Archival Report

Characterizing Thalamocortical (Dys)connectivity Following D-Amphetamine, LSD, and MDMA Administration

Mihai Avram, Felix Müller, Helena Rogg, Alexandra Korda, Christina Andreou, Friederike Holze, Patrick Vizeli, Laura Ley, Matthias E. Liechti, and Stefan Borgwardt

ABSTRACT

BACKGROUND: Patients with psychotic disorders present alterations in thalamocortical intrinsic functional connectivity as measured by resting-state functional magnetic resonance imaging. Specifically, thalamic intrinsic functional connectivity is increased with sensorimotor cortices (hyperconnectivity) and decreased with prefrontal limbic cortices (hypoconnectivity). Psychedelics such as lysergic acid diethlyamide (LSD) elicit similar thalamocortical hyperconnectivity with sensorimotor areas in healthy volunteers. It is unclear whether LSD also induces thalamocortical hypoconnectivity with prefrontal limbic cortices, because current findings are equivocal. Thalamocortical hyperconnectivity was associated with psychotic symptoms in patients and substance-induced altered states of consciousness in healthy volunteers. Thalamocortical dysconnectivity is likely evoked by altered neurotransmission, e.g., via dopaminergic excess in psychotic disorders and serotonergic agonism in psychedelic-induced states. It is unclear whether thalamocortical dysconnectivity is also elicited by amphetamine-type substances, broadly releasing monoamines (i.e., dopamine, norepinephrine) but producing fewer perceptual effects than psychedelics.

METHODS: We administrated LSD, d-amphetamine, and 3,4-methylenedioxymethamphetamine (MDMA) in 28 healthy volunteers and investigated their effects on thalamic intrinsic functional connectivity with 2 brain networks (auditory-sensorimotor and salience networks, corresponding to sensorimotor and prefrontal limbic cortices, respectively), using a double-blind, placebo-controlled, crossover design.

RESULTS: All active substances elicited auditory-sensorimotor–thalamic hyperconnectivity compared with placebo, despite predominantly distinct pharmacological actions and subjective effects. LSD-induced effects correlated with subjective changes in perception, indicating a link between hyperconnectivity and psychedelic-type perceptual alterations. Unlike d-amphetamine and MDMA, which induced hypoconnectivity with the salience network, LSD elicited hyperconnectivity. D-amphetamine and MDMA evoked similar thalamocortical dysconnectivity patterns.

CONCLUSIONS: Psychedelics, empathogens, and psychostimulants evoke thalamocortical hyperconnectivity with sensorimotor areas, akin to findings in patients with psychotic disorders.

https://doi.org/10.1016/j.bpsc.2022.04.003

Early theories on schizophrenia hypothesized a dysconnection syndrome, mainly involving disturbances in cortico-striato-pallido-thalamocortical circuits (1,2). Animal studies demonstrated that these circuits are organized topographically—e.g., prefrontal cortices preferentially connect to mediodorsal thalamic nuclei, while sensorimotor areas connect to lateral/posterior thalamic nuclei (3). Findings from in vivo investigations in healthy volunteers with resting-state functional magnetic resonance imaging (rs-fMRI) support this topographical organization. Specifically, patterns of intrinsic functional connectivity (iFC) (i.e., statistical correlations between signal time courses of distinct [sets of] brain regions) were identified between thalamic nuclei and cortical areas, in line with the largely parallel subcircuits of thalamocortical connections (4). Consistent with the dysconnection theories,

altered thalamocortical iFC is one of the most robust large-scale in vivo brain imaging findings in schizophrenia (5). Two patterns of thalamocortical dysconnectivity [i.e., reflecting both increased and decreased iFC, not to be confused with disconnectivity, which denotes a decrease in function only (6)] have been identified consistently: compared with healthy control subjects, patients exhibit 1) increased iFC (hyperconnectivity) between primary sensory/motor cortices and the posterior/ventrolateral thalamus and 2) decreased iFC (hypoconnectivity) between prefrontal limbic cortices and the anterior/mediodorsal thalamus.

Thalamocortical dysconnectivity has been reported in patients with established schizophrenia (7–9), bipolar disorder (10,11), and first-episode psychosis (12) and individuals at risk for psychosis (13), suggesting a ubiquitous phenomenon

across psychotic disorders. The mechanism underlying thalamocortical dysconnectivity remains unclear but may be related to alterations in neurotransmission because these appear to modulate iFC [e.g., changes in dopamine transmission modify iFC strength (14)]. Therefore, experimental manipulations of neurotransmission could inform on mechanisms underlying thalamocortical dysconnectivity in psychotic disorders.

Research in psychiatry has used substance-induced phenomena to model aspects of psychosis (15). For instance, amphetamine has a long-standing tradition as a model for psychosis (16), based on 2 lines of evidence. First, amphetamine increases dopaminergic tone by interacting with the dopamine transporter and releasing dopamine (17). This elevation in dopaminergic transmission mirrors increased dopamine levels reported in patients with psychosis (18,19). Second, amphetamine can induce psychotic states and exacerbate psychotic symptoms in patients with schizophrenia (20,21). At lower doses, however, psychotic phenomena are not common (22). It is unclear whether amphetamine induces thalamocortical dysconnectivity because fMRI reports are scarce.

While current models of psychosis are dominated by dopaminergic and glutamatergic hypotheses (23), the first substance-induced model of psychosis was motivated by lysergic acid diethylamide (LSD)–induced effects (24). Typical effects may include altered visual and auditory perceptions, audiovisual synesthesia, derealization, and depersonalization (25,26). Similar to other classic psychedelics, LSD acts as a partial agonist at the serotonergic 5-HT$_{2A}$ receptor (25,27,28). The apparent similarities between some of the LSD-induced effects and psychotic symptoms catalyzed the serotonergic hypothesis of schizophrenia (15). Certain aspects of this hypothesis may still be relevant today because psychedelic-induced experiences seem to mimic (some of) the mental phenomena apparent in emerging psychosis (15,29). We recently argued that thalamocortical hyperconnectivity with sensorimotor regions may underlie altered perception because this pattern is consistently reported in both psychedelic-induced and psychotic states (30). Furthermore, thalamocortical hyperconnectivity is associated with subjective changes in perception following LSD administration (31) and with psychotic symptoms in schizophrenia (32). A neurobiological mechanism underlying such shared phenomena has been suggested in the form of altered thalamic gating (33,34). The disrupted thalamic filter model postulates that endogenous or exogenous alterations in neurotransmission (e.g., dopaminergic, serotonergic) potentially disrupt thalamic gating (e.g., via thalamic disinhibition), resulting in cortical sensory flooding, potentially leading to altered mental phenomena. In support, altered dopaminergic transmission (i.e., dopamine synthesis capacity) correlates with thalamocortical dysconnectivity in schizophrenia (9), and psychedelics, which induce alterations in serotonergic transmission, evoke thalamocortical hyperconnectivity (31,35,36). It is unclear whether LSD also induces thalamocortical hypoconnectivity with prefrontal limbic cortices. Preller et al. (36) found LSD-induced thalamic hypoconnectivity with prefrontal limbic areas and demonstrated that this effect was dependent on 5-HT$_{2A}$ receptor signaling. Notably, this result was affected by global signal regression (GSR). Using a similar approach without GSR, Müller et al. (31) demonstrated an overall increase in thalamocortical iFC,

including to prefrontal limbic areas, and, in another study, increased iFC between several resting-state networks (RSNs) covering prefrontal areas and the thalamus (37).

A special case is to be made for 3,4-methylenedioxymethamphetamine (MDMA), the active compound in the recreational drug ecstasy, which combines amphetamine-like and LSD-like properties and may therefore inform on mechanisms of action that are neither amphetamine- nor psychedelic-specific. MDMA is an amphetamine that elicits its effects mainly via serotonergic rather than dopaminergic neurotransmission (22,26) and also partly via 5-HT$_{2A}$ receptors (38). MDMA typically induces mild alterations in perception, along with increased feelings of well-being (39). Although not typically used to model psychosis, MDMA can induce psychotic symptoms (40,41), including delusions, hallucinations, and conceptual disorganization (42). In line with its serotonergic mode of action, evidence indicates that MDMA-induced effects are akin to some LSD-induced neural effects (43), but it remains to be determined whether thalamocortical dysconnectivity is also elicited.

We administered d-amphetamine, LSD, and MDMA in healthy volunteers and used rs-fMRI with a double-blind, placebo-controlled, crossover design to investigate substance-induced effects on thalamocortical iFC. In line with the disrupted thalamic filter model, we hypothesized that all 3 substances would elicit thalamocortical hyperconnectivity with sensorimotor cortices. Concerning prefrontal-limbic-thalamic iFC, we expected a more nuanced effect, with iFC increases following LSD and MDMA administration and decreases after d-amphetamine administration, based on a previous report (44). Substance-induced alterations in thalamocortical iFC were assessed voxelwise by correlating the time series of 2 RSNs previously used in psychosis studies, i.e., the auditory-sensorimotor network (ASM), as proxy for sensorimotor cortices, and the salience network (SAL), corresponding to prefrontal limbic cortices, and the thalamus (8,9). Putative relationships between thalamocortical (dys)connectivity and subjective drug effects were assessed with correlation analyses.

METHODS AND MATERIALS

Data analyzed herein were derived from the clinical trial NCT03019822 (26), which was conducted in Basel, Switzerland, and approved by the Ethics Committee for Northwest/Central Switzerland and by the Federal Office of Public Health. All participants gave their written informed consent after receiving a complete description of the study and received monetary compensation.

Participants and Study Design

A total of 28 healthy volunteers were recruited for the study (14 women, mean age = 28 ± 4 years). See Supplemental Methods and (26) for detailed participant description and study procedures.

The effects of 40 mg d-amphetamine, 0.1 mg LSD, and 125 mg MDMA were investigated using a double-blind, placebo-controlled, crossover design, comprising 4 experimental sessions with d-amphetamine, LSD, MDMA, or placebo in a random and counterbalanced order. Study details and substance-induced subjective and autonomic effects have been described previously (26).

Assessment of Subjective and Autonomic Effects

The substance-induced subjective peak effects were assessed 11 hours after substance administration with the 5 Dimensions of Altered States of Consciousness Questionnaire (5D-ASC) (45). We evaluated the overall strength of the drug effects (i.e., "any drug effect" from the visual analog scales) (26) by averaging the scores recorded immediately before (1.5 hours after substance administration) and after (2.5 hours after substance administration) the fMRI scan.

Autonomic effects were assessed by measuring several physiological parameters (PPs), including blood pressure, heart rate, and tympanic body temperature immediately before (1.5 hours after substance administration) and after (2.5 hours after substance administration) the fMRI scan (26). Average values of pre- and post-fMRI autonomic effects were used in subsequent analyses.

rs-fMRI: Data Acquisition and Preprocessing

For all conditions, structural and functional MRI data were acquired using a 3T MRI system (Magnetom Prisma, Siemens Healthcare) with a 20-channel phased-array radio-frequency head coil. See Supplemental Methods for imaging parameters.

The Configurable Pipeline for the Analysis of Connectomes (version 1.7.0., https://fcp-indi.github.io/) was used to preprocess the MRI data. We used the default preconfigured pipeline C-PAC unless otherwise specified (https://fcp-indi.github.io/docs/v1.8.3/user/pipelines/preconfig). Preprocessing steps included slice timing correction, motion correction, scrubbing, intensity normalization, nuisance signal regression followed by bandpass filtering (0.01–0.1 Hz), registration to anatomical space, and normalization to Montreal Neurological Institute 3 mm^3 space with FSL FLIRT/FNIRT. The nuisance signal regression was performed as a single multiple linear regression model and included component-based noise correction (aCompCor) to remove physiological noise (46). Notably, aCompCor was performed on eroded white matter and cerebrospinal fluid masks. Head motion effects were regressed out with the Friston 24-parameter model (i.e., 6 head motion parameters, 6 head motion parameters 1 time point before, and the 12 corresponding squared items). Data were analyzed twice, with the above-mentioned standard pipeline and by adding GSR to the above-mentioned steps. One participant was removed owing to excessive head motion, estimated with mean framewise displacement (47), in 1 session (placebo [framewise displacement > 0.2 mm]). Two additional participants were removed owing to missing sessions.

Seed-Based Correlation Analysis

Thalamocortical connectivity was investigated with seed-based correlation analysis. Seeds were chosen based on previous studies investigating thalamocortical dysconnectivity in patients with schizophrenia (8,9). Specifically, 2 networks were selected from a 7-network parcellation (48), namely the ASM and SAL. iFC was computed between each network and every voxel in the thalamus (created from the Harvard-Oxford subcortical atlas), resulting in z-maps reflecting ASM-thalamic and SAL-thalamic iFC.

Statistical Analyses

Voxelwise group statistics were performed by applying one-way repeated-measures analyses of variance (ANOVAs) to the thalamocortical iFC parameter maps using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). A flexible full factorial design was configured using participants as a between-participant factor and condition as a within-participant factor (levels: d-amphetamine, LSD, MDMA, and placebo). Statistical testing was limited to voxels contained in the thalamus mask used as the target region for the seed-based analysis. Significant differences were based on a familywise error rate of $p < .05$ at the cluster level (height threshold $p = .001$). The outcomes of interest were thalamocortical iFC changes induced by the active conditions (d-amphetamine, LSD, MDMA) versus placebo. Thalamic subregions were labeled according to the Automated Anatomical Labeling atlas (49). iFC values from the thalamic clusters showing substance-induced hypo/hyperconnectivity (vs. placebo) were extracted, averaged, and correlated with the subscales of the 5D-ASC with Pearson correlation analyses. p values were Bonferroni adjusted to account for multiple testing.

In addition, we used a region-of-interest–based approach to test whether thalamocortical iFC values differed between the active conditions (d-amphetamine, LSD, MDMA). Specifically, we extracted and averaged the iFC values from the whole thalamus (i.e., values reflect connectivity, not dysconnectivity) for each active condition and assessed differences between them with repeated-measures ANOVAs computed with Jamovi (https://www.jamovi.org).

Because all 3 active substances can modify the PPs acquired for this study (26), which could in turn bias rs-fMRI results (50), we computed several control analyses to evaluate the influence of PPs (see Supplemental Methods).

RESULTS

The final sample used for the fMRI data analysis included 25 subjects (mean age = 28.2 ± 4.35 years, range = 25–45 years, 12 females). Results regarding substance-induced subjective and autonomic effects have been fully reported elsewhere (26). For the smaller imaging sample (n = 25), see Supplemental Results and Figures S1 and S2. Repeated-measures ANOVAs demonstrated that experimental sessions did not differ from placebo or each other in framewise displacement–based head motion ($F_{3,72}$ = 1.80, p = .15) or number of censored volumes ($F_{3,72}$ = 0.75, p = .52). Notably, the active conditions differed in the overall strength of the drug effect ($F_{2,48}$ = 52.9, $p < .001$), with LSD eliciting a stronger effect than both d-amphetamine (t_{48} = 10.17, $p < .001$) and MDMA (t_{48} = 6.39, $p < .001$). MDMA elicited a stronger drug effect than d-amphetamine (t_{48} = 3.78, $p < .001$).

Thalamocortical Hyperconnectivity With the ASM Network

Thalamocortical iFC followed the expected patterns under physiological conditions (i.e., placebo) (see Supplemental Results and Figure S3).

Compared with placebo, each active substance elicited ASM-thalamic hyperconnectivity (Figure 1). D-amphetamine elicited hyperconnectivity in one cluster, mainly covering ventrolateral nuclei (Table 1). LSD-induced hyperconnectivity
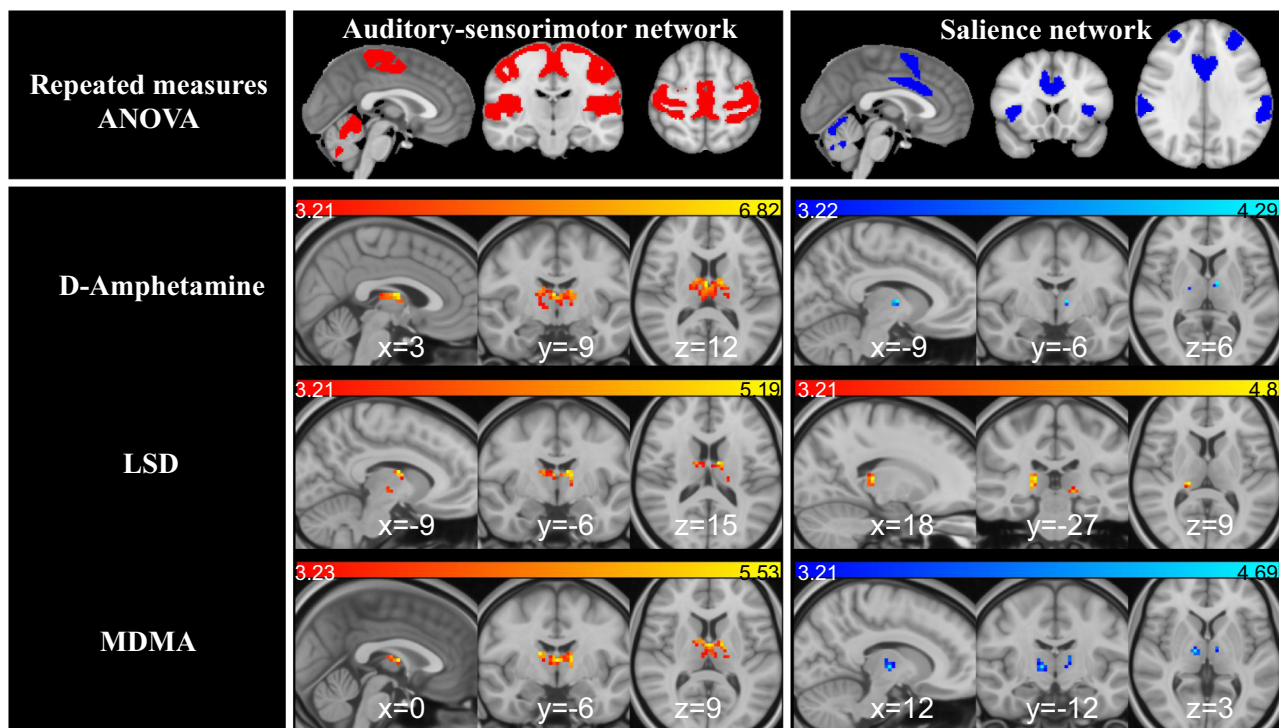
Figure 1. Depicted are voxelwise repeated-measures analysis of variance (ANOVA) parametric maps reflecting contrasts between active substances and placebo for intrinsic functional connectivity between the thalamus and the auditory-sensorimotor network (ASM) and salience network (SAL). All 3 substances elicited ASM-thalamic hyperconnectivity compared with placebo (shown in yellow/red). While d-amphetamine and MDMA elicited SAL-thalamic hypoconnectivity compared with placebo (shown in blue), LSD elicited hyperconnectivity. Color bars reflecting t values are shown for each contrast. The analyses were computed in SPM12 ($p < .001$, cluster-level familywise error–corrected $p < .05$); x, y, and z indicate Montreal Neurological Institute coordinates.

was found in 3 clusters, covering ventrolateral and posterolateral nuclei. MDMA evoked hyperconnectivity in one cluster, mainly covering the ventrolateral nuclei.

Next, we used a region-of-interest–based approach to test whether the active substances differed in ASM-thalamic iFC by contrasting them with each other. A repeated-measures

Table 1. Thalamocortical Connectivity Peaks for the Active Substances Compared With Placebo

Thalamus	Auditory-Sensorimotor Network			Salience Network		
	D-Amphetamine	LSD	MDMA	D-Amphetamine	LSD	MDMA
iFC Changes vs. Placebo	Increase	Increase	Increase	Decrease	Increase	Decrease
iFC Peak and Cluster Size	MDm_R: x = 3, y = −9, z = 12; 174 voxels	VL_L: x = −9, y = −6, z = 15; 32 voxels VA_R: x = 9, y = 0, z = 9; 22 voxels VPL_L: x = −15, y = −21, z = 12; 12 voxels	MDm_R: x = 0, y = −6, z = 9; 117 voxels	VA_L: x = −9, y = −6, z = 6; 5 voxels VL_R: x = 15, y = −15, z = 9; 6 voxels	PuM_R: x = 18, y = −27, z = 9; 17 voxels MDm_L: x = −3, y = −9, z = 15; 7 voxels MGN_L: x = −15, y = −27, z = −3; 11 voxels	VL_R: x = 12, y = −12, z = 3; 23 voxels VL_L: x = −12, y = −15, z = 12; 17 voxels
Cluster Label	VL_L: 16.09% VL_R: 12.64%	VL_L: 46.88% VA_L: 21.88% VA_R: 18.18% VL_R: 13.64% VPL_L: 83.33% PuL_L: 16.67%	VL_L: 13.68% VL_R: 11.11%	VL_L: 40.00% VA_L: 40.00% IL_L: 20.00% VL_R: 100.00%	PuM_R: 29.41% VPL_R: 29.41% PuL_R: 11.76% AV_L: 14.29% PuL_L: 27.27% VPL_L: 18.18%	VL_R: 91.30% VL_R: 64.71% IL_L: 11.76% VPL_L: 11.76%

The table depicts functional connectivity cluster peaks with the corresponding MNI coordinates (upper row) and cluster labels (lower row). The percentages (%) shown for the cluster labels reflect the percentage of overlap between a given iFC cluster and the corresponding thalamic nuclei from the AAL.

AAL, Automated Anatomical Labeling atlas; AV, anteroventral nucleus; iFC, intrinsic functional connectivity; IL, intralaminar nucleus; L, left; MDm, mediodorsal medial magnocellular nucleus; MGN, medial geniculate nucleus; MNI, Montreal Neurological Institute; PuL, pulvinar lateral; PuM, pulvinar medial; R, right; VA, ventral anterior nucleus; VL, ventrolateral nucleus; VPL, ventral posterolateral nucleus.

ANOVA demonstrated that ASM-thalamic hyperconnectivity did not differ significantly between substances ($F_{2,48} = 0.85$, $p = .43$), indicating similar substance-induced changes. Controlling for the overall strength of the drug effects (i.e., including these as covariates of no interest in the ANOVA) did not influence the results ($F_{2,42} = 0.31$, $p = .73$).

Controlling for PPs in the repeated-measures ANOVA did not affect the hyperconnectivity results (Figure S4). Furthermore, ASM-thalamic hyperconnectivity did not correlate with ΔPP for any of the substances (Table S1) or with the overall strength of the drug effect (d-amphetamine: $r = 0.22$, $p = .28$; LSD: $r = 0.17$, $p = .40$; MDMA: $r = -0.12$, $p = .54$).

In a separate control analysis, GSR was included as an additional step in the preprocessing pipeline. While GSR attenuated the main results somewhat, ASM-thalamic hyperconnectivity remained significant for the active substances (Figure S5).

Distinct Thalamocortical Connectivity Patterns With the SAL Network

The active substances elicited distinct thalamocortical iFC with the SAL compared with placebo (Figure 1). Following d-amphetamine administration, SAL-thalamic iFC was reduced in 2 clusters, mainly covering the ventrolateral nuclei (Table 1). In contrast, LSD elicited hyperconnectivity in 3 clusters, mainly covering the posterior nuclei but also parts of the mediodorsal thalamus. Following MDMA administration, SAL-thalamic iFC was reduced in 2 clusters, mainly covering the ventrolateral nuclei.

Using a region-of-interest–based approach, we showed that SAL-thalamic dysconnectivity differed significantly between substances ($F_{2,48} = 6.73$, $p = .003$), with LSD eliciting higher iFC values in the whole thalamus than both d-amphetamine ($t_{48} = 2.97$, $p = .01$) and MDMA ($t_{48} = 3.34$, $p = .004$), which did not differ from one another ($t_{48} = 0.37$, $p = .92$). This difference in substance-induced SAL-thalamic dysconnectivity was influenced by the overall strength of the drug effect, i.e., the differences were no longer significant after including the overall strength of the drug effects as covariates of no interest in the ANOVA ($F_{2,42} = 0.43$, $p = .64$).

Control analyses demonstrated that PPs did not influence substance-induced SAL-thalamic iFC alterations (Figure S4). SAL-thalamic hypo/hyperconnectivity did not correlate with ΔPP for any of the substances (Table S1) nor with the overall strength of the drug effects (d-amphetamine: $r = -0.22$, $p = .28$; LSD: $r = 0.36$, $p = .07$; MDMA: $r = -0.11$, $p = .59$).

In contrast, GSR markedly altered LSD- and MDMA-induced SAL-thalamic dysconnectivity changes, which were no longer significant, but not d-amphetamine–induced changes (Figure S5). Because GSR also corrects for global effects brought about by distinct PPs and because substances differed in several PPs, we ran a control analysis in which the effects of GSR on SAL-thalamic iFC were investigated while also controlling for PPs. Controlling for PPs in addition to GSR did not modify the results (Figure S6).

SAL-thalamic hypoconnectivity did not correlate with ASM-thalamic hyperconnectivity for d-amphetamine and MDMA, but SAL-thalamic hyperconnectivity correlated with ASM-thalamic hyperconnectivity for LSD (see Supplemental Results).

Associations Among Thalamocortical Connectivity and Subjective Effects

We assessed whether thalamocortical dysconnectivity was associated with substance-induced subjective effects by correlating values extracted from thalamic voxels showing hyper/hypoconnectivity with each of the 5D-ASC 11 subscales.

D-amphetamine– and MDMA-induced thalamocortical dysconnectivity did not correlate with any of the 5D-ASC subscales (Table S2 and Figure S7). In contrast, LSD-induced ASM-thalamic hyperconnectivity positively correlated with "blissful state" ($r = 0.44$, $p = .02$), "insightfulness" ($r = 0.49$, $p = .01$), "audio-visual synesthesia" ($r = 0.48$, $p = .01$), and "changed meaning of percepts" ($r = 0.58$, $p = .002$) (Figure 2). Only the latter remained significant after adjusting for multiple comparisons (i.e., corrected to $p = .004$ [.05/11]). Similarly, SAL-thalamic hyperconnectivity also correlated with "audio-visual synesthesia" ($r = 0.44$, $p = .02$) and "changed meaning of percepts" ($r = 0.50$, $p = .01$) but did not survive correction for multiple comparisons.

Finally, no main effect of ΔPP was found on the associations between LSD-induced thalamocortical dysconnectivity and 5D-ASC subscales with hierarchical multiple regressions (Supplemental Results and Table S3).

DISCUSSION

We used pharmacological rs-fMRI with a double-blind, placebo-controlled, crossover design in healthy volunteers to test whether d-amphetamine, LSD, and MDMA elicited thalamocortical dysconnectivity with 2 RSNs covering ASM and prefrontal-limbic cortices (SAL), respectively. Compared with placebo, all 3 substances induced thalamocortical hyperconnectivity with ASM. The active substances did not differ in ASM-thalamic iFC, suggesting a similar effect despite distinct pharmacological actions. These findings mirror ASM-thalamic hyperconnectivity reports in patients with psychotic disorders and provide support for the disrupted thalamic filter model. Compared with placebo, LSD elicited SAL-thalamic hyperconnectivity, whereas d-amphetamine and MDMA elicited hypoconnectivity. Unlike reports in patients with psychotic disorders, however, substance-induced SAL-thalamic hypoconnectivity was mainly found in sensorimotor thalamic nuclei. In addition, LSD-induced subjective effects differed significantly from d-amphetamine– and MDMA-induced subjective effects and correlated with ASM-thalamic hyperconnectivity.

Substance-Induced ASM–Thalamic Hyperconnectivity

Compared with placebo, all active substances elicited ASM-thalamic hyperconnectivity (Figure 1). Control analyses demonstrated that PPs did not influence the results (Figure S4). Although GSR reduced the number of thalamic voxels showing hyperconnectivity with ASM, the results remained significant for all substances (Figure S5).

Consistent with our findings, several studies report LSD-induced thalamocortical hyperconnectivity with sensorimotor cortices (31,36,51). Such effects may be induced by stimulation of 5-HT$_{2A}$ receptors, increasing the activity of both pyramidal neurons in the cortex and cortical and subcortical (i.e.,
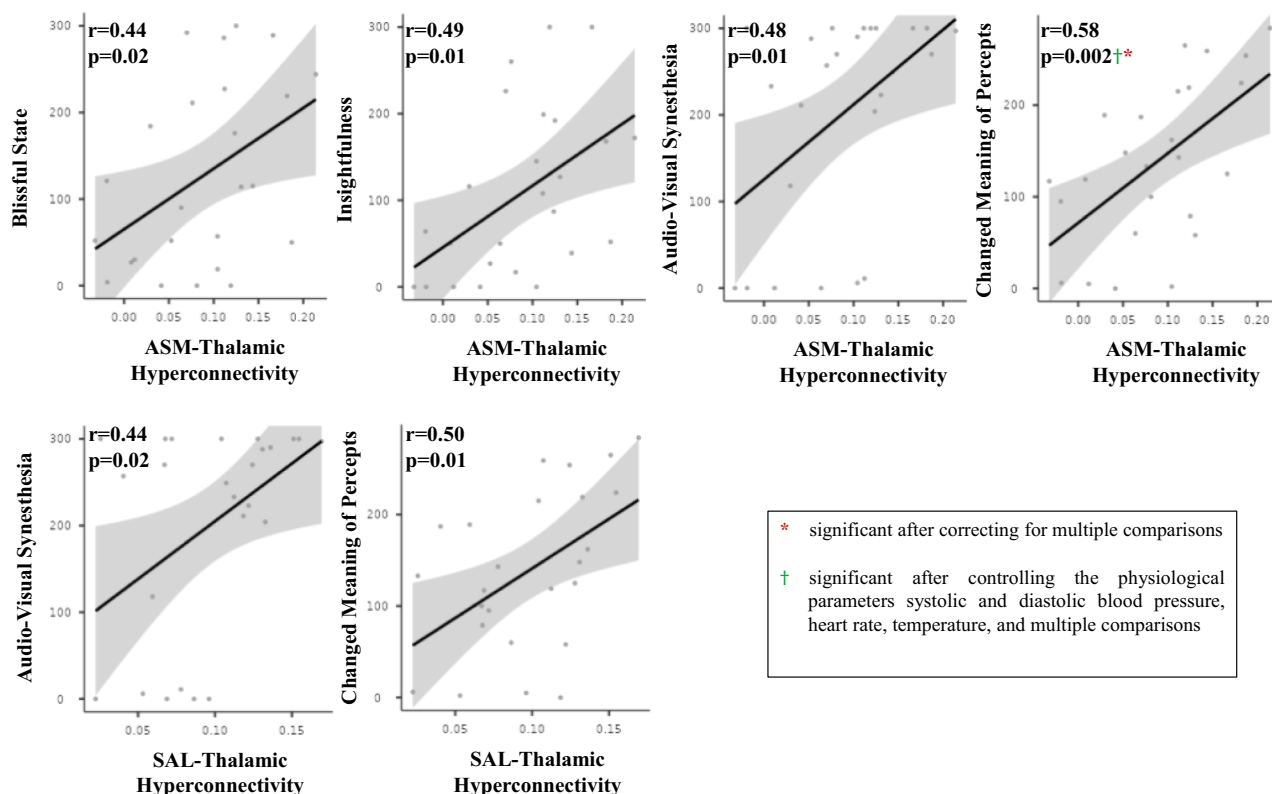
Figure 2. Correlations between LSD-induced thalamocortical hyperconnectivity and 5 Dimensions of Altered States of Consciousness Questionnaire measures. Top: Correlations for LSD-induced auditory-sensorimotor network (ASM)–thalamic hyperconnectivity. Bottom: Correlations for LSD-induced salience network (SAL)–thalamic hyperconnectivity.

basal ganglia) interneurons, which project to the thalamus, putatively leading to thalamic disinhibition (34). We are not aware of any studies directly investing the effects of d-amphetamine or MDMA on thalamic connectivity with cortical regions/RSNs. However, similar findings have been reported for methamphetamine and methylphenidate. For instance, increased iFC between the thalamus and postcentral cortices was reported in healthy volunteers following methamphetamine administration (52). Methylphenidate binds to dopamine transporter and blocks dopamine reuptake and thereby increases dopamine concentration in the synaptic cleft, similar to d-amphetamine (53). Evidence indicates that methylphenidate also induces hyperconnectivity between a sensorimotor network and a thalamic network (54). Psychostimulant-induced ASM-thalamic hyperconnectivity may reflect an elevation in dopaminergic transmission, putatively increasing the activity of striatal medium spiny neurons, which inhibit the pallidal neurons that control thalamic activity, thereby leading to thalamic disinhibition (30,55). Taken together, these findings provide support for the disrupted thalamic filter model (33) because this model predicts an increase in thalamocortical interactions. ASM-thalamic hyperconnectivity mainly covered thalamic sensorimotor nuclei (i.e., ventrolateral and posterior thalamic nuclei) for all substances (Table 1). Dysconnectivity peaks differed between substances, possibly due to distinct pharmacological actions or dopaminergic and serotonergic

receptor distribution. It is worth noting that the thalamus is not a unitary structure and that thalamic nuclei express distinct dopaminergic D_2-like (56) and 5-HT$_{2A}$ receptor densities (57), which directly affect thalamic function. Therefore, regional differences in receptor distribution may influence changes in thalamocortical iFC. However, specific receptor-related effects may be difficult to disentangle, due to D_2-like and 5-HT$_{2A}$ receptor overlap in some nuclei (e.g., mediodorsal nucleus, pulvinar) and several other sources that also modulate activity in thalamic nuclei (e.g., striato-pallidal) (see Supplemental Discussion).

Hyperconnectivity between the ASM and thalamic sensorimotor nuclei mirrors previous findings in psychotic disorders (8,12). The link between alterations in dopaminergic transmission and sensorimotor thalamic hyperconnectivity is in line with several models of psychosis (2,55,58). In addition, there is also evidence of altered serotonergic transmission in schizophrenia (59). A recent postmortem study using [³H]LSD as a radiotracer demonstrated increased 5-HT$_{2A}$ receptor density in the prefrontal cortex of antipsychotic-naïve patients with schizophrenia, possibly indicating a higher functional sensitivity for this receptor in schizophrenia (60). Furthermore, there is considerable overlap between serotonergic and dopaminergic innervations (e.g., in the striatum) and evidence for serotonergic modulation (i.e., via psilocybin) of dopamine release in the striatum of healthy participants (61). It is unclear

whether changes in only one neurotransmitter system are sufficient to drive ASM-thalamic hyperconnectivity. Notably, patients with schizophrenia receiving antipsychotic medication (i.e., having antagonistic effects at the D_2 receptor) still present ASM-thalamic hyperconnectivity ([9]). However, LSD-induced thalamic hyperconnectivity with posterior associative cortices appears dependent on the 5-HT$_{2A}$ receptor, but some striatal-thalamic interactions do not ([62]). Some atypical antipsychotics (e.g., clozapine, olanzapine) also block 5-HT$_{2A}$ receptors ([63]), but it is unknown whether patients treated with these medications show ASM-thalamic hyperconnectivity.

Substance-Induced SAL–Thalamic Dysconnectivity

The active substances differentially affected SAL-thalamic iFC (Figure 1). Compared with placebo, d-amphetamine and MDMA induced SAL-thalamic hypoconnectivity, whereas LSD induced hyperconnectivity. Control analyses demonstrated that PPs did not influence these results (Figure S4), in contrast to GSR, which led to significant changes (Figure S5). Specifically, while d-amphetamine–induced hypoconnectivity was slightly enhanced, MDMA-induced hypoconnectivity and LSD-induced hyperconnectivity were no longer significant. See Supplemental Discussion for details.

In contrast to our hypothesis regarding SAL-thalamic iFC, we found that the neural effects of d-amphetamine and MDMA were similar, despite their predominantly different pharmacological actions ([26]). However, d-amphetamine and MDMA are structurally related, and both stimulate norepinephrine release ([64]). Furthermore, neurotransmitter systems have complex interactions at different levels, which might explain the similar neural response ([65]). Previous findings support d-amphetamine– and MDMA-induced SAL-thalamic hypoconnectivity. For example, a study reported decreased iFC between the anterior cingulum and a cortico-striato-thalamic network following d-amphetamine administration ([44]). Similarly, methylphenidate was reported to reduce iFC between SAL and a thalamic network in healthy volunteers ([54]). Reduced iFC between the thalamus and prefrontal areas was also reported following MDMA administration ([66]). SAL-thalamic hypoconnectivity mainly covered ventrolateral nuclei (Table 1). This finding indicates a functional decoupling between the SAL and sensorimotor thalamic nuclei. We speculate that the decoupling between associative cortical and sensorimotor thalamic regions indicates an attenuation of putative sources of noise in the regulation of other cognitive processes (e.g., attentional for d-amphetamine, prosocial for MDMA). In support of this idea, we note that methylphenidate also leads to a decoupling between the prefrontal cortices and sensorimotor thalamic nuclei, while sparing other thalamic functional subdivisions ([67]). The location of the main effects in sensorimotor thalamic nuclei contrasts with findings in patients with psychotic disorders. Specifically, in patients, SAL-thalamic hypoconnectivity was reported in associative thalamic nuclei, especially the mediodorsal nucleus ([8,12,68]). Indeed, there is consistent evidence that this nucleus is involved in the pathophysiology of schizophrenia and that it may play a major role in patients' cognitive difficulties ([69,70]).

We observed an increase in functional coupling between association nuclei in the thalamus and prefrontal limbic areas for LSD. Specifically, LSD-induced hyperconnectivity with SAL mainly covered the pulvinar and peaked in the pulvinar, mediodorsal nucleus, and medial geniculate. This finding is in line with previous reports of increased iFC between distinct associative regions following LSD administration. For instance, increased iFC between the ventromedial prefrontal cortex and several other prefrontal regions has been reported ([71]), as well as increased iFC between several brain networks covering associative cortices (e.g., SAL and default mode network) and between these and the thalamus ([37,71]). However, in contrast to our finding, Preller *et al.* ([36]) reported LSD-induced hypoconnectivity with prefrontal limbic areas. We note that this result was affected by GSR. We detected a somewhat similar effect herein; namely, SAL-thalamic hyperconnectivity was no longer significant after GSR (see Supplemental Discussion). Finally, LSD-induced SAL hyperconnectivity with thalamic association nuclei contrasts with SAL-mediodorsal hypoconnectivity reported in psychotic disorders ([8,12]), suggesting distinct neural phenomena.

We note that despite the disrupted thalamic filter model predictions (i.e., cortical flooding), we did not observe undifferentiated increases in thalamocortical iFC. Indeed, SAL-thalamic hypoconnectivity findings reported for d-amphetamine and MDMA depict functional decoupling rather than an increase in thalamocortical interactions. However, iFC does not allow for the quantification of directionality, and it is unclear whether the thalamus drove SAL-thalamic hypoconnectivity or whether the thalamus caused hyperconnectivity with sensorimotor areas. These issues may be clarified by using effective connectivity to assess the potentially causal role of the thalamus in thalamocortical dysconnectivity.

Associations Among LSD-Induced ASM-Thalamic Hyperconnectivity and Subjective Effects

D-amphetamine– and MDMA-induced changes in thalamocortical iFC were not associated with drug-induced subjective effects. Notably, d-amphetamine– and MDMA-induced subjective effects were very mild and, with one exception ("blissful state" for MDMA), did not differ significantly from placebo (Figure S1). While some studies indicate stronger effects on 5D-ASC following MDMA administration compared with placebo, including LSD in the study appears to minimize such differences [for detailed discussion, see ([26])]. Furthermore, we note that brain-behavior relations are in general difficult to map ([72]). It is possible that the subjective effects elicited by these substances were too weak to allow for correlations with iFC, indicating an issue with the overall strength of the drug effect (i.e., much weaker effect than LSD) but possibly also the higher specificity of 5D-ASC for psychedelic phenomena, i.e., classic psychedelics in general elicit stronger effects on the 5D-ASC than d-amphetamine or MDMA ([26,73]).

LSD elicited typical subjective psychedelic effects ([45]). Remarkably, ASM-thalamic hyperconnectivity correlated with several subscales of the 5D-ASC (Figure 2). Such associations are supported by a previous study, which reported significant correlations between subjective changes in visual and auditory

perception and thalamocortical hyperconnectivity following LSD administration (31). The strongest correlation found in our study was between ASM-thalamic hyperconnectivity and the item "changed meaning of percepts." This association remained significant after controlling for the effects of PPs and multiple comparisons. Based on the 5D-ASC items covered by this subscale, it is pertinent to assume that both changes in perception and the interpretation of such changes are assessed, and these are partially reflected in some of the iFC changes identified in this study (see Supplemental Discussion). Therefore, this subscale may be relevant for psychotic disorders because changes in the interpretation of a percept may explain (some) psychotic symptoms (e.g., delusions) (29).

Strengths and Limitations

To our knowledge, this is the first study that investigated the neural effects of prototypical psychedelics (LSD), empathogens (MDMA), and psychostimulants (d-amphetamine) in the same participants using a within-subject design. Our results replicate several disparate findings for LSD (31,36,51), MDMA (66), and psychostimulants with a similar pharmacological action as d-amphetamine (54). This study also has some limitations. First, we found that the overall strength in drug effect differed considerably between substances. While trying to match the qualitative character of these compounds is not feasible, we note that the between-substance differences in SAL-thalamic iFC may have been driven by differences in the overall strength of the drug effects. This indicates that, beyond pharmacological effects, the overall strength of the drug effect may also influence thalamocortical iFC. Second, subjective effects (i.e., 5D-ASC) were evaluated retrospectively in this study (approximately 11 hours after substance administration); however, evidence indicates that the timing of the assessment (during peak effects or the next day) does not have a big impact on the ratings (74). Third, while LSD-induced changes in thalamocortical iFC are in line with the a priori expectations of functional manipulations in thalamic nuclei expressing 5-HT$_{2A}$ receptors, the localization of dopaminergic and serotonergic receptors alone did not accurately explain thalamocortical dysconnectivity induced by d-amphetamine or MDMA. Nevertheless, other sources may also modulate iFC in these regions. Fourth, it is possible that substance-induced thalamocortical dysconnectivity was secondary to within-network iFC changes, following widespread changes in corticocortical iFC. However, control analyses demonstrated that within-network iFC was similarly affected by all substances, despite distinct thalamocortical effects (see Supplemental Results and Figure S8).

Conclusions

Prototypical psychedelics, empathogens, and psychostimulants elicit thalamocortical dysconnectivity. Despite predominately distinct pharmacological actions and subjective effects, common changes included increased connectivity between the thalamus and sensorimotor cortices. LSD induced an overall increase in thalamocortical connectivity, whereas d-amphetamine and MDMA elicited more nuanced but remarkably similar neural changes.

ARTICLE INFORMATION

From the Translational Psychiatry (MA, HR, AK, CA, SB), Department of Psychiatry and Psychotherapy, University of Lübeck, Lübeck, Germany; Department of Psychiatry (FM) and the Division of Clinical Pharmacology and Toxicology (FH, PV, LL, MEL), Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland.

Address correspondence to Mihai Avram, Ph.D., at mihai.avram@uksh.de.

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