Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Reconsidering the Psychotomimetic Properties of LSD: Connectome-Based Classification Reveals Partial Overlap with First Episode Psychosis

Haley Maria Dourron

haley.dourron@liu.se

Linköping University

Manoj K. Doss

The University of Texas at Austin

Jessica A. Turner

The Ohio State University

Melissa Bradley

University of Alabama at Birmingham

Christopher R. Nicholas

University of Wisconsin–Madison

Adrienne Lahti

University of Alabama at Birmingham

Felix Müller

University of Basel

Robin Carhart-Harris

University of California, San Francisco

Rebecca Boehme

Linköping University

Matthias E. Liechti

University of Basel

Friederike Holze

University of Basel

Patrick Vizeli

University of Basel

Anna M. Becker

University of Basel

Laura Ley

University of Basel

Aaron Klaiber

University of Basel

Undine E. Lang

University of Basel

Peter S. Hendricks
University of Alabama at Birmingham

Article

Keywords: psychosis; lysergic acid diethylamide, psychedelic, fMRI, functional connectivity

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11539750/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: Competing interest reported. CRN receives consultant fees from MindMed, Lykos Therapeutics, and Usona Institute, and holds equity in Psilera as a scientific advisor. RC-H reports receiving consulting fees from COMPASS Pathways, Entheon Biomedical, Mydecine, Synthesis Institute, Tryp Therapeutics, and Usona Institute. MEL is a consultant for Mind Medicine, Inc. FH is an intern for NPP. PSH reports receiving grants from Beckley Psytech, Reunion Neuroscience, and Usona Institute; personal fees from Bright Minds Biosciences, Journey Colab Corporation, Negev Labs, Otsuka Pharmaceutical Development and Commercialization, and Reunion Neuroscience; and owning equity or stock options in AtaiBeckley, Inc., and Negev Labs. He previously had paid advisory relationships with Eleusis Benefit Corporation, Reset Pharmaceuticals Inc., and Silo Pharma and currently has paid advisory relationships with Bright Minds Biosciences Ltd. and Journey Colab Corporation. He is also a cofounder of Equulus Therapeutics and Mycelial Health and has a pending patent (63/804,162). All disclosures are outside the submitted work. All other authors report no biomedical financial interests or potential conflicts of interest.

Abstract

The acute effects of lysergic acid diethylamide (LSD) have long been compared to early psychosis. Despite this, no studies have compared the acute effects of LSD and psychosis on resting-state functional connectivity (RSFC) with parallel approaches. We used connectome-based classification, a data-driven method, to distinguish between medication-naïve, non-affective first episode psychosis (FEP) and the acute effects of LSD. Separate classifiers were trained to distinguish the acute effects of LSD from placebo and FEP patients from matched healthy controls. The LSD-placebo classifier was then validated on an external LSD-placebo dataset. The network-interaction classifiers with good discriminability were then applied across datasets to evaluate whether LSD-related connectivity patterns could classify FEP as being LSD-like and vice versa. Subsequently, we investigated univariate RSFC between select networks, based on which network-interactions the classifiers suggested might overlap in LSD and FEP. Cross-application of externally validated LSD-placebo classifiers revealed partial overlap between LSD and FEP, particularly involving the dorsal attention network (DAN) and sensorimotor network (SMN). Application of the most discriminant FEP-HC network-interaction classifiers revealed that LSD displayed select similarities with FEP. Univariate network analysis also supports between-network DAN and SMN dysconnectivity being a point of convergence. Our findings indicate that neural correlates of FEP might have select overlaps with changes in brain functioning produced by LSD. These results suggest serotonergic dysfunction might play a role in the early stages of psychosis and necessitate future studies directly comparing FEP and LSD.

Introduction

Psychedelics, or drugs with significant serotonin (5-HT) 2A agonism and salient psychoactive effects, have shown promising preliminary results for their efficacy as treatments for various psychiatric disorders[1–3]. However, much of the early work examining psychedelics paradoxically focused on their ability to function as psychotomimetics, or drugs that model psychosis[4–6]. Some of the earliest psychedelic neuroimaging studies compared the acute neural effects of mescaline and psilocybin to psychosis[7,8]. Additionally, several mechanistic theories of psychedelics are influenced by these putative psychotomimetic properties[4,9–15]. Despite the long speculated psychotomimetic nature of the psychedelic experience, no study has compared the acute effects of psychedelics on resting-state functional connectivity (RSFC) measured with functional magnetic resonance imaging (fMRI) to RSFC in patients with psychotic disorders[16,17].

The majority of studies examining the neural effects of psychedelics in humans have probed changes in RSFC, finding widespread increases in transmodal (default, limbic) and sensory network (visual and somatomotor) between-network connectivity[18,19]. Some of these studies made conceptual comparisons to psychotic disorders by describing changes in default mode network (DN) and control network (CN) connectivity orthogonality[19–21]. Psychotic disorders are also associated with widespread changes in RSFC, also involving the DN, salience network (SN), and CN [23,24]. However, there are a wide range of often contradictory findings, in part due to the high individual variance depending on the stage of the condition, the effects of medication, and general heterogeneity of psychotic disorders[25–27].

The acute effects of psychedelics have been proposed to model early psychosis, especially non-affective psychosis such as schizophrenia [4,12,14]. The early stages of psychotic disorders are more likely to have a

predominance of positive symptoms, such as hallucinations and delusions, compared to more chronic stages in which negative symptoms and cognitive deficits tend to be more prominent [4,11,12]. Additionally, the earlier stages of psychotic disorders are less confounded by the effects of medication[26,27] or the health issues prevalent in people with chronic psychotic conditions (e.g., diabetes)[28], both of which can impact brain function [27,29].

Despite all psychedelics acting on the 5-HT_{2A} receptors and having comparable largely subjective effects, psychedelics vary in secondary pharmacology[30,31]. Lysergic acid diethylamide (LSD) has some activity at dopamine D_2 receptors, which are widely targeted by antipsychotic medications [31–33]. Furthermore, LSD has been the drug most historically implicated in comparing psychedelics to psychotic disorders [5]. LSD may also have an elevated risk of producing persisting visual distortions potentially similar to visual alterations that occur in psychotic disorders despite auditory hallucinations being more prevalent in psychosis[34–36]. For these reasons, we focused on LSD as the psychedelic with the highest potential of having psychosis-like neural correlates and available fMRI data.

Here, the neural correlates of the acute effects of LSD and non-affective first episode medication-naïve psychosis (FEP) were compared using connectome-based classification (CBC), a technique similar to connectome-based predictive modeling[1–3]. Specifically, classifiers were trained on the full connectome or specific within- and between-network interactions to discriminate between placebo versus the acute effects of LSD and healthy controls (HC) versus patients with FEP [39,40]. Cross-application of FEP-HC and LSD-placebo classifiers was then assessed by applying the most discriminative classifiers to the alternative dataset. Next, we explored univariate RSFC between select networks, based on which network-interaction classifiers suggested might be similar in FEP and LSD to understand if these changes were marked by similar increases or decreases in connectivity across conditions. Our findings could assist in both the refinement of mechanistic psychedelic classifiers and the clarification of potential neurobiological overlap between psychosis and psychedelics [41,42].

Results

Demographic & Clinical Characteristics

An overview of age, sex, and mean FD across datasets is provided in Supplementary Table S2. The FEP and HC dataset was matched for age ($t(142.5) = -0.34$, $p = .73$), sex ($\chi^2(1) = 0.45$, $p = .51$), and mean FD ($t(143.8) = -1.32$, $p = .19$). The Basel datasets and Imperial datasets did not differ in age ($t(39.3) = -0.33$, $p = .75$). But the Imperial dataset contained significantly more males than the Basel dataset ($\chi^2(1) = 4.36$, $p = .04$). Comparing the FEP-HC and Basel datasets revealed no significant differences in sex ($\chi^2(1) = 0.37$, $p = .54$), but that the FEP-HC sample was significantly younger than the Basel datasets ($t(277.5) = 9.44$, $p < .001$). Mean FD did significantly differ for the LSD scans compared to placebo both the Basel ($t(75) = 4.07$, $p < .001$) and Imperial datasets ($t(14) = 3.00$, $p = .01$). For an overview of clinical characteristics of FEP patients, see Supplementary Table S3.

Classification

Connectome-Based Classification

The full connectome classifiers demonstrated robust discrimination of LSD scans compared to placebo (d' = 2.04; 95% CI [2.03, 2.06]) and moderate discrimination of FEP from HCs (d' = 1.17; 95% CI [1.15, 1.20] (Supplementary Fig. S1). Across the distribution of all 153 within- and between-network-interaction classifiers, 10 within-network and 130 between-network LSD-placebo network-interaction classifiers and only 3 within-network and 9 between-network FEP-HC network-interaction classifiers achieved our discriminability threshold ($d' \geq 0.70$) for subsequent cross-application (Fig. 1).

Basel LSD-Placebo Classifier & External Validation

Although the full connectome LSD-placebo classifier trained on the Basel data performed below-threshold on the Imperial dataset (d' = 0.32), 15 of the 141 network-interaction classifiers that achieved a $d' \geq 0.7$ also achieved a $d' \geq 0.7$ when applied to the Imperial Dataset (Table 1). Network-interaction classifiers with external validity consistently involved sensory and limbic subnetworks. However, the CN.B-DN.C network-interaction classifier showed the greatest discrimination (d' = 1.59) in the external Imperial dataset. Of the network-interaction classifiers that transferred, 6 of the equivalent FEP-HC classifiers showed moderate ($d' \geq 0.5$) discriminability within their dataset. These network-interaction classifiers involved the DAN, DN, visual (Vis), and somatomotor (SMN) networks, suggesting that in both LSD and FEP, these networks display dysconnectivity distinct from placebo or HCs.

Table 1
Externally Validating Basel LSD-Placebo Classifiers and Performance of Equivalent FEP-HC Classifier

Classifier Network-Interaction	Basel *d′* [95% CI]	Basel Hit	Basel False Alarm	Imperial *d′*	Imperial Hit	Imperial False Alarm	FEP *d′* [95% CI]
Lim.B-DN.C	1.46 [1.44, 1.48]	81.5%	27.9%	0.805	10 (66.7%)	5 (33.3%)	0.78 [0.76, 0.81]
Vis.B-SAL.B	1.38 [1.36, 1.39]	79.9%	28.9%	1.158	11 (73.3%)	4 (26.7%)	0.68 [0.65, 0.70]
CoN.B-DN.C	1.35 [1.33, 1.37]	78.5%	28.2%	1.589	13 (86.7%)	4 (26.7%)	-0.11 [-0.13, -0.08]
DAN.A-DN.A	1.33 [1.31, 1.34]	80.7%	31.6%	0.805	10 (66.7%)	5 (33.3%)	0.56 [0.54, 0.58]
Vis.B-CoN.A	1.29 [1.28, 1.31]	78.4%	30.1%	0.981	10 (66.7%)	4 (26.7%)	0.24 [0.22, 0.26]
DAN.A-TPar	1.29 [1.27, 1.30]	74.8%	26.3%	0.981	10 (66.7%)	4 (26.7%)	-0.03 [-0.05, -0.00]
Vis.B-Lim.A	1.25 [1.24, 1.27]	77.3%	30.2%	1.412	13 (86.7%)	5 (33.3%)	0.29 [0.27, 0.31]
SMN.B-Lim.A	1.22 [1.20, 1.24]	77.6%	31.9%	0.981	11 (73.3%)	5 (33.3%)	0.22 [0.19, 0.24]
Vis.B-SMN.B	1.18 [1.16, 1.19]	78.3%	34.1%	1.179	10 (66.7%)	3 (20.0%)	0.58 [0.56, 0.60]
Vis.B-Lim.B	1.10 [1.08, 1.12]	76.8%	35.1%	0.816	9 (60.0%)	4 (26.7%)	0.45 [0.42, 0.47]
SMN.B-DAN.B	1.00 [0.99, 1.02]	71.6%	32.9%	0.981	11 (73.3%)	5 (33.3%)	0.55 [0.53, 0.57]

Note. Classifier performance of the LSD-Placebo classifier is shown based on performance across all iterations (100 iterations for each classifier) along with the hit rate (classifying LSD as LSD) and false alarm rate (classifying placebo as LSD). Discriminant classifiers were then applied to an external LSD dataset with different scanning parameters and a mode of administration (oral in the Basel dataset, intravenous in the Imperial dataset). Network-interaction classifiers that achieved $d' \geq 0.70$ were then deemed to be externally validated discriminant LSD-Placebo classifiers. The hit and false alarm rate of the Basel LSD-Placebo classifier applied to the Imperial dataset and *d'* are shown. To understand the relative importance of these network-interaction classifiers for discriminating FEP from HC, the network-interaction classifier *d'* values are shown for FEP-HC. Abbreviations: Vis = visual network, SMN = somatomotor network, DAN = dorsal attention network, SAL = salience network, Lim = limbic network, CoN = control network, DN = default mode network, TPar = temporal-parietal network, and FEP = first-episode psychosis.

Classifier Network-Interaction	Basel *d′* [95% CI]	Basel Hit	Basel False Alarm	Imperial *d′*	Imperial Hit	Imperial False Alarm	FEP *d′* [95% CI]
CoN.A	0.97 [0.95, 0.98]	70.6%	33.2%	0.816	9 (60.0%)	4 (26.7%)	0.53 [0.51, 0.56]
DAN.B-Lim.B	0.88 [0.86, 0.89]	66.5%	32.3%	1.356	12 (80.0%)	4 (26.7%)	0.17 [0.15, 0.19]
DAN.B-CoN.C	0.87 [0.85, 0.89]	68.0%	34.1%	1.014	9 (60.0%)	3 (20.0%)	0.29 [0.27, 0.32]
SMN.A-SAL.B	0.74 [0.72, 0.76]	67.6%	38.7%	0.981	10 (66.7%)	4 (26.7%)	0.37 [0.35, 0.39]

Note. Classifier performance of the LSD-Placebo classifier is shown based on performance across all iterations (100 iterations for each classifier) along with the hit rate (classifying LSD as LSD) and false alarm rate (classifying placebo as LSD). Discriminant classifiers were then applied to an external LSD dataset with different scanning parameters and a mode of administration (oral in the Basel dataset, intravenous in the Imperial dataset). Network-interaction classifiers that achieved $d' \geq 0.70$ were then deemed to be externally validated discriminant LSD-Placebo classifiers. The hit and false alarm rate of the Basel LSD-Placebo classifier applied to the Imperial dataset and *d′* are shown. To understand the relative importance of these network-interaction classifiers for discriminating FEP from HC, the network-interaction classifier *d′* values are shown for FEP-HC. Abbreviations: Vis = visual network, SMN = somatomotor network, DAN = dorsal attention network, SAL = salience network, Lim = limbic network, CoN = control network, DN = default mode network, TPar = temporal-parietal network, and FEP = first-episode psychosis.

FEP-HC Classifiers

The Vis.A-SMN.A emerged as the most predictive network-interaction classifier for FEP, with greater discrimination than the full connectome (Table 2). This classifier was also highly discriminative within the Basel dataset, suggesting the importance of sensory network RSFC for both FEP and LSD. Only the temporoparietal (TPar) network classifier was discriminative for FEP-HC but did not yield a highly discriminative classifier for LSD-HC. This suggests that FEP might have more RSFC dysconnectivity within TPar than LSD. Only Limbic.B-DN.C emerged as a classifier that was discriminant for FEP-HC and had an LSD-Placebo Classifier that was externally validated in the Imperial LSD-placebo dataset.

Table 2
Discriminant FEP-HC Classifiers and Performance of Equivalent LSD-Placebo Classifiers

Classifier **Network-Interaction**	**FEP** ***d'*** **[95% CI]**	**Hit**	**False Alarm**	**Basel LSD-Placebo** ***d'*** **[95% CI]**	**Basel** **Hit**	**Basel** **False Alarm**	**Imperial** ***d'***	**Imperial** **Hit**	**Imperial** **False Alarm**
Vis.A-SMN.A	1.00 [0.97, 1.02]	73.7%	35.3%	1.43 [1.42, 1.45]	82.2%	29.7%	-0.16	6 (40.0%)	7 (46.7%)
Lim.A-CoN.B	0.86 [0.85, 0.88]	66.6%	32.7%	1.19 [1.17, 1.20]	74.7%	29.6%	0.32	9 (60.0%)	7 (46.7%)
Lim.A-TPar	0.86 [0.84, 0.88]	63.5%	30.0%	1.41 [1.39, 1.43]	81.7%	29.8%	-0.16	6 (40.0%)	7 (46.7%)
DN.C	0.86 [0.84, 0.88]	65.6%	31.9%	1.66 [1.64, 1.68]	82.4%	22.5%	0.16	9 (60.0%)	8 (53.3%)
Vis.B-DAN.A	0.81 [0.78, 0.83]	67.2%	35.5%	1.73 [1.71, 1.75]	86.8%	26.2%	0.66	8 (53.3%)	4 (26.7%)
DAN.B-CoN.A	0.80 [0.78, 0.81]	65.9%	34.4%	1.03 [1.02, 1.05]	68.2%	28.3%	0.16	9 (60.0%)	8 (53.3%)
Lim.B-DN.C	0.78 [0.76, 0.81]	66.1%	35.2%	1.46 [1.44, 1.48]	81.5%	27.9%	0.80	10 (66.7%)	5 (33.3%)
TPar	0.78 [0.75, 0.80]	69.1%	38.6%	0.41 [0.39, 0.43]	58.8%	42.4%	-0.32	7 (46.7%)	9 (60.0%)
CoN.C-TPar	0.77 [0.75, 0.79]	61.5%	31.4%	1.14 [1.12, 1.16]	72.5%	29.0%	-0.82	6 (40.0%)	11 (73.3%)
Lim.A-CoN.C	0.76 [0.74, 0.78]	62.8%	32.9%	1.40 [1.38, 1.41]	78.1%	26.0%	0.48	8 (53.3%)	5 (33.3%)
SAL.A	0.75 [0.73, 0.77]	66.9%	37.5%	1.24 [1.22, 1.25]	78.2%	31.9%	-0.16	6 (40.0%)	7 (46.7%)

Note. FEP-HC classifiers that achieved $d' \geq 0.7$ based on average performance across all iterations (100 iterations for each classifier) are shown. The discriminant score, along with the hit rate (classifying FEP as FEP) and false alarm rate (FEP as HC), are shown. To show whether these network-interactions are also important for distinguishing the acute effects of LSD from placebo, the Basel LSD-Placebo classifier results are also shown alongside the performance of the Basel-trained classifier in the LSD-Placebo Imperial dataset. Abbreviations: Vis = visual network, SMN = somatomotor network, DAN = dorsal attention network, SAL = salience network, Lim = limbic network, CoN = control network, DN = default mode network, TPar = temporal-parietal network, FEP = first-episode psychosis, and LSD = lysergic acid diethylamide.

Classifier Network-Interaction	FEP *d*′ [95% CI]	Hit	False Alarm	Basel LSD-Placebo *d*′ [95% CI]	Basel Hit	Basel False Alarm	Imperial *d*′	Imperial Hit	Imperial False Alarm
DAN.B-DN.B	0.74 [0.72, 0.77]	64.5%	35.1%	1.03 [1.01, 1.04]	73.4%	34.0%	0.32	7 (46.7%)	5 (33.3%)

Note. FEP-HC classifiers that achieved *d*′ ≥ 0.7 based on average performance across all iterations (100 iterations for each classifier) are shown. The discriminant score, along with the hit rate (classifying FEP as FEP) and false alarm rate (FEP as HC), are shown. To show whether these network-interactions are also important for distinguishing the acute effects of LSD from placebo, the Basel LSD-Placebo classifier results are also shown alongside the performance of the Basel-trained classifier in the LSD-Placebo Imperial dataset. Abbreviations: Vis = visual network, SMN = somatomotor network, DAN = dorsal attention network, SAL = salience network, Lim = limbic network, CoN = control network, DN = default mode network, TPar = temporal-parietal network, FEP = first-episode psychosis, and LSD = lysergic acid diethylamide.

Cross-Application of Connectome-Based Classifiers

Validated LSD-Placebo Classifier Cross-Application to FEP-HC

Cross-application of the validated LSD-placebo classifiers showed some trends for FEP being more LSD-like than HCs for select network-interaction classifiers, mostly involving network-interaction classifiers involving the DAN (Table 3). Nevertheless, the network-interaction classifier that had the highest transference *d*′, the SMN.B-DAN.B network-interaction classifier (transfer *d*′ = *0*.34), only classified 63% of FEP patients as LSD-like. Two validated LSD-placebo network-interaction classifiers, both involving the visual subnetwork, were more likely to classify HCs as LSD-like than FEP patients, thereby producing negative *d*′-values.

Table 3
Externally Validated LSD-Placebo Classifiers Applied to FEP-HC Dataset

Classifier Network-Interaction	Basel *d*′ [95% CI]	FEP Transfer *d*′	Hit (FEP→LSD)	False Alarm (HC→LSD)
SMN.B-DAN.B	1.00 [0.99, 1.02]	0.34	46 (63.0%)	36 (49.3%)
Vis.B-SAL.B	1.38 [1.36, 1.39]	0.34	40 (54.8%)	30 (41.1%)
DAN.A-TPar	1.29 [1.27, 1.30]	0.34	40 (54.8%)	30 (41.1%)
DAN.A-DN.A	1.33 [1.31, 1.34]	0.31	41 (56.2%)	32 (43.8%)
Lim.B-DN.C	1.46 [1.44, 1.48]	0.27	41 (56.2%)	33 (45.2%)
CoN.A	0.97 [0.95, 0.98]	0.24	42 (57.5%)	35 (47.9%)
DAN.B-CoN.C	0.87 [0.85, 0.89]	0.20	39 (53.4%)	33 (45.2%)
Vis.B-Lim.A	1.25 [1.24, 1.27]	0.10	41 (56.2%)	38 (52.1%)
SMN.B-Lim.A	1.22 [1.20, 1.24]	0.03	36 (49.3%)	35 (47.9%)
DAN.B-Lim.B	0.88 [0.86, 0.89]	-0.03	36 (49.3%)	37 (50.7%)
CoN.B-DN.C	1.35 [1.33, 1.37]	-0.07	36 (49.3%)	38 (52.1%)
SMN.A-SAL.B	0.74 [0.72, 0.76]	-0.07	37 (50.7%)	39 (53.4%)
Vis.B-CoN.A	1.29 [1.28, 1.31]	-0.10	35 (47.9%)	38 (52.1%)
Vis.B-SMN.B	1.18 [1.16, 1.19]	-0.38	30 (41.1%)	41 (56.2%)
Vis.B-Lim.B	1.10 [1.08, 1.12]	-0.51	29 (39.7%)	44 (60.3%)

Note. Validated LSD-Placebo classifiers were applied to the FEP-HC dataset. The transfer *d*′ for the cross-application of LSD-placebo classifiers was defined as a hit being the classification of FEP as LSD-like, whereas a false alarm was defined as HC being classified as LSD-like. Classifiers are ranked by transfer *d*′. The original *d*′ values for the LSD-placebo classifiers are shown to allow readers to contextualize the cross-application to the FEP-HC dataset relative to classifier performance in the initial dataset. Abbreviations: Vis = visual network, DAN = dorsal attention network, SMN = somatomotor network, SAL = salience network, Lim = limbic network, DN = default mode network, CoN = control network, FEP = first-episode psychosis, HC = healthy control, LSD = lysergic acid diethylamide.

Cross-Application of FEP-HC to LSD-Placebo Datasets

The 12 FEP-HC classifiers that surpassed the *d*′ > 0.7 threshold were applied separately to the Basel and Imperial datasets (Table 4). There was convergent classification of LSD as FEP-like for the Vis.A-SMN.A and DAN.B-DN.B network-interaction classifiers across both datasets. More specifically, the Vis.A-SMN.A classifier reached the highest transfer in both the Basel (*d*′ = 0.80) and Imperial (*d*′ = 0.98) datasets. The DAN.B-DN.B network-interaction classifier had the next highest transfer consistently across both the Basel (*d*′ = 0.53) and Imperial (*d*′ = 0.48) datasets. No other classifiers showed comparably strong and consistent classification of LSD as FEP-like across both datasets. Several network-interaction classifiers showed substantial differences in transfer between the Basel and Imperial datasets.

Table 4
Cross-Application of FEP-HC to LSD Datasets

Classifier Network-Interaction	FEP *d′* [95% CI]	Basel Transfer *d′*	Imperial Transfer *d′*	Basel Hit (LSD→FEP)	Basel False Alarm (Placebo→FEP)	Imperial Hit (LSD→FEP)	Imperial False Alarm (Placebo→FEP)
Vis.A-SMN.A	1.00 [0.97, 1.02]	0.80	0.98	48 (63.2%)	24 (31.6%)	11 (73.3%)	5 (33.3%)
DAN.B-DN.B	0.74 [0.72, 0.77]	0.53	0.48	45 (59.2%)	29 (38.2%)	8 (53.3%)	5 (33.3%)
SAL.A	0.75 [0.73, 0.77]	0.20	0.64	46 (60.5%)	40 (52.6%)	9 (60.0%)	5 (33.3%)
DAN.B-CoN.A	0.80 [0.78, 0.81]	0.16	0.47	40 (52.6%)	35 (46.1%)	9 (60.0%)	6 (40.0%)
Lim.A-TPar	0.86 [0.84, 0.88]	0.16	0.32	41 (53.9%)	36 (47.4%)	8 (53.3%)	6 (40.0%)
Vis.B-DAN.A	0.81 [0.78, 0.83]	0.13	0.00	42 (55.3%)	38 (50.0%)	8 (53.3%)	8 (53.3%)
Lim.A-CoN.B	0.86 [0.85, 0.88]	0.13	-0.47	39 (51.3%)	35 (46.1%)	6 (40.0%)	9 (60.0%)
DN.C	0.86 [0.84, 0.88]	0.07	0.16	40 (52.6%)	38 (50.0%)	8 (53.3%)	7 (46.7%)
TPar	0.78 [0.75, 0.80]	0.03	0.16	39 (51.3%)	38 (50.0%)	8 (53.3%)	7 (46.7%)
CoN.C-TPar	0.77 [0.75, 0.79]	0.00	0.64	40 (52.6%)	40 (52.6%)	10 (66.7%)	6 (40.0%)
Lim.B-DN.C	0.78 [0.76, 0.81]	-0.16	0.32	38 (50.0%)	43 (56.6%)	8 (53.3%)	6 (40.0%)

Note. The transfer *d′* for the cross-application of FEP-HC classifiers was defined as a hit being the classification of LSD as FEP-like, whereas a false alarm was defined as placebo being classified as FEP-like. Classifiers are ranked by transfer *d′*. The original *d′* values for the FEP-HC classifiers are shown to allow readers to contextualize the cross-application to the FEP-HC dataset relative to classifier performance in the FEP-HC dataset. Abbreviations: Vis, Visual; SMN, Somatomotor; DAN, Dorsal Attention; SAL, Salience; Lim., Limbic; CoN, Control; DN, Default Mode; TPar, Temporal Parietal; LSD, Lysergic Acid Diethylamide; FEP, First Episode Psychosis

Classifier Network-Interaction	FEP *d'* [95% CI]	Basel Transfer *d'*	Imperial Transfer *d'*	Basel Hit (LSD→FEP)	Basel False Alarm (Placebo→FEP)	Imperial Hit (LSD→FEP)	Imperial False Alarm (Placebo→FEP)
Lim.A-CoN.C	0.76 [0.74, 0.78]	-0.53	0.64	30 (39.5%)	46 (60.5%)	9 (60.0%)	5 (33.3%)

Note. The transfer *d'* for the cross-application of FEP-HC classifiers was defined as a hit being the classification of LSD as FEP-like, whereas a false alarm was defined as placebo being classified as FEP-like. Classifiers are ranked by transfer *d'*. The original *d'* values for the FEP-HC classifiers are shown to allow readers to contextualize the cross-application to the FEP-HC dataset relative to classifier performance in the FEP-HC dataset. Abbreviations: Vis, Visual; SMN, Somatomotor; DAN, Dorsal Attention; SAL, Salience; Lim., Limbic; CoN, Control; DN, Default Mode; TPar, Temporal Parietal; LSD, Lysergic Acid Diethylamide; FEP, First Episode Psychosis

Classifier-Guided Examination of Functional Connectivity

LSD-Like FEP Network-Interactions

For the 4 LSD-placebo classifiers were there was some discriminability of the FEP patients as LSD-like (*d'* > 0.3), we examined average RSFC of these network interactions (See Fig. 2 and Supplemental Table 4). FEP patients had greater RSFC within those between-network interactions than HCs. More specifically, FEP patients had higher between-network connectivity than HCs for DAN.A-DM.A ($t(144) = 3.26$, $p = .001$, $d = 0.54$), Vis.B-SN.B ($t(144) = 2.67$, $p = .009$, $d = 0.44$), DAN.A-TPar ($t(144) = 2.28$, $p = .024$, $d = 0.38$), and SMN.B-DAN.B ($t(144) = 2.06$, $p = .041$, $d = 0.34$). FEP patients who were classified as LSD-like also had significantly greater connectivity across these network-interactions than FEP patients classified as placebo-like between the SMN.B-DAN.B ($t(71) = 9.28$, $p<.001$, d = 2.25) and the DAN.A-TPar ($t(71) = 4.93$, $p < .001$, d = 1.16). For results where patients were classified as more placebo-like than controls (Vis.B-SMN.B and Vis.B-Limbic.B), see Supplemental Fig. 2.

FEP-Like LSD Network-Interactions

For the two FEP classifiers that consistently discriminated LSD scans as FEP-like (*d'* > 0.3) in both the Basel and Imperial datasets, we examined the average RSFC of these network interactions (Fig. 3; Supplemental Table 5). There were significant increases in connectivity between DAN.B-DN.B during the acute effects of LSD in the Basel dataset compared to placebo ($t(75) = 4.00$, $p<.001$, $d = 0.46$). However, in the Imperial dataset, there were no increases between the LSD and placebo scans ($t(14) = 0.89$, $p=.388$, $d = 0.23$) but, LSD scans classified as FEP-like had significantly greater connectivity between DAN.B-DN.B ($t(13) = 2.87$, $p=.013$, $d = 1.49$) (Fig. 3). There were no significant changes in connectivity between the Vis.A-SMN.A during the acute effects of LSD compared to placebo for either dataset nor was there a difference in Vis.A-SMN.A connectivity between LSD scans classified as FEP-like versus those classified as HC-like in either dataset. Despite this, patients consistently had greater connectivity between Vis.A-SMN.B than healthy controls ($t(144) = 2.50$, $p=.013$, $d = 0.41$). For results from network-interactions with contradictory classification findings in the Basel and Imperial datasets using the FEP-HC classifiers, see supplemental materials.

Relationship between Psychotic Symptoms and LSD-like Neural Activity in FEP patients

We next conducted an exploratory analysis to examine the relationship between psychotic symptom severity (PANSS score) and RSFC within the 4 network-interactions (DAN.A-DN.A, Vis.B-SAL.B, DAN.A-TPar, and SMN.B-DAN.B) in which the LSD-placebo network-interactions classified FEP as more LSD-like compared to HCs. This revealed no significant relationships between patients' RSFC connectivity in these networks and symptom severity (Supplemental Table 4). We compared patients who were classified as LSD-like compared to placebo-like for these network-interactions and did not find a relationship (Supplemental Table 5).

Discussion

This study provides the first formal comparison of the neural correlates of the acute effects of LSD and medication-naïve FEP. We analyzed resting-state scans using data-driven, multivariate connectome-based classification. Both LSD-placebo and FEP-HC datasets yieled network-interaction classifiers with good discrimination of the target class. Our within-dataset results suggest that the neural effects of LSD are driven primarily by coupling between sensory-transmodal and some transmodal-transmodal network-interactions rather than changes in within-network connectivity. In contrast, the neural differences between FEP and HC primarily involved transmodal-transmodal network-interactions or alterations in within-network connectivity, although a sensory-sensory network-interaction classifier (SMN-Vis) showed the greatest discrimination. Our findings with LSD are in concordance with a recent mega-analysis across 281 participants that failed to replicate decreases in within-network RSFC and broad increases in between-network FC under acute psychedelic effects found in individual studies but instead found that psychedelics selectively increased coupling between sensory and transmodal networks [18]. Prior studies with medication-naïve FEP have also found dysconnectivity both within and between transmodal networks [23,24,43,44]. Taken together, these findings highlight differences in the acute effects of LSD compared to FEP despite a number of select overlaps.

Although many of the network-interactions with good within-dataset discriminability failed to cross-classify, cross-application of select network-interaction classifiers and follow-up analysis examining univariate RSFC revealed some similarities between LSD and FEP. Both cross-application of the FEP-HC and LSD-placebo classifiers provided results converging on between-network DAN and SMN dysconnectivity occurring in both conditions. Moreover, in follow-up univariate analysis, we found that the DAN showed greater connectivity with the DN, TPar, and SMN in both FEP and LSD (although follow-up analysis did support increases in DAN-DN connectivity in the Imperial dataset, potentially due to sample size). Overall, these results suggest a convergent point of dysconnectivity for the acute effects of LSD and FEP, implicating both the DAN and SMN.

The DAN is known to normalize with medication in FEP patients in both resting state and during an attention task [51–53]. This might suggest that early medication-naïve psychosis might share more neural similarities to the acute effects of LSD than chronic psychotic disorders [4,8,11,21]. However, validating this hypothesis would require further work comparing LSD's effects to the neural changes seen in chronic psychotic disorders. Our results also hint that it is plausible that the 5-HT_{2A} antagonism of atypical antipsychotics, such as risperidone, might play a role in the normalization of these networks rather than this effect being driven by the dopaminergic effects alone [32,45,47]. Nevertheless, it should be noted that LSD is a promiscuous substance and also has dopaminergic activity both indirectly and directly at the D_2 receptors [54–56].

Our results did not find a relationship between symptomology and DAN dysconnectivity in FEP patients, despite DAN dysconnectivity being a notable point of convergence with LSD-induced neural changes. Prior studies examining DAN dysconnectivity in medication-naïve FEP have reported that DAN dysconnectivity was not directly related to symptoms [45] but did predict treatment response to risperidone [47]. Broadly, the DAN is associated with voluntary sustained attention, with prior work suggesting RSFC of the DAN can predict performance on visual attention tasks [51,52]. Both FEP [53] and the acute effects of psychedelics are marked by impairments of sustained attention [54]. Collectively, this might suggest that dysconnectivity of the DAN might relate more to cognitive performance, especially in the domain of attention, rather than being directly related to positive or negative psychotic symptoms. Further studies should probe potential similarities in the neural correlates of impaired attention in tasks related to DAN functionality, such as those related to sustained attention [51,52].

In addition to the DAN findings, another potential point of similarity emerged. The FEP-HC classifier suggested that LSD might produce FEP-like changes in connectivity between the visual-sensorimotor networks. Likewise, the DAN-SMN LSD-placebo classifier also reported that FEP patients displayed LSD-like connectivity. Alterations in somato-visual connectivity have been previously reported to be a consistent biomarker in both medication-naïve and chronic psychosis patients [55]. Altered SMN connectivity has also been reported in methamphetamine-related psychosis [56], while increases in visual-somatomotor connectivity during LSD have been linked to subjective drug effects [22]. Together, these findings suggest that FEP and LSD might share alterations in low-level sensory processing networks. Nevertheless, despite increases in connectivity in the FEP sample between these networks, there were no univariate increases in connectivity between the visual and somatomotor set for both Basel and Imperial datasets. This finding highlights the discrepancy between multivariate and univariate methods of analysis and suggests that the similarities between LSD and FEP visual-somatomotor network interactions are more complex than simple increases or decreases. Nevertheless, the LSD-placebo classifier based on SMN-DAN interactions provided results suggestive of increases in connectivity between these networks being present in both FEP and the acute effects of LSD.

In summary, this study provided a data-driven approach to understanding the neural similarities between LSD and FEP during resting state. Psychedelics have been historically compared to the neural alterations in psychosis without providing a formal analysis to support these claims [8,11,21,57,58]. Our cross-application of data-driven classifiers supports that there is limited overlap between the acute effects of LSD and FEP. Differences between scanning protocols might have made it more difficult to find similarities, making these findings more suggestive of potential similarity while also increasing the odds of false negatives. Indeed, a study comparing the neural effects of hypnosis, meditation, LSD, and psilocybin failed to find similarities between the pharmacological interventions and non-pharmacological interventions using a data-driven approach with scanners with more similar sequences [59]. These results might therefore suggest that the neurobiological effects of LSD have more similarities to those of FEP than those of meditation or hypnosis. Future work should also investigate whether the converging similarities between FEP and LSD in altered DAN and SMN connectivity predict treatment outcomes of psychedelic-assisted therapy and antipsychotic medication use.

Limitations

The primary limitation of this study is the differing scanning parameters and participant instructions for resting-state (e.g., eyes-closed versus eyes-open) across datasets. Open-eye versus closed-eye resting-state impacts functional connectivity, particularly of the visual and default mode networks [60,61]. Most studies, in general, use an open-eyes resting state, which has been shown to have better test-retest reliability and minimizes sleep (something that could happen under placebo conditions but is unlikely under psychedelics, which typically preclude sleep)[62,63]. However, no studies of the acute effects of LSD at psychedelic doses have used open-eye resting-state [19].

We attempted to mitigate the potential effects of differences in scanner acquisition by externally validating our LSD-placebo classifier in an LSD dataset with different scanner acquisition protocols and different modes of administration. We presumed that classifiers that transferred to a dataset with differences in study design were more reliable than those that did not transfer. Nevertheless, the small sample of our external LSD-placebo dataset limits the reliability of our external validation. This limitation makes potential similarities we found more noteworthy but, also stresses the need for follow-up studies with identical scanning parameters.

Additionally, the FEP-HC sample size was limited by the selection of relatively stringent motion exclusion criteria in order to minimize bias when conducting classifier cross-application. Additionally, we only focused on cortical resting-state networks. Future studies should also examine subcortical and thalamic regions as these may also have potentially overlapping changes in RSFC [4,15]. Fluctuations in psychotic symptoms are also a potential concern. Subsequent studies might attempt to account for fluctuations in symptoms by tracking auditory hallucinations or other symptoms during the scans [64,65].

Conclusion

Our data-driven approach provides found limited similarity in RSFC of the acute effects of LSD and patients with FEP. The acute effects of LSD produce more consistent changes in RSFC across transmodal-sensory networks than within FEP, which shows more discriminant alterations in transmodal between- and within-network functioning. Given the high heterogeneity of FEP, LSD is unlikely to serve as a comprehensive model of psychosis. Still, our results indicated that alterations in DAN and SMN connectivity were present in both FEP and LSD. These results overall suggest that LSD might produce some neural changes that overlap with those seen in medication-naïve psychosis. Ultimately, more direct comparisons are needed to understand how psychedelics model certain aspects of psychosis and what this might mean for the mechanism of atypical antipsychotics and the therapeutic and iatrogenic mechanisms of psychedelics.

Methods and Materials

LSD Datasets

Four existing studies of the acute effects of LSD were used for this study, with three studies using identical scanning sequences being used as training data [20,30,66,67], and a smaller dataset with a different scanning protocol being used for external validation [68]. All LSD studies used a within-subject cross-over design. The studies, imaging protocols and exclusion criteria from each source are described in-depth in the supplemental

materials (Supplementary Table S1). All LSD datasets used a closed-eye resting-state paradigm, which is the historic norm in fMRI studies of the acute effects of psychedelics [19].

FEP Dataset

We used data from a longitudinal study of medication-naïve FEP patients (n = 108) alongside healthy controls (n = 117) [27]. Medication-naïve FEP patients were recruited from the emergency department, outpatient clinics, and inpatient services at the University of Alabama at Birmingham. Psychotic symptom severity was assessed with the clinician-administered Positive and Negative Syndrome Scale (PANSS) at the time of scanning [69]. Only baseline fMRI scans (i.e., prior to the initiation of antipsychotic medication) were used given our focus on comparing early psychosis not confounded by medication and disease progression to the acute effects of LSD. Subjects were instructed to keep their eyes open and let their mind wander during this scan (we return to this difference in eyes-open versus eyes-closed in the Discussion).

Ethics

All studies received ethical approval from their respective review committees. Specifically, the Basel datasets were approved by the Ethics Committee for Northwest/Central Switzerland (EKNZ) and the Swiss Federal Office of Public Health; the Imperial dataset was approved by the National Research Ethics Service Committee London–West London; and the FEP dataset was approved by the University of Alabama at Birmingham Institutional Review Board. The Basel studies were registered on ClinicalTrials.gov under identifiers NCT02308969, NCT03019822, and NCT04227756, while the FEP study was registered under NCT03442101. The Imperial study was not registered on ClinicalTrials.gov. All participants provided informed consent prior to active participation. All studies were conducted in accordance with the Declaration of Helsinki and all relevant ethical guidelines and regulations.

Analyses

Preprocessing & Functional Connectivity

Preprocessing was conducted using fMRIPrep and is described in detail in the supplemental materials [70]. For quality control, relatively strict motion inclusion criteria were selected, as this study seeks to create classifiers with transferability between datasets. We retained 73 scans of FEP patients and excluded 24 patients due to excessive motion and 11 patients due to affective psychotic disorders. Among healthy controls, 101 participants remained after applying motion exclusion criteria. Because an imbalance in data between classes using partial least squares discriminant analysis (PLS-DA) can lead to a preference for the more common class, we randomly selected 73 HC participants using MATLAB's randperm function with a fixed random seed. FEP and HC participants were matched for age, sex, and mean framewise displacement (FD; see Supplementary Table S2). For our LSD-placebo data, we removed participants who had excessive motion during either the LSD or placebo scan. Of 84 participants, we retained 76 subject pairs after excluding 8 due to excessive motion. Out of our

smaller study validation sample, we retained 15 participants after removing 5 due to motion. We then created within-subject classifiers of LSD-placebo scans using the Basel datasets with 76 subject pairs.

Whole-brain connectomes were calculated as Pearson's correlation coefficients between the timeseries of all pairwise combinations of regions in the 100-region Schaefer-Yeo atlas, resulting in 4,950 edges [71]. Pearson's *r*-values were then Fisher *z*-transformed prior to analysis. For network-level analyses, regions were grouped according to the Schaefer-Yeo 17-network parcellation, resulting in 136 between-network and 17 within-network interactions [71]. These correlation matrices were then used for CBC. Controlling for confounds between subjects (e.g., age, sex, and mean FD) is discussed within the classifier analyses, as controlling for covariates presents a potential source of data leakage.

Connectome-Based Classification

Using PLS-DA, we classified scans in the within-subject LSD-placebo classifiers as either LSD or placebo and in the FEP-HC classifiers as either FEP or HC, based on either the full connectome (4,950 edges) or network-interaction classifiers. For network-interaction classifiers, we included all individual edges corresponding to the specific network-interaction as separate features in the classifier, resulting in 136 between-network and 17 within-network classifiers. We used 10-fold cross-validation for both the FEP-HC classifiers and the within-subject LSD-placebo classifiers. We split the scans and subject-level covariates (age, sex, and mean FD) into training and test data. The training scans were then adjusted for covariates using linear regression. Test scans were adjusted for covariates using the beta coefficients derived from the training dataset. Feature *z*-scoring parameters were estimated from the training data and then applied separately to the test data. Training and testing data were separated for residualization and standardization (*z*-scoring) to prevent data leakage. For the LSD-placebo classifiers, LSD and placebo data for each subject were kept in either the training or testing sets per fold.

To reduce volatility, 100 iterations of 10-fold cross-validation were conducted, with a new subject partition each iteration. We limited PLS-DA to 3 components to prevent overfitting. Then, we evaluated the final classification performance by averaging results across all folds and iterations (i.e., across 1,000 repeats of a given classifier). Discrimination scores (*d'*) were computed based on hit rate (LSD classified as LSD, FEP as FEP) and false alarms (placebo classified as LSD, HC classified as LSD) for all classifiers. The distribution of *d'* scores across iterations was examined by calculating the mean and 95% confidence intervals based on the *t*-distribution from the *d'* scores across 100 iterations.

Cross-Application of Classifiers to Alternative Datasets

Final classifier weights (beta coefficients) were averaged across all cross-validation iterations for both LSD-placebo and FEP-HC classifiers so that they could be applied to the alternative dataset. Only classifiers demonstrating at least moderate discriminability ($d' \geq 0.7$) in their original dataset were examined for validation and/or cross-application. To apply the averaged classifiers to alternative datasets, we first *z*-scored the edges in the testing dataset using the mean and standard deviation parameters from the original training dataset. This standardization ensures that the input data for the classifier is on the same scale as the training data, which is essential as PLS regression is sensitive to the magnitude of input features. The testing dataset scans controlled

for age, sex, and mean FD controlled when validating the LSD classifiers with the external dataset and cross-application of the classifiers (i.e., LSD-placebo to FEP-HC and vice versa).

LSD-placebo classifiers trained on the Basel datasets with good discriminability in the external Imperial dataset ($d' \geq 0.7$) were applied to the FEP-HC dataset to explore potential similarities between LSD-induced brain changes and FEP. We selected to apply the classifiers derived from within-subject classification as these classifiers would classify based exclusively on LSD-associated brain changes rather than any subclinical psychotic-like brain connectivity that exists with some variation in the general population [72].

No additional FEP-HC dataset was available. Therefore, instead of validating the FEP-HC classifiers in another FEP-HC dataset, we examined whether cross-application of discriminant classifiers ($d' \geq 0.7$) showed convergent classification of LSD and placebo data (as either HC or FEP) in both the Basel and Imperial datasets.

Finally, we examined transfer d' scores for the cross-applications of classifiers. Hits were defined as the classification of FEP as LSD and vice versa, whereas false alarms were defined as HC being classified as LSD and placebo classified as FEP.

Targeted Examination of RSFC Based on Cross-Application of Classifiers

For network-interaction models in which cross-application indicated that FEP or LSD displayed LSD-like or FEP-like connectivity, respectively, we examined average connectivity of these network interactions for both the LSD-placebo and FEP-HC datasets. Specifically, we averaged all edges for the specific network interaction. For the FEP-HC dataset, independent-samples *t*-tests were conducted (FEP > HC), and for the LSD datasets, paired sample *t*-tests were conducted (LSD > Placebo). As a follow-up analysis, we also examined whether there were differences in connectivity between FEP patients classified as LSD-like versus placebo-like and LSD scans classified as FEP-like versus HC-like using independent-samples *t*-tests. We did not examine network interactions outside of those that emerged from our classification analyses to take a targeted approach and minimize multiple comparisons.

Relationship between LSD-like Neural Activity and Psychotic Symptom Severity

In cases where externally validated LSD-placebo classifiers cross-application suggested a similarity between FEP and LSD (transfer $d' > 0.3$), we explored psychotic symptom severity as measured with the PANSS. We examined both whether patients classified as LSD-like had greater symptom severity than patients classified as placebo-like and whether univariate RSFC within specified network-interactions correlated with symptom severity.

Declarations

Competing Interests

CRN receives consultant fees from MindMed, Lykos Therapeutics, and Usona Institute, and holds equity in Psilera as a scientific advisor. RC-H reports receiving consulting fees from COMPASS Pathways, Entheon Biomedical, Mydecine, Synthesis Institute, Tryp Therapeutics, and Usona Institute. MEL is a consultant for Mind Medicine, Inc. FH is an intern for NPP. PSH reports receiving grants from Beckley Psytech, Reunion Neuroscience, and Usona Institute; personal fees from Bright Minds Biosciences, Journey Colab Corporation, Negev Labs, Otsuka Pharmaceutical Development and Commercialization, and Reunion Neuroscience; and owning equity or stock options in AtaiBeckley, Inc., and Negev Labs. He previously had paid advisory relationships with Eleusis Benefit Corporation, Reset Pharmaceuticals Inc., and Silo Pharma and currently has paid advisory relationships with Bright Minds Biosciences Ltd. and Journey Colab Corporation. He is also a cofounder of Equulus Therapeutics and Mycelial Health and has a pending patent (63/804,162). All disclosures are outside the submitted work. All other authors report no biomedical financial interests or potential conflicts of interest.

Author Contribution

HMD: Conceptualization; Formal analysis; Visualization; Writing - original draft; Writing - review & editing. MKD: Methodology; Writing - review & editing. JAT: Methodology; Supervision; Writing - review & editing. MB: Methodology; Writing - review & editing. CRN: Methodology; Supervision; Writing - review & editing. AL: Investigation. FM: Investigation; Writing - review & editing. RCH: Investigation; Writing - review & editing. RB: Writing - review & editing. MEL: Investigation. FH: Investigation. PV: Investigation. AMB: Investigation. LL: Investigation. AK: Investigation. UEL: Investigation. PSH: Supervision; Writing - review & editing. All authors approved the final manuscript.

Data Availability

Data access requests can be addressed to the respective study authors. Specifically, Adrienne Lahti for first episode psychosis data, Felix Müller for Basel datasets, and Robin Carhart-Harris for Imperial LSD data.

Funding Declaration

No funding was received for this study.

References

1. Andersen, K. A. A., Carhart-Harris, R., Nutt, D. J. & Erritzoe, D. Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies. *Acta Psychiatry. Scand.* **143**, 101–118 (2021).
2. Nichols, D. E., Nichols, C. D. & Hendricks, P. S. Proposed Consensus Statement on Defining Psychedelic Drugs. *Psychedelic Med.* **1**, 12–13 (2023).
3. Norring, S. A. & Spigarelli, M. G. The Promise of Therapeutic Psilocybin: An Evaluation of the 134 Clinical Trials, 54 Potential Indications, and 0 Marketing Approvals on ClinicalTrials.gov. *Drug Des. Devel Ther.* **18**, 1143–1151 (2024).

4. Dourron, H. M., Strauss, C. & Hendricks, P. S. Self-Entropic Broadening Theory: Toward a New Understanding of Self and Behavior Change Informed by Psychedelics and Psychosis. *Pharmacol. Rev.* **74**, 982–1027 (2022).
5. Friesen, P. Psychosis and psychedelics: Historical entanglements and contemporary contrasts. *Transcult Psychiatry*. **59**, 592–609 (2022).
6. Nichols, D. E. & Walter, H. The History of Psychedelics in Psychiatry. *Pharmacopsychiatry* **54**, 151–166 (2021).
7. Hermle, L. et al. Mescaline-induced psychopathological, neuropsychological, and neurometabolic effects in normal subjects: experimental psychosis as a tool for psychiatric research. *Biol. Psychiatry*. **32**, 976–991 (1992).
8. Vollenweider, F. Positron Emission Tomography and Fluorodeoxyglucose Studies of Metabolic Hyperfrontality and Psychopathology in the Psilocybin Model of Psychosis. *Neuropsychopharmacology* **16**, 357–372 (1997).
9. Brouwer, A. & Carhart-Harris, R. L. Pivotal mental states. *J. Psychopharmacol.* **35**, 319–352 (2021).
10. Carhart-Harris, R. L. The entropic brain - revisited. *Neuropharmacology* **142**, 167–178 (2018).
11. Carhart-Harris, R. L. et al. The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. *Front Hum. Neurosci* **8**, (2014).
12. Carhart-Harris, R. L. & Friston, K. J. REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. *Pharmacol. Rev.* **71**, 316–344 (2019).
13. Geyer, M. & Vollenweider, F. Serotonin research: contributions to understanding psychoses. *Trends Pharmacol. Sci.* **29**, 445–453 (2008).
14. Vollenweider, F. X. & Geyer, M. A. A systems model of altered consciousness: integrating natural and drug-induced psychoses. *Brain Res. Bull.* **56**, 495–507 (2001).
15. Vollenweider, F. X. & Preller, K. H. Psychedelic drugs: neurobiology and potential for treatment of psychiatric disorders. *Nat. Rev. Neurosci.* **21**, 611–624 (2020).
16. Hofmann, A. *LSD, My Problem Child* (McGraw-Hill, 1980).
17. Tanne, J. H., Humphry & Osmond *BMJ* **328**, 713 (2004).
18. Girn, M. et al. An international mega-analysis of psychedelic drug effects on brain circuit function. *Nat. Med.* **32**, 1543–1554 (2026).
19. McCulloch, D. E. W. et al. Psychedelic resting-state neuroimaging: A review and perspective on balancing replication and novel analyses. *Neurosci. Biobehav Rev.* **138**, 104689 (2022).
20. Avram, M. et al. Bridging the Gap? Altered Thalamocortical Connectivity in Psychotic and Psychedelic States. *Frontiers Psychiatry* **12**, (2021).
21. Carhart-Harris, R. L. et al. Functional Connectivity Measures After Psilocybin Inform a Novel Hypothesis of Early Psychosis. *Schizophr Bull.* **39**, 1343–1351 (2013).
22. Preller, K. H. et al. Changes in global and thalamic brain connectivity in LSD-induced altered states of consciousness are attributable to the 5-HT2A receptor. *Elife* **7**, e35082 (2018).
23. O'Neill, A., Mechelli, A. & Bhattacharyya, S. Dysconnectivity of Large-Scale Functional Networks in Early Psychosis: A Meta-analysis. *Schizophr. Bull.* **45**, 579–590 (2019).

24. Li, S. et al. Dysconnectivity of Multiple Brain Networks in Schizophrenia: A Meta-Analysis of Resting-State Functional Connectivity. *Front. Psychiatry*. **10**, 482 (2019).
25. Keane, B. P., Abrham, Y. T., Hearne, L. J., Bi, H. & Hu, B. Increased whole-brain functional heterogeneity in psychosis during rest and task. *NeuroImage: Clin.* **43**, 103630 (2024).
26. Yang, C. et al. The Effects of Antipsychotic Treatment on the Brain of Patients With First-Episode Schizophrenia: A Selective Review of Longitudinal MRI Studies. *Front. Psychiatry*. **12**, 593703 (2021).
27. Maximo, J. O., Nelson, E. A., Armstrong, W. P., Kraguljac, N. V. & Lahti, A. C. Duration of Untreated Psychosis Correlates With Brain Connectivity and Morphology in Medication-Naïve Patients With First-Episode Psychosis. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging*. **5**, 231–238 (2020).
28. Chung, J. & Miller, B. J. Meta-analysis of comorbid diabetes and family history of diabetes in non-affective psychosis. *Schizophr. Res.* **216**, 41–47 (2020).
29. Cui, Y. et al. Aberrant functional connectivity of default-mode network in type 2 diabetes patients. *Eur. Radiol.* **25**, 3238–3246 (2015).
30. Holze, F. et al. Direct comparison of the acute effects of lysergic acid diethylamide and psilocybin in a double-blind placebo-controlled study in healthy subjects. *Neuropsychopharmacol* **47**, 1180–1187 (2022).
31. Inserra, A., De Gregorio, D. & Gobbi, G. Psychedelics in Psychiatry: Neuroplastic, Immunomodulatory, and Neurotransmitter Mechanisms. *Pharmacol. Rev.* **73**, 202–277 (2021).
32. Aringhieri, S. et al. Molecular targets of atypical antipsychotics: From mechanism of action to clinical differences. *Pharmacol. Ther.* **192**, 20–41 (2018).
33. Giacomelli, S., Palmery, M., Romanelli, L., Cheng, C. Y. & Silvestrini, B. Lysergic acid diethylamide (LSD) is a partial agonist of D2 dopaminergic receptors and it potentiates dopamine-mediated prolactin secretion in lactotrophs in vitro. *Life Sci.* **63**, 215–222 (1998).
34. De Gregorio, D., Comai, S., Posa, L. & Gobbi, G. d-Lysergic Acid Diethylamide (LSD) as a Model of Psychosis: Mechanism of Action and Pharmacology. *Int. J. Mol. Sci.* **17**, 1953 (2016).
35. Baggott, M. J., Coyle, J. R., Erowid, E., Erowid, F. & Robertson, L. C. Abnormal visual experiences in individuals with histories of hallucinogen use: A web-based questionnaire. *Drug Alcohol Depend.* **114**, 61–67 (2011).
36. Vis, P. J., Goudriaan, A. E., Meulen, B. C. & Blom, J. D. ter On Perception and Consciousness in HPPD: A Systematic Review. *Front. Neurosci.* 15, 675768 (2021).
37. Silverstein, S. M. & Lai, A. The Phenomenology and Neurobiology of Visual Distortions and Hallucinations in Schizophrenia: An Update. *Front. Psychiatry*. **12**, 684720 (2021).
38. Yoo, K. et al. Connectome-based predictive modeling of attention: Comparing different functional connectivity features and prediction methods across datasets. *NeuroImage* **167**, 11–22 (2018).
39. Doss, M. K. et al. The Acute Effects of the Atypical Dissociative Hallucinogen Salvinorin A on Functional Connectivity in the Human Brain. *Sci. Rep.* **10**, 16392 (2020).
40. Shen, X. et al. Using connectome-based predictive modeling to predict individual behavior from brain connectivity. *Nat. Protoc.* **12**, 506–518 (2017).
41. Carhart-Harris, R. L. et al. The paradoxical psychological effects of lysergic acid diethylamide (LSD). *Psychol. Med.* **46**, 1379–1390 (2016).

42. Wießner, I. et al. LSD, madness and healing: Mystical experiences as possible link between psychosis model and therapy model. *Psychol. Med.* 1–15. 10.1017/S0033291721002531 (2021).
43. Collin, G. et al. Brain functional connectivity data enhance prediction of clinical outcome in youth at risk for psychosis. *NeuroImage: Clin.* **26**, 102108 (2020).
44. Gong, Q. et al. Network-Level Dysconnectivity in Drug-Naïve First-Episode Psychosis: Dissociating Transdiagnostic and Diagnosis-Specific Alterations. *Neuropsychopharmacol* **42**, 933–940 (2017).
45. Gao, Z. et al. Multilayer network analysis reveals instability of brain dynamics in untreated first-episode schizophrenia. *Cereb. Cortex*. **34**, bhae402 (2024).
46. Keedy, S. K., Reilly, J. L., Bishop, J. R., Weiden, P. J. & Sweeney, J. A. Impact of Antipsychotic Treatment on Attention and Motor Learning Systems in First-Episode Schizophrenia. *Schizophr Bull.* **41**, 355–365 (2015).
47. Kraguljac, N. V. et al. Abnormalities in large scale functional networks in unmedicated patients with schizophrenia and effects of risperidone. *NeuroImage: Clin.* **10**, 146–158 (2016).
48. Borroto-Escuela, D. O. et al. Hallucinogenic 5-HT2AR agonists LSD and DOI enhance dopamine D2R protomer recognition and signaling of D2-5-HT2A heteroreceptor complexes. *Biochem. Biophys. Res. Commun.* **443**, 278–284 (2014).
49. Marona-Lewicka, D., Thisted, R. A. & Nichols, D. E. Distinct temporal phases in the behavioral pharmacology of LSD: dopamine D2 receptor-mediated effects in the rat and implications for psychosis. *Psychopharmacol. (Berl)*. **180**, 427–435 (2005).
50. Nichols, D. E. & Psychedelics *Pharmacol. Rev.* **68**, 264–355 (2016).
51. Machner, B. et al. Resting-State Functional Connectivity in the Dorsal Attention Network Relates to Behavioral Performance in Spatial Attention Tasks and May Show Task-Related Adaptation. *Front. Hum. Neurosci.* **15**, 757128 (2022).
52. Vossel, S., Geng, J. J. & Fink, G. R. Dorsal and Ventral Attention Systems. *Neuroscientist* **20**, 150–159 (2014).
53. Aas, M. et al. A Systematic Review of Cognitive Function in First-Episode Psychosis, Including a Discussion on Childhood Trauma, Stress, and Inflammation. *Front. Psychiatry*. **4**, 182 (2014).
54. Meshkat, S. et al. Impact of psilocybin on cognitive function: A systematic review. *Psychiatry Clin. Neurosci.* **78**, 744–764 (2024).
55. Keane, B. P. et al. Functional dysconnectivity of visual and somatomotor networks yields a simple and robust biomarker for psychosis. *Mol. Psychiatry*. **30**, 1539–1547 (2025).
56. Hwang, Z. A. et al. The distinct functional brain network and its association with psychotic symptom severity in men with methamphetamine-associated psychosis. *BMC Psychiatry*. **24**, 671 (2024).
57. Avram, M. et al. Characterizing thalamocortical (dys)connectivity following d-amphetamine, LSD, and MDMA administration. *Biol. Psychiatry: Cogn. Neurosci. Neuroimaging*. **S2451902222000969** 10.1016/j.bpsc.2022.04.003 (2022).
58. Leptourgos, P. et al. Hallucinations Under Psychedelics and in the Schizophrenia Spectrum: An Interdisciplinary and Multiscale Comparison. *Schizophr. Bull.* **46**, 1396–1408 (2020).
59. Moujaes, F. et al. Comparing Neural Correlates of Consciousness: From Psychedelics to Hypnosis and Meditation. *Biol. Psychiatry: Cogn. Neurosci. Neuroimaging*. **9**, 533–543 (2024).

60. Han, J. et al. Eyes-Open and Eyes-Closed Resting State Network Connectivity Differences. *Brain Sci.* **13**, 122 (2023).
61. Costumero, V., Bueichekú, E., Adrián-Ventura, J. & Ávila, C. Opening or closing eyes at rest modulates the functional connectivity of V1 with default and salience networks. *Sci. Rep.* **10**, 9137 (2020).
62. Agcaoglu, O., Wilson, T. W., Wang, Y., Stephen, J. & Calhoun, V. D. Resting state connectivity differences in eyes open versus eyes closed conditions. *Hum. Brain Mapp.* **40**, 2488–2498 (2019).
63. Patriat, R. et al. The effect of resting condition on resting-state fMRI reliability and consistency: A comparison between resting with eyes open, closed, and fixated. *Neuroimage* **78**, 463–473 (2013).
64. Leroy, A. et al. fMRI capture of auditory hallucinations: Validation of the two-steps method. *Hum. Brain Mapp.* **38**, 4966–4979 (2017).
65. Gill, K. et al. Real-Time Symptom Capture of Hallucinations in Schizophrenia with fMRI: Absence of Duration-Dependent Activity. *Schizophr Bull. Open.* **3**, sgac050 (2022).
66. Holze, F. et al. Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects. *Neuropsychopharmacology* **45**, 462–471 (2020).
67. Müller, F. et al. Increased thalamic resting-state connectivity as a core driver of LSD-induced hallucinations. *Acta Psychiatr Scand.* **136**, 648–657 (2017).
68. Carhart-Harris, R. L. et al. Neural correlates of the LSD experience revealed by multimodal neuroimaging. *PNAS* **113**, 4853–4858 (2016).
69. Kay, S. R., Fiszbein, A. & Opler, L. A. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophr. Bull.* **13**, 261–276 (1987).
70. Esteban, O. et al. FMRIPrep: a robust preprocessing pipeline for functional MRI. [object Object] (2018). https://doi.org/10.24433/CO.ED5DDFEF-76A3-4996-B298-E3200F69141B
71. Schaefer, A. et al. Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cereb. Cortex*. **28**, 3095–3114 (2018).
72. Ma, Y. et al. Resting-State Functional Connectivity Explained Psychotic-like Experiences in the General Population and Partially Generalized to Patients and Relatives. *Biol. Psychiatry Glob Open. Sci.* **3**, 1094–1103 (2023).

Figures

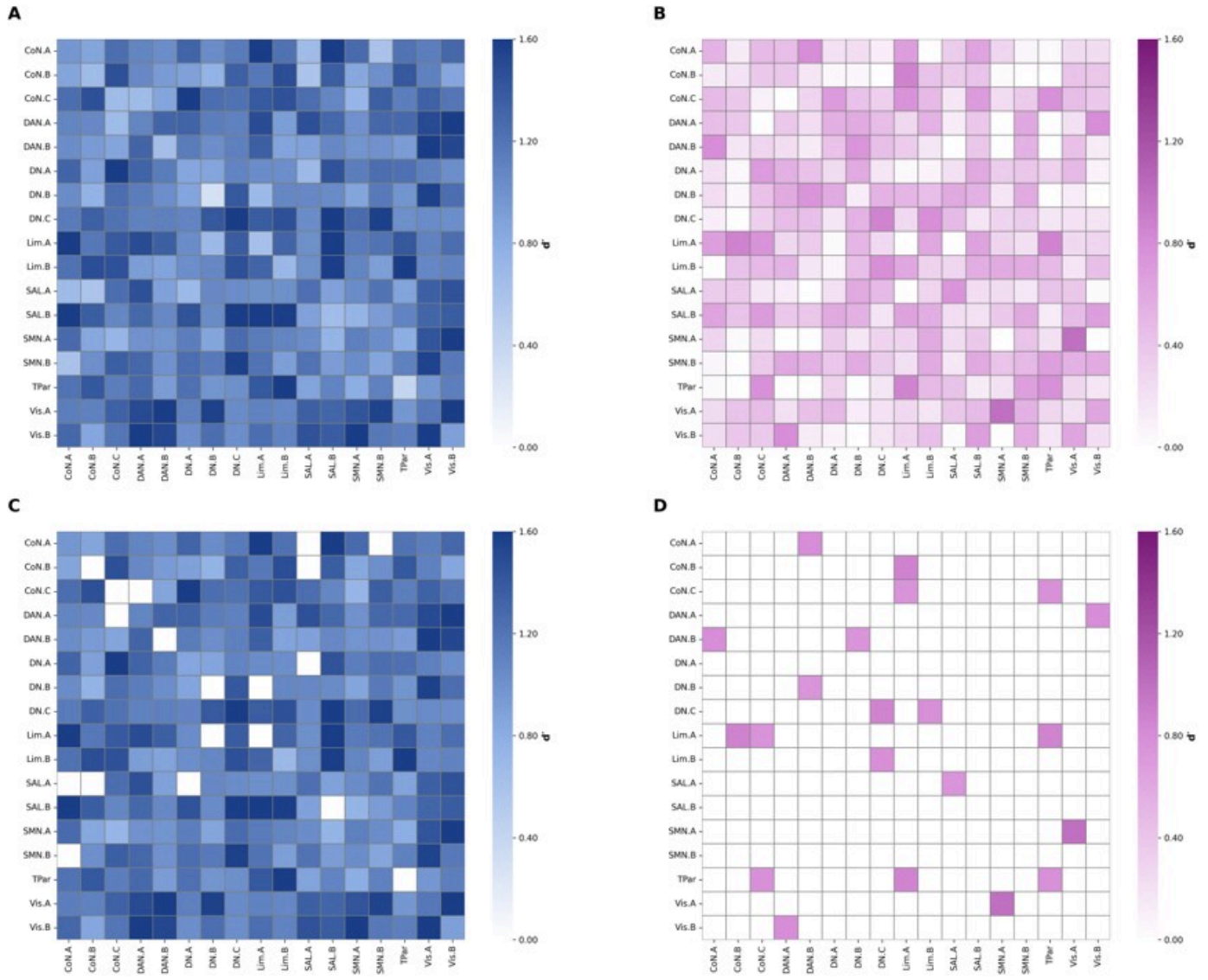


Figure 1

Discrimination of Network-Interaction Classifiers in LSD-Placebo and FEP-HC Datasets

Note. Network-interaction classifiers that achieved *d'* > 0.0 for discriminating LSD from placebo and FEP from HC are depicted in panel A showing the discrimination scores of LSD-Placebo classifiers for discriminating LSD from placebo within the Basel dataset and panel B showing the discrimination scores of FEP-HC classifiers for discriminating FEP from HC. Network-classifiers with a *d'* ≥ 0.70 are shown in panel C for LSD-placebo, and D for FEP-HC, respectively. Classifiers were trained using 10-fold cross-validation (100 iterations), with results averaged across all folds and repetitions. Abbreviations: LSD = lysergic acid diethylamide, FEP = first-episode psychosis, HC = healthy control, CoN = control network, DAN = dorsal attention network, DN = default mode network, Lim = limbic network, SMN = somatomotor network, SAL = salience network, TPar = temporal-parietal network, and Vis = visual network.

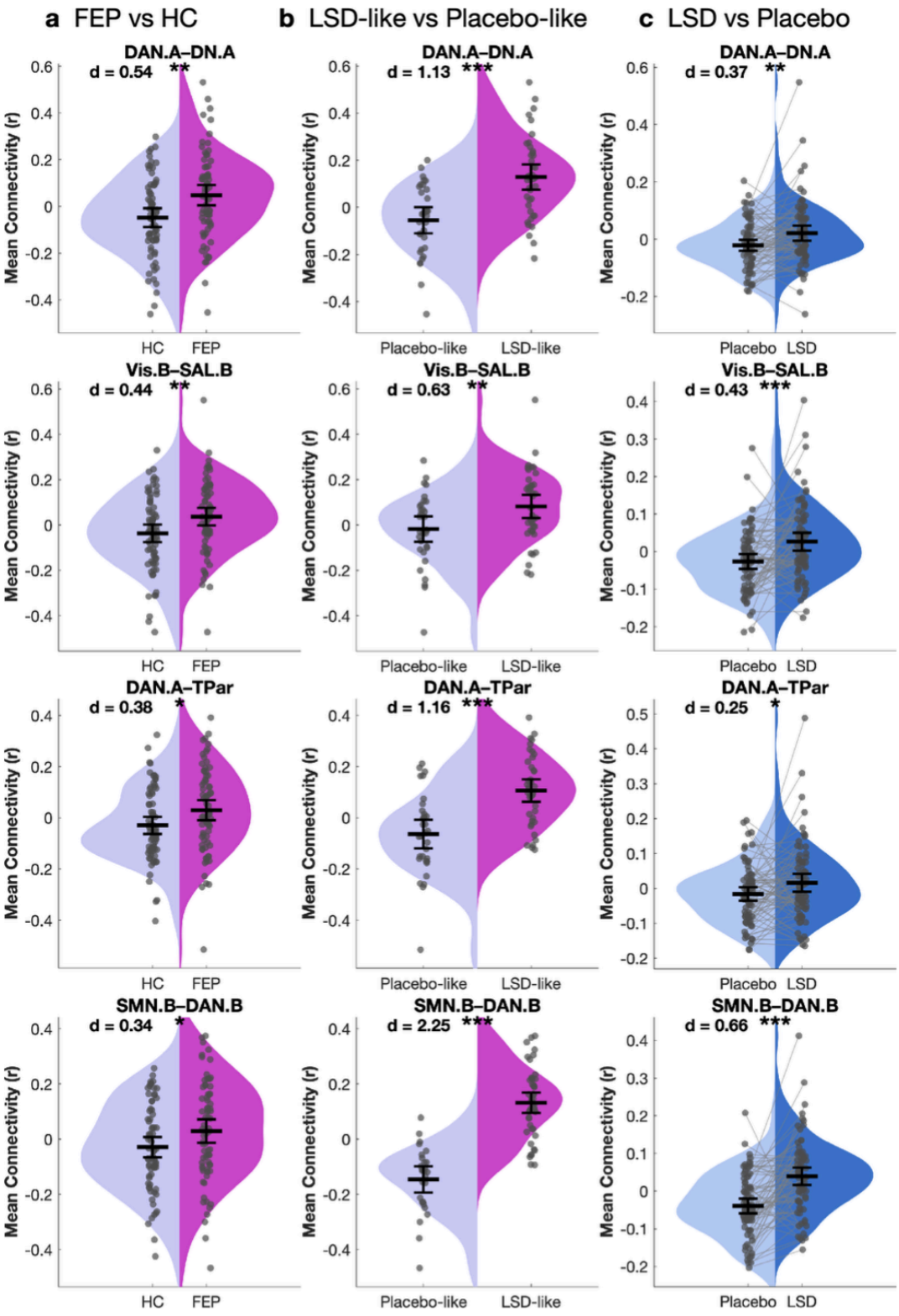


Figure 2

Examining FEP-HC Functional Connectivity in LSD-like Network-Interactions

Note. For the network-interactions that suggested FEP might have LSD-like connectivity based on the cross-application of the LSD-placebo classifier, we examined functional connectivity. The column A presents the difference between FEP patients and healthy controls. Column B presents the differences between FEP patients classified as LSD-like versus placebo-like. Column C shows the differences between LSD and placebo scans

within the Basel dataset (the dataset the LSD-placebo classifiers were trained on). The lines on the LSD-placebo violin plots reflect change in connectivity within participants. Horizontal bars reflect the mean, and error bars reflect the 95% confidence interval. *p < 0.05, **p < 0.01, ***p < 0.001.

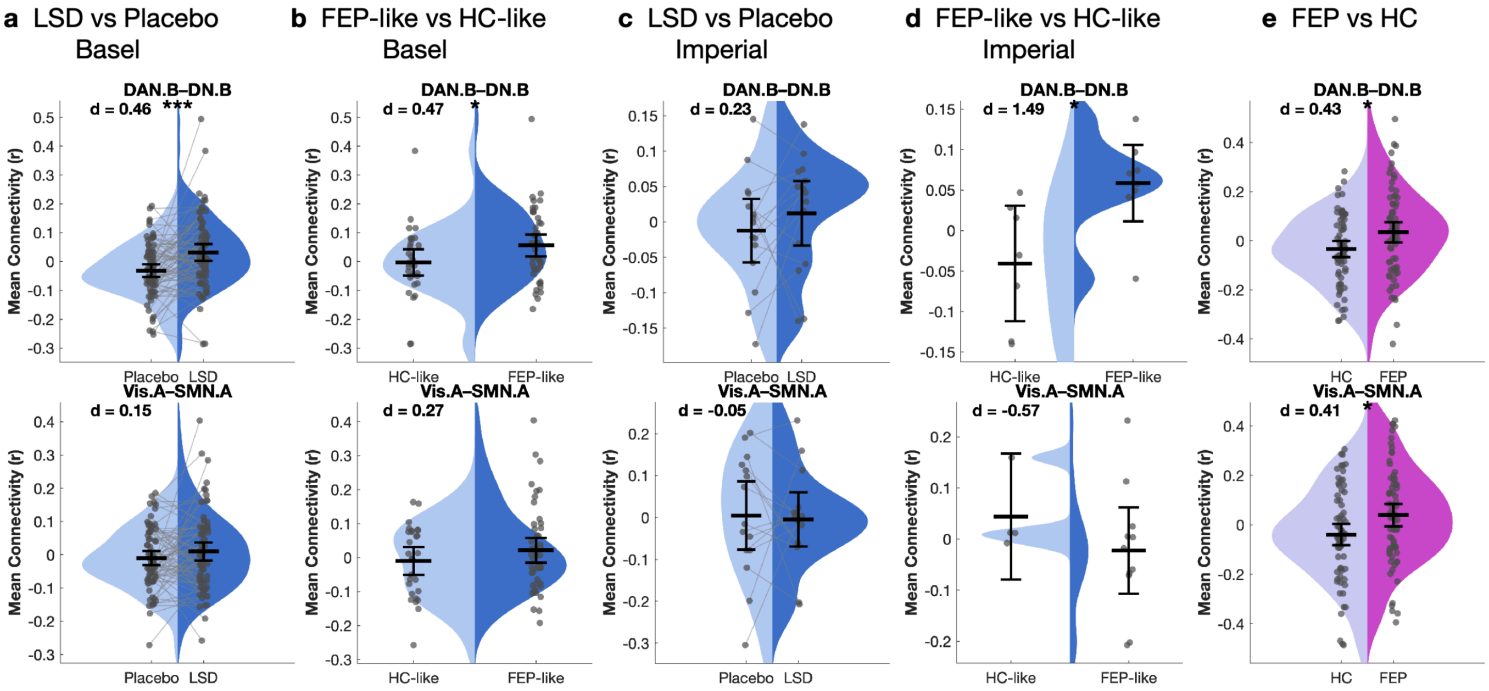


Figure 3

Functional Connectivity in FEP-like Network-Interactions

Note. Based on the cross-application of the FEP-HC classifier to both LSD datasets, we examined RSFC for network-interaction classifiers that suggested LSD might have FEP-like connectivity in both datasets. The first column presents the differences within-subject between placebo and LSD scans in the Basel dataset. The second column presents differences in RSFC in these network-interactions for LSD scans classified as FEP-like versus HC-like within the Basel dataset. This is followed by the column showing within-subject changes in RSFC for the Imperial LSD-placebo dataset, followed by comparison between subjects classified as FEP-like versus HC-like. The fourth column shows the difference between FEP patients and healthy controls. The lines on the LSD-placebo violin plots reflect change in connectivity within participants. Horizontal bars reflect the mean, and error bars reflect the 95% confidence interval. *p < 0.05, **p < 0.01, ***p < 0.001