Brain stimulation applied in this window of heightened neuroplasticity produced distinct shifts in brain state compared to brain stimulation applied 24 hours after saline.

Conclusions: Despite the acute effects of LSD disappearing after 24 hours, there are still latent effects that synergize with brain stimulation to create different changes in brain activity compared to brain stimulation alone. Our findings are the first to suggest that psychedelics could have a role clinically in combination with brain stimulation to achieve enhanced effects on brain activity and clinical outcomes.

Keywords: psychedelics, neuromodulation, electrophysiology, rodent

Introduction

Psychedelics have achieved breakthrough status from the Food and Drug Administration after remarkable success for the treatment of depression (1) and post-traumatic stress disorder (2). Research with classic psychedelics, like psilocybin and lysergic acid diethylamide (LSD), has demonstrated a correlation between acute subjective effects (e.g., a mystical experience) and reported therapeutic effects (3,4). However, it remains unclear if the mystical experience or other subjective effects are merely a proxy of achieving a therapeutic dose related to another mechanism or if the experience itself plays a necessary role in therapeutic efficacy (4). The brain activity changes that coincide with the acute subjective effects have been described in human and animal studies using functional brain imaging and electrophysiologic approaches. These systems-level brain activity readouts indicate that, acutely, psychedelics disrupt the coordination of brain activity within and between brain regions. For example, imaging studies in humans reveal reduced connectivity between nodes of the default mode network (5,6) and recordings of neural oscillations (e.g,. electroencephalography, EEG; or local field potentials, LFP) show that psychedelics reduce power across frequencies, particularly low frequencies (7). Beyond the subjective effects and immediate changes in brain activity induced by psychedelics, preclinical work has uncovered alternative, or complementary, mechanisms of enhanced neural plasticity.

Both *in vitro* and *in vivo* psychedelics have been shown to open a window of enhanced neural plasticity (8) as well as produce anti-inflammatory effects (9–11). Both mechanisms represent biologically plausible mechanisms of therapeutic efficacy. The plastogenic properties of psychedelics include the growth of new neuronal processes, like dendritic spines, with about one third of these spines becoming persistent, functional synapses (12). It is theorized that the enhanced neural plasticity induced by psychedelics could contribute to the reported persistent therapeutic effects. For example, in a pre-clinical rat model ketamine acutely ameliorates

depressive behaviors before inducing new spine growth, with the long-term effects of ketamine dependent on the newly formed spines (13). This work suggests that although there are potentially clinically meaningful acute effects of psychedelics, the long term success of psychedelics to change behavior is primarily mediated by the growth of new functional connections between neurons.

We theorized that directed intervention such as psychotherapy or brain stimulation is able to guide the neuroplastic changes induced by psychedelics to create lasting changes in synaptic organization and ultimately in behavior. We hypothesized that cortical-striatal oscillations recorded in rats would confirm the well characterized effects of psychedelics (tested here with LSD) and show for the first time the systems-level brain activity changes corresponding to the period of enhanced neural plasticity approximately 24 hours after LSD administration. Next, we characterized how brain stimulation targeting the rat infralimbic cortex (a medial frontal region) altered cortical-striatal oscillations when rats were given LSD or saline 24 hours before stimulation. This allowed us to determine if LSD allows brain stimulation to have different and/or larger effects on brain activity than saline given before stimulation. We used a rodent model to remove the unavoidable biases inherent to psychedelic research in humans, and used brain stimulation to manipulate brain activity rather than psychotherapy, to begin probing the potential interaction of an external manipulation of brain activity and the window of psychedelic induced neural plasticity. The results presented below begin to reveal the potential synergy between an external manipulation of brain activity and the window of enhanced neural plasticity created by psychedelics. Beyond probing the systems-level brain activity mechanisms that could underlie the synergy between psychedelics and psychotherapy reported clinically, this work also investigates the potential synergy of psychedelics and brain stimulation—a novel therapeutic approach.

Methods

Cohorts

We used two cohorts of Sprague Dawley rats of each sex for these experiments. The first cohort (n = 11; 5 male and 6 female) came from the control group of a separate experiment. The second cohort (n = 5; 2 male and 3 female) had been trained on the delayed discounting task for a separate experiment (14). Both cohorts were given at least one month before incorporating into these experiments.

Electrode implantation

After habituating the rats to the animal facility, we anesthetized them with isoflourane/oxygen (5% isoflourane for induction and 2% for maintenance) and stereotactically implanted with one of two custom electrode arrays to record LFPs and deliver electrical stimulation (described previously (15)). The first array for the first cohort targeted the bilateral infralimbic cortex—IL (AP 3.4 mm; ML ±0.75 mm; and DV -5.0 mm), and nucleus accumbens shell—NAcS (AP 1.2 mm; ML ±1.0; and DV -7.6 mm). The second array for the second cohort targeted the same bilateral IL and NAcS as well as orbitofrontal cortex—OFC (AP 3.4 mm; ML ±3.0 mm; and DV -6.0 mm), and the nucleus accumbens core—NAcC (AP 1.2 mm; ML ±2.4 mm; and DV -7.6 mm). All coordinates are relative to bregma.

Local field potential processing

We assessed the brain states of the rats using LFP features, power and imaginary coherence, within 6 frequency ranges: delta (Δ) = 1-4 Hz, theta (θ) = 5-10 Hz, alpha (α) = 11-14 Hz, beta (β) = 15-30 Hz, low gamma (lγ) = 45-65 Hz, and high gamma (hγ) = 70-90 Hz. We used the imaginary component of coherence to minimize the influence of volume conduction and a common reference (16). From the 8 recording locations, we obtained 48 power features and

168 coherence features, providing a total of 216 features to describe brain states. Apart from the use of imaginary coherence, all signal processing was done as previously described (17).

Measuring the acute effects of LSD

In the first cohort of rats we recorded LFPs from bilateral NAcS and IL for 10 minutes to obtain baseline brain activity, administered LSD (0.15 mg/kp i.p.; n = 6; 3 male and 3 female;) or saline (n = 5; 2 male and 3 female), and then recorded LFPs for another 90 minutes. To quantify how an injection of LSD or saline (SAL) changed brain activity we subtracted baseline features from the post-injection power and coherence within each frequency range. We then trained logistic regressions on each combination of 5 LSD and 4 SAL rats, leaving out one rat from each group for testing (leave-one out, LOO), resulting in 30 iterations of model building and testing. We used the distribution of these model performances to estimate the magnitude of the difference between brain activity from LSD or SAL exposed rats. We then built models using each LFP feature separately to assess individual contribution. We repeated the model building using data collected from the same rats 24 hours after injection to determine if the effects of LSD persist. To estimate by-chance model performance we also repeated the model building and testing on permuted data in which the assignment of brain data to a group (i.e., LSD or SAL) was randomized. As LSD causes acute ataxia, we limited the data used for modeling to the last 30 minutes of the recording when both groups of rats had similar levels of resting behavior defined by manually scored periods of inactivity (**Supplemental Figure 1**).

Measuring the effects of brain stimulation 24 hours after LSD

In the second cohort of rats, we first administered SAL and waited 24 hours. We then recorded LFPs from bilateral NAcS, NAcC, IL, and OFC for 10 minutes to obtain baseline brain activity and administered IL stimulation (monopolar, 130 Hz, 90 μs pulse width, and 200 μA) for 120 minutes while recording. After three sessions of brain stimulation we allowed at least 1 week for stimulation effects to wash out before injecting LSD (0.2 mg/kg i.p.), waiting 24 hours, and

repeating the record/stimulation paradigm. We then did a baseline subtraction from the stimulated power and coherence in each frequency range. First, we trained logistic regressions to differentiate between brain activity at baseline and during stimulation for both SAL and LSD. Next, we built logistic regressions to differentiate directly between the effects of brain stimulation with LSD or SAL given 24 hours earlier. We used 80% of the data, with equal contributions from each rat, to train the models and tested them on the remaining 20%.

Results

LSD leads to acute decreases in power and mixed effects in coherence

LSD leads to acute changes in LFPs that are differentiable from the changes induced by SAL using logistic regressions with LOO testing (acute = 0.79±0.02 vs. permuted = 0.5±0.04; **Fig 1A**). However, these changes in LFPs disappear within 24 hours (24 hrs = 0.45±0.037; **Fig 1C**). Building logistic regression models with one LFP feature at a time revealed that LSD leads to acute decreases in NAcS and IL power across all frequency ranges and a mixture of increased and decreased coherence (**Fig 1B**). For a more detailed visualization of the difference between the effects of LSD and SAL on power and coherence, see **Supplemental Fig 2**. The average performance of each feature is also listed in **Table 1**.

LSD synergizes with brain stimulation

Despite brain activity being indistinguishable between rats given LSD or SAL 24 hours prior (**Fig 1C**), IL stimulation is able to create larger changes in brain activity from baseline in rats given LSD (0.90±0.005; **Fig 2A**) compared to SAL (0.84±0.006; **Fig 2A**). Further, in the rats given LSD 24 hour before stimulation, the effects of stimulation are highly distinguishable from the effects of stimulation in rats given SAL (0.90±0.004; **Fig 2B**). Visualizing the performance of

each feature in distinguishing LSD+stim vs. SAL+stim highlights that giving a rat LSD 24 hours before brain stimulation primarily leads to differential effects on coherence with increases in delta coherence and decreases in theta, alpha, and beta coherence and selective delta and high gamma power increases (**Fig 2C**).

Plotting the performance of each feature in differentiating either LSD+stim or SAL+stim from baseline brain activity highlights that regardless of whether a rat was given LSD or SAL, IL stimulation lead to broad decreases in power (blue dots; **Fig 2C**) and mixed effects in coherence (red dots; **Fig 2C**). This manifests as all power features falling along the black dashed line in quadrant III and coherence features existing in all quadrants. The features that fall along the black dashed line (quadrants I and III) change in the same direction relative to baseline activity, although to different degrees. For example, the second best performing single feature (Δ power at the right NAcC, AUC = -0.63; **Table 2**) had large decreases in rats given SAL before stimulation and modest decreases in rats given LSD before stimulation (-0.75 vs. -0.63; **Table 2**). The features along the gray dashed line (quadrants II and IV) change in opposite directions relative to baseline activity. For example, the third best performing feature (α coherence between left OFC and right NAcC, AUC = 0.64; **Table 2**) increased slightly when the rat was given SAL 24 hours prior, to decreasing slightly when given LSD 24 hours prior (0.55 vs. -0.58; **Table 2**).

Discussion

These results further characterize the acute changes induced by psychedelics (e.g., LSD) on cortical-striatal brain states and demonstrate these altered states return to baseline after 24 hours. However, a focal intervention applied in this window of heightened neuroplasticity (24 hours after LSD) produced distinct shifts in brain state compared to brain stimulation applied 24 hours after SAL. These results suggest that despite the neuroplastic changes reported 24 hours after a single dose of LSD (8), we were unable to identify any systems-level brain activity

differences using neural oscillations. However, when we applied brain stimulation, we found significant differences in brain activity changes depending on whether the rat was given LSD or SAL 24 hours prior. Thus, the LSD-induced neuroplastic changes led to a latent state with an altered potential to respond to external manipulations or interventions (**Figure 3**).

Acute electrophysiological effects of LSD

Although there is a paucity of studies examining the acute effects of psychedelics on intracranial LFPs, our findings of broad decreases in power and mixed disruptions in coherence (**Fig 1**), particularly at low frequencies, align with the reported decrease in accumbal high gamma power (18) and the cortical effects of LSD (measured by epidural electrodes) (4,19) found in previous studies. There is also evidence of the same broad decreases in low frequency power from rodents given other serotonergic psychedelics, like psilocybin/psilocin (19), 1-(2,5-dimethoxy-4-iodophenyl-2-aminopropane) (DOI) (20,21), and 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT) (22) although the effects of 5-MeO-DMT could not be replicated in freely behaving, non-anesthetized, rats (23). Magnetoencephalography (MEG) in humans given LSD has revealed a similar signature of broadband decreases in power across the brain with the largest effects occurring at lower frequencies paired with mixed effects on connectivity (6,24–27). Similarly, the acute effects of LSD have been measured in humans using functional magnetic resonance imaging (25,28–30) and electroencephalography (31,32), again finding disruptions in low frequency activity and widespread changes in connectivity. It is difficult to translate these findings to specific alterations in LFPs (33–35); however, there is convergence to an increase of disorder in the brain through the 5HT2A receptor (36,37).

Synergy between LSD and brain stimulation

To our knowledge, there have been no publications pairing brain stimulation with LSD in freely behaving animals. However, there is a growing pool of evidence that ketamine is able to

facilitate long term potentiation both *in vitro* (38–40) and *in vivo* (41,42), with the discrepancies between studies being attributed to differing doses of ketamine, differing time points, the concurrent use of anesthetics, and the intrinsic differences between *in vitro* and *in vivo* electrophysiology. Although there are non-trivial differences between ketamine and classical psychedelics like LSD, there is also emerging evidence these drugs activate the same downstream molecular pathways regulating neuroplasticity (43).

In particular, classical psychedelics like LSD and psilocybin are known to induce rapid and persistent growth of dendritic spines (8,12). The exact mechanism behind this plastogenesis is still an area of rich research, but it is likely that it is at least in part mediated by $5HT_{2A}R$, brain-derived neurotrophic factor (BDNF), tyrosine receptor kinase B (trkB), and mammalian target of rapamyacin signaling pathways (mTOR) (44,45) [for reviews: (46,47)] as well as long term changes in gene expression (48).

Although we found that LSD+stim led to larger changes in brain activity compared to SAL+stim (**Fig 2A**) and the LSD+stim changes were easily distinguishable from SAL+stim (**Fig 2B**), about half of the features changed in the same direction, albeit with differences in magnitude, between LSD+stim and SAL+stim. The other half of the features changed in opposite directions (e.g., decreased with LSD+stim and increased with SAL+stim), but these features had AUCs <0.60 when distinguishing from baseline brain activity. Therefore, it appears that LSD not only modulates the effects of brain stimulation but also has the potential to induce opposite and novel changes in brain activity than brain stimulation alone produces.

While the presented experiments were not designed to determine if LSD lengthens the duration of the effects of brain stimulation, it is important for this to be evaluated in future studies. It is also important to determine if the LSD+stim induced changes in brain activity have a behavioral correlate. Currently, brain stimulation is either delivered chronically in the case of invasive deep brain stimulation or over repeated non-invasive (e.g., transcranial magnetic stimulation; TMS) intervention sessions combined with follow-up sessions (49–51). Ideally, these treatment

courses could be shortened by creating longer lasting changes in structural connectivity and/or synaptic weights which would manifest as longer lasting therapeutic changes.

Limitations and future directions

Although this work provides a proof-of-concept that psychedelics synergize with brain stimulation, a next step is to determine if the changes in brain activity correlate with a change in behavior. Similarly, we did not assess whether LSD+stim lead to longer lasting changes in brain activity than stimulation alone. As LSD is opening a window of enhanced neural plasticity, it could be the case that stimulation delivered during this window would be capable of inducing more persistent changes in brain activity.

Here we delivered brain stimulation during the putative window of enhanced neural plasticity (24 hours after LSD administration); however, there is also evidence that during the acute effects of LSD the brain is more malleable by external stimuli. For example, music played during the LSD experience augments both the subjective effects of LSD and the LSD-induced changes in brain activity (52–54). Further, a theoretical computational study recently suggested that during the acute effects of LSD, perturbations similar to brain stimulation could lead to longer lasting changes in brain activity (55). Future work should directly compare the effects of stimulation applied during the acute effects of LSD versus during the window of enhanced neural plasticity.

Although we balanced our groups to include roughly equal numbers of males and females, we did not have enough samples to adequately power comparisons between sexes. In humans, sex is not predictive of the effects or optimal dosing of psychedelics including LSD (56). However, in rats there is some evidence that LSD and other psychedelics have slightly different behavioral effects in males and females (57,58). Thus, future work should continue to include both sexes and when possible be powered to compare between sexes directly.

There is increasing interest in the discovery and testing of other compounds capable of inducing neural plasticity, especially compounds without the acute perceptual effects of psychedelics

(59). Beyond structural imaging of neurons to assess neuroplasticity, we hypothesize that pairing these new compounds with brain stimulation could provide a neural systems-level readout of plastogenic potential.

Conclusion

We have further confirmed the findings of acutely decreased low frequency power across the brain when rats are given LSD. We have extended these findings to show that despite these acute effects disappearing after 24 hours, there are still latent effects of LSD that synergize with brain stimulation to create different changes in brain activity compared to brain stimulation alone. Combined with the knowledge that LSD opens a window of enhanced neural plasticity, our findings are the first to suggest that psychedelics could have a role clinically in combination with brain stimulation (e.g., TMS, electroconvulsive therapy, or deep brain stimulation) to achieve enhanced effects on brain activity and relevant clinical outcomes.

Funding

This work was partially funded by an NIAAA training grant (F31AA027441; LD), the Hitchcock Foundation (AH), a NIDA T32 training grant (DA037202; AH), an LRP grant from NIH NCATS (KL2TR001088; WD), and a K08 grant from NIMH (1K08MH117347-01A1; WD).

Author contributions

Lucas Dwiel: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, visualization, writing - original draft

Wilder Doucette: Conceptualization, funding acquisition, methodology, project administration, supervision, writing - review & editing

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Conflict of interests

The authors have no competing interests to report.

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feature	performance (AUC)	feature	performance (AUC)
lIL θ	-0.78	lIL-lNAcS θ	0.64
rIL θ	-0.73	lNAcS lγ	-0.63
lIL β	-0.72	rNAcS lγ	-0.62
lIL lγ	-0.70	rIL Δ	-0.62
lIL α	-0.70	lNAcS Δ	-0.61
lIL Δ	-0.69	lNAcS α	-0.61
lNAcS β	-0.69	rIL-rNAcS hγ	-0.61
lNAcS θ	-0.68	lIL-lNAcS Δ	0.61
rIL lγ	-0.68	rNAcS α	-0.60
lIL hγ	-0.67	lNAcS hγ	-0.60
rNAcS θ	-0.67	lNAcS-rIL θ	-0.60
rNAcS β	-0.65	lIL-lNAcS hγ	-0.60
rIL hγ	-0.64		
rIL α	-0.64		
rIL β	-0.64		

Table 1 Brain features most predictive of whether a rat was given LSD vs. saline. Features are notated with a lowercase letter indicating hemisphere (left, l; right, r). A single brain region indicates power from that region while two regions combined with a hyphen indicates coherence between those regions. For example, the first feature (lIL θ) is theta power from left infralimbic cortex. NAcC, nucleus accumbens core; NAcS, nucleus accumbens shell; IL, infralimbic cortex; OFC, orbitofrontal cortex; Δ, delta; θ, theta; α, alpha; β, beta; lγ, low gamma; hγ, high gamma.

	feature	LSD+stim vs. SAL+stim (AUROC)	SAL+stim (AUROC)	LSD+stim (AUROC)
1	lIL-lNAcC Δ	0.65	0.57	0.7
2	rNAcC Δ	0.64	-0.75	-0.63
3	lOFC-rNAcC α	-0.63	0.55	-0.58
4	lNAcC hγ	0.62	-0.61	-0.56
5	lNAcC-rNAcC Δ	-0.62	-0.5	-0.63
6	lOFC-rNAcC θ	-0.62	0.57	-0.57
7	rNAcS-rNAcC α	-0.62	0.52	-0.56
8	lIL-lOFC Δ	0.62	-0.56	0.57
9	lNAcS-lNAcC Δ	0.61	0.52	0.68
10	lOFC-rNAcC β	-0.61	0.52	-0.53
11	lNAcC-rNAcC θ	-0.61	0.52	-0.58
12	rNAcS-rNAcC β	-0.61	0.53	-0.54
13	rIL-rNAcC θ	-0.6	-0.51	-0.64
14	lIL Δ	0.6	-0.7	-0.68

Table 2 Top performing features in distinguishing the effects of brain stimulation with LSD given 24 hours previously from the effects of brain stimulation with saline (SAL) given 24 hours previously (LSD+stim vs. SAL+stim). For comparison, the performance of each of these features in the two models comparing intervention to baseline (LSD+stim and SAL+stim) are displayed to the right. All performances are reported as the area under the receiver operator characteristic curve (AUROC) with the sign indicating the direction of the correlation. Features are notated with a lowercase letter indicating hemisphere (left, l; right, r). A single brain region indicates power from that region while two regions combined with a hyphen indicates coherence between those regions. For example, the third best feature (lOFC-rNAcC α) is alpha coherence between left orbitofrontal cortex and right nucleus accumbens core; the negative sign indicates that higher coherence correlates with SAL+stim versus LSD+stim (i.e., LSD+stim leads to lower lOFC-rNAcC α coherence than SAL+stim). NAcC, nucleus accumbens core; NAcS, nucleus accumbens shell; IL, infralimbic cortex; OFC, orbitofrontal cortex; Δ, delta; θ, theta; α, alpha; β, beta; hγ, high gamma.

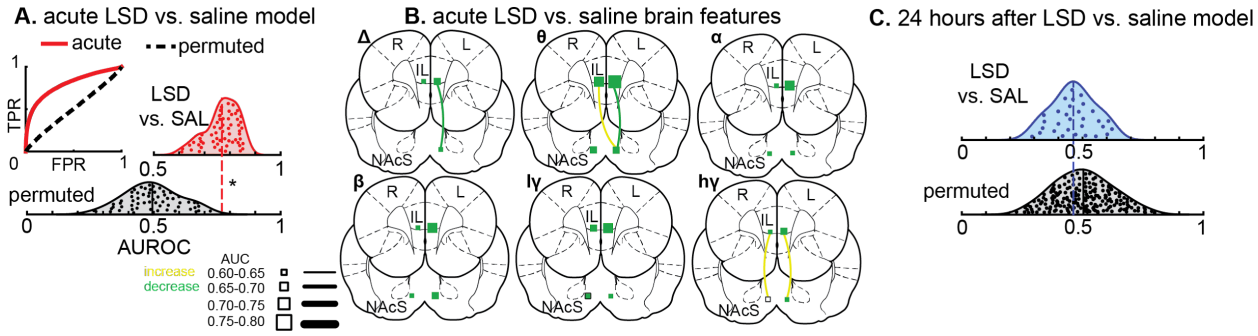


Figure 1 Compared to saline, LSD leads to global decreases in power and mixed changes in coherence; however, these differences disappear within 24 hours. **A** Rats given LSD can be differentiated from those given saline (SAL) using all of the acute changes in power and coherence between SAL and LSD in logistic regressions (acute; black solid line) compared to permuted data (black dashed line). However, there were no detectable differences in brain activity 24 hours later (24 hrs; gray solid line). **B** The performance of logistic regressions built using individual brain activity features with squares representing power at a specific brain location and lines connecting brain regions representing coherence between specific brain regions. The size of the square or weight of the line indicates the model performance (area under the receiver operator characteristic curve; AUROC). N.B.: all coherence feature performances fall within the same range (0.60-0.65). Green indicates a relative decrease in that brain feature with LSD compared to SAL and yellow indicates a relative increase. The data summarized here are shown in more detail in Supplemental Figure 2. Right, R; left, L; infralimbic cortex, IL; nucleus accumbens shell, NAcS; delta, Δ; theta, θ; alpha, α; beta, β; low gamma, lγ; high gamma, hγ. **C** Rats given LSD are indistinguishable from rats given SAL 24 hours after drug administration.

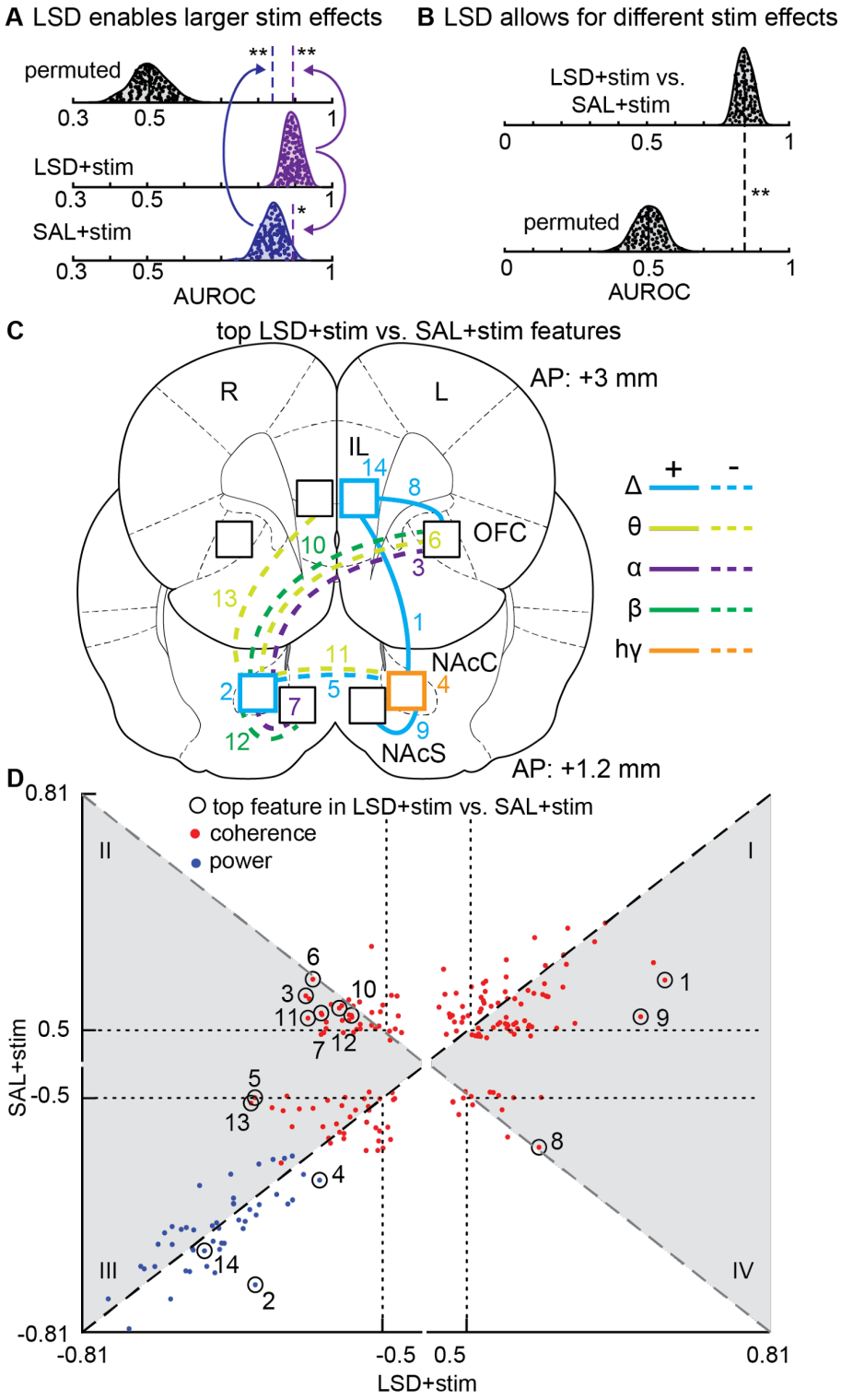


Figure 2 LSD synergizes with brain stimulation to create larger and different changes in brain activity. **A** Logistic regressions built to distinguish between baseline brain activity and stimulated brain activity perform better when the rats were given LSD 24 hours before stimulation

(LSD+stim = 0.90±0.005; gray solid line) compared to saline (SAL+stim = 0.84±0.006; solid black line). Both LSD+stim and SAL+stim out-performed permuted data (0.49±0.01; dashed black line). All model performances are reported as the mean±95% confidence interval of the distributions of the area under the receiver operator characteristic curves (AUROCs). **B** Logistic regressions built to distinguish the change in brain activity seen in LSD+stim vs. SAL+stim (0.90±0.004; solid line) out-perform permuted data (0.50±0.01; dashed line). All model performances are reported as the mean±95% confidence interval of the distributions of AUROCs. **C** Visualization of the top features from distinguishing LSD+stim from SAL+stim (**B**) superimposed on the rat brain. Brain features came from left (L) and right (R) infralimbic cortex (IL), orbitofrontal cortex (OFC), and nucleus accumbens core (NAcC) and shell (NAcS). Outlines represent power at a given brain region and lines between brain regions represent coherence. Solid lines/outlines indicate a relative increase in that brain feature with LSD+stim compared to SAL+stim and dashed lines/outlines indicate a relative decrease. The color of the line/outline indicates the frequency range. **D** Visualization of all single feature model performances from distinguishing LSD+stim (x-axis) or SAL+stim (y-axis) from baseline (**A**) with positive values indicating a relative increase in that feature from baseline and negative values indicating a relative decrease in that feature from baseline. Features are numbered in descending order from the highest |AUROC| (**Table 2**). Blue dots are power features and red dots are coherence features. Circled features were the top performers in the models distinguishing between LSD+stim and SAL+stim (**B**). Light gray background highlights features with a higher |AUROC| in LSD+stim than SAL+stim; white background highlights features with lower |AUROC| in LSD+stim models than SAL+stim models. Features that fall along the dashed gray diagonal line have opposite correlations in LSD+stim compared to SAL+stim and features that fall along the dashed black diagonal line have correlations in the same direction in LSD+stim models compared to SAL+stim models. Dotted black lines delineate the 4 quadrants (I, II, III, and IV) of |AUROC|>0.5 for both models.

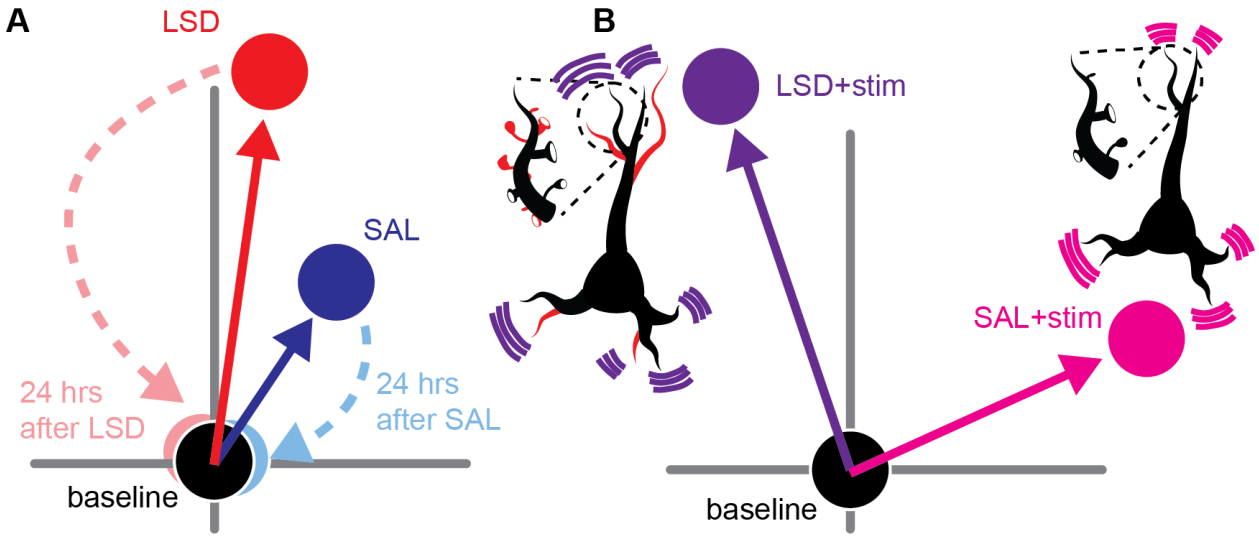
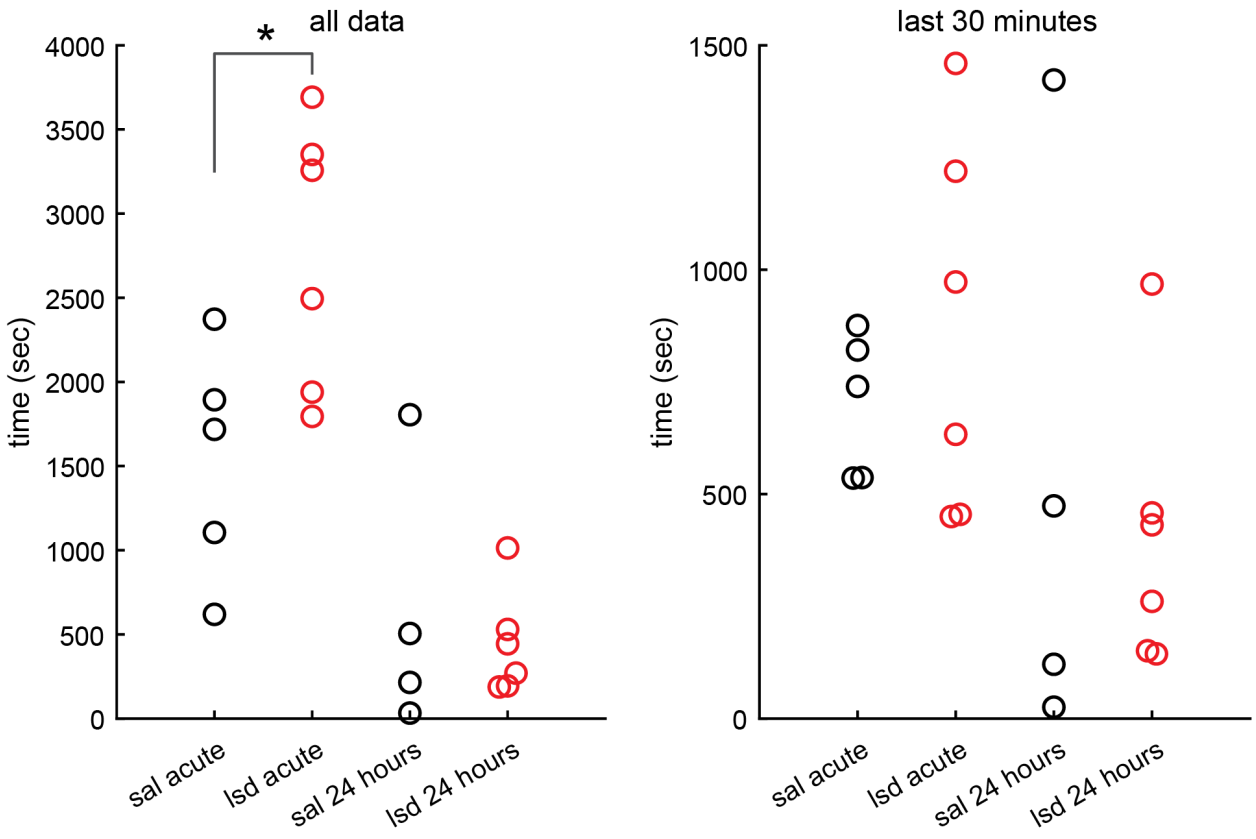
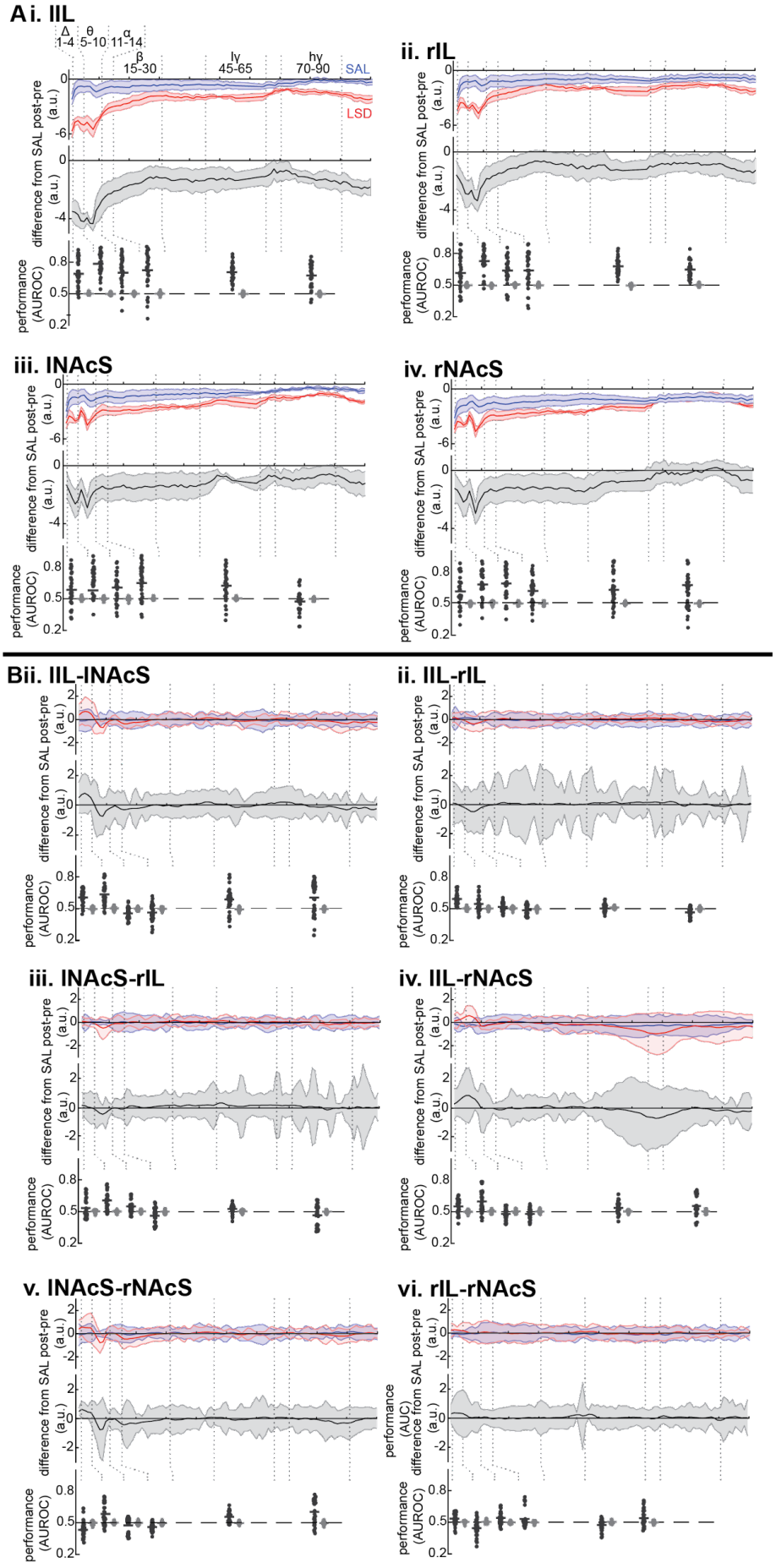


Figure 3 Conceptual diagram of the acute effects of LSD and SAL and the interaction between LSD and brain stimulation. **A** Acute LSD and SAL lead to differentiable effects in brain activity from baseline represented by the distance between the circles representing the brain state space during baseline (black circle) and after LSD injection (red circle and arrow) or after SAL injection (blue circle and arrow). 24 hours after injections, brain activity is no longer differentiable between groups (24 hours after LSD, light red circle and dashed arrow; and 24 hours after SAL, light blue circle and dashed arrow). **B** Brain stimulation applied 24 hours after LSD or SAL injections leads to large and different changes in brain activity. Brain stimulation after LSD (purple circle and arrow) may be interacting with the induced neural plasticity (red dendrites and spines in inset neuron) leading to different changes in brain activity than stimulation after SAL (pink circle and arrow).



Supplemental Figure 1 Time spent at rest throughout recordings. **A** Time (seconds) spent at rest for entire recording (~100 minutes). Rats given LSD spend significantly more time at rest than those given SAL. 24 hours later, both groups spend equal time at rest. **B** Time spent at rest during last 30 minutes of recording. Both groups spent equal time at rest ~1 hour after injection of LSD or SAL and 24 hours after injections.



Supplemental Figure 2 Power and coherence changes from pre- to post-injection of either saline (SAL) or LSD. **A** Top: change in power from pre to post injection of either SAL (blue) or LSD (red) in arbitrary units (a.u.) with ±1 standard deviation shaded. Middle: the difference in power between the SAL and LSD (black) with ±1 standard deviation shaded. Bottom: the distribution of single feature model AUCs from leave-one out testing (black) and permuted data (gray); horizontal lines indicate means. Brain regions are denoted as either right (r) or left (l) such that lIL (**Ai**) is the left infralimbic cortex. **B** Changes in coherence between SAL and LSD organized as in **A** with pairs of brain regions denoted such that lIL-lNAcS (**Bi**) is coherence between left infralimbic cortex and left nucleus accumbens shell.