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Effective Connectivity of Thalamocortical Interactions Following d-Amphetamine, LSD, and MDMA Administration

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ABSTRACT

BACKGROUND: While the exploration of serotonergic psychedelics as psychiatric medicines deepens, so does the pressure to better understand how these compounds act on the brain.

METHODS: We used a double-blind, placebo-controlled, crossover design and administered lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA), and d-amphetamine in 25 healthy participants. By using spectral dynamic causal modeling, we mapped substance-induced changes in effective connectivity between the thalamus and different cortex types (unimodal vs. transmodal) derived from a previous study with resting-state functional magnetic resonance imaging data. Due to the distinct pharmacological modes of action of the 3 substances, we were able to investigate specific effects mainly driven by different neurotransmitter systems on thalamocortical and corticothalamic interactions.

RESULTS: Compared with placebo, all 3 substances increased the effective connectivity from the thalamus to specific unimodal cortices, whereas the influence of these cortices on the thalamus was reduced. These results indicate increased bottom-up and decreased top-down information flow between the thalamus and some unimodal cortices. However, for the amphetamines, we found the opposite effects when examining the effective connectivity with transmodal cortices, including parts of the salience network. Intriguingly, LSD increased the effective connectivity from the thalamus to both unimodal and transmodal cortices, indicating a breach in the hierarchical organization of ongoing brain activity.

CONCLUSIONS: The results advance our knowledge about the action of psychedelics on the brain and refine current models aiming to explain the underlying neurobiological processes.

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The renewed interest in psychedelics builds on the apparent efficacy that these compounds have in relieving symptoms of distinct psychiatric disorders, including depression, anxiety, and addiction (1–6). However, the mechanism(s) through which therapeutic efficacy is elicited remains elusive. While some aspects of psychedelic action on the brain have been demonstrated, e.g., via (partial) agonism at the serotonin 2A (5-HT_{2A}) receptors, the impact and consequences of activating these receptors remain incompletely understood. Several biological models, not necessarily mutually exclusive, have been proposed to explain how psychedelic phenomena are generated in the brain (7). Some of these models suggest that an interplay between the cortex and distinct subcortical structures is relevant for the mode of action of psychedelics.

Herein, we focus on one of these models, which enunciates the role of thalamocortical interactions. Thalamocortical interactions are part of larger, topographically organized circuits involving corticostriatal and striato-pallidal connections (8). These subcortical structures and their connections are modulated by distinct neurotransmitters, including dopamine and serotonin (9,10). In this framework, thalamocortical projections represent the last part of the circuit, which provides the cortex with feedback. The disrupted thalamic filter model (TFM) hypothesizes that changes in some aspects of neurotransmission (e.g., increases in dopaminergic tone) can potentially lead to disruptions of the thalamic filter function, resulting in cortical flooding, which is thought to underlie altered mental phenomena (11–13). In its original conception, this model aimed to explain the action of not only psychedelics but also other substances (e.g., ketamine) and endogenous psychosis (11). In support of such a hypothesis, a link between dopamine synthesis capacity and thalamocortical dysconnectivity has been reported in patients with schizophrenia (14). Regarding the specific mechanism of psychedelics, the model is supported by several lines of evidence, including human in vivo neuroimaging (7,12). Thalamocortical interactions have been investigated in several studies by quantifying intrinsic functional connectivity (iFC) derived from resting-state functional magnetic resonance imaging (fMRI) [for a review, see (15)]. Consistent findings

indicate an increase in thalamocortical iFC following psychedelics, which is consistent with the prediction that disrupted thalamic filtering would be accompanied by an increase in thalamic activity and influence on the cortex (16–19). More recent studies have refined these findings by demonstrating that thalamocortical dysconnectivity is mainly localized in nuclei containing (or more susceptible to the activation of) 5-HT_{2A} receptors (20,21).

However, based on the predictions of TFM, an initial question arises: Are these effects specific to psychedelics or do other substances (affecting neurotransmitters known to modulate cortico-striato-thalamo-cortical circuitry) generate similar phenomena? We recently demonstrated that beyond lysergic acid diethylamide (LSD), substances broadly releasing monoamines—but producing less pronounced perceptual effects than LSD, namely d-amphetamine and 3,4-methylenedioxymethamphetamine (MDMA)—also elicit thalamocortical dysconnectivity (21). Interestingly, all 3 substances induced hyperconnectivity between the thalamus and sensorimotor/unimodal cortices despite their distinct pharmacological modes of action and subjective effects. However, only LSD increased iFC between the thalamus and associative/transmodal cortices, whereas the amphetamines reduced iFC between these regions. While the latter finding is inconsistent with the predictions of undifferentiated increases in thalamocortical interactions, iFC does not assess causality/direction but rather statistical dependencies (22,23). Therefore, it remains unclear whether substance-induced thalamic dysconnectivity is driven by the thalamus. This issue can be overcome by using effective connectivity, which assesses directed causal influences between regions and can be estimated from fMRI data with dynamic causal modeling (DCM) (24). This leads to a second question: Is substance-induced thalamocortical dysconnectivity driven by the thalamus or the cortex, and are different types of cortex relevant?

To address these questions, we investigated substance-induced changes in effective connectivity between the thalamus and unimodal and transmodal regions derived from (21). Effective connectivity allows for the assessment of activity change in one region as a function of activity change in another region (22,24,25). The primary aim was to investigate the effects of d-amphetamine, LSD, and MDMA on the interactions between cortical and thalamic areas that were shown to contribute to substance-induced thalamocortical dysconnectivity in our previous study (21). Consistent with TFM and our previous iFC findings, we hypothesized that LSD, d-amphetamine, and MDMA would increase the effective connectivity from the thalamus to the unimodal cortices. Similarly, we expected LSD to increase the effective connectivity from the thalamus to the transmodal regions, consistent with previous reports (13,26). In contrast, we hypothesized that d-amphetamine and MDMA would decrease the effective connectivity from the thalamus to the transmodal areas, following our previous findings of thalamocortical hypoconnectivity.

METHODS AND MATERIALS

Participants and Procedures

We investigated 25 healthy volunteers for this study (12 female, mean age 28.2 ± 4.35 years). For detailed participant description and procedures, see the Supplement and (27). Briefly, we studied the effects of 0.1 mg LSD, 125 mg MDMA, 40 mg d-amphetamine, and placebo (ethanol/mannitol) in the same group of participants using a double-blind, placebo-controlled, crossover design with 4 sessions in a random and counterbalanced order.

The neuroimaging data from these 25 participants were analyzed previously (21). The participants had excellent quality neuroimaging data, and there were no differences between sessions in head motion (i.e., mean framewise displacement $F_{3,72} = 1.80$, $p = .15$).

Subjective effects relevant for the current study were derived from visual analog scales (VASs), which were administered immediately before and after the fMRI scan; i.e., average values were computed for the 2 measurements (21,27).

Data Acquisition and Preprocessing

Across all conditions, structural and functional fMRI data were acquired on a 3T MRI system (Magnetom Prisma, Siemens Healthcare) with a 20-channel phased array radio-frequency head coil. For imaging parameters, see the Supplement.

Data were analyzed with SPM12 (Wellcome Department of Cognitive Neurology) in MATLAB (The MathWorks, Inc.). Preprocessing steps included slice-timing correction, realignment, and spatial normalization to a 3-mm^3 standard template (Montreal Neurological Institute). Finally, normalized images were smoothed with a 6 mm full width at half maximum isotropic Gaussian kernel.

Dynamic Causal Modeling

Regions of Interest: Selection and Time-Series Extraction. First, we aimed to determine whether thalamocortical dysconnectivity was driven by the thalamus. Second, we investigated whether changes in thalamocortical/cortico-thalamic effective connectivity differed between the substances. Therefore, we were interested in regions that contributed to thalamocortical dysconnectivity across all substances and cortical regions. Cortical regions were selected from the original auditory-sensorimotor network–thalamic and salience network (SAL)–thalamic seed-based iFC analyses, respectively (21). Briefly, 6 sets of coordinates were derived from additional thalamic–whole-brain seed-based analyses (see Supplemental Methods), which were used to define regions of interest (ROIs) for the DCM analysis (Table S1; Figure 1 and Figure S1). Because these ROIs were involved in all conditions and networks, the DCM analysis allowed comparisons in effective connectivity between all conditions in one model. However, this approach only generated ROIs centered in unimodal regions (auditory cortex and postcentral gyrus, overlapping with the auditory-sensorimotor network template, as well as visual regions, i.e., lingual gyrus and cuneus). Because some of the investigated substances elicited both thalamocortical hyper- and hypoconnectivity for distinct cortex types, we also studied thalamic effective connectivity with transmodal areas derived from the SAL (see Supplemental Methods) (Table S1 and Figure 2). Notably, for this second model, thalamic ROIs were defined separately for each substance, with thalamic coordinates derived from the

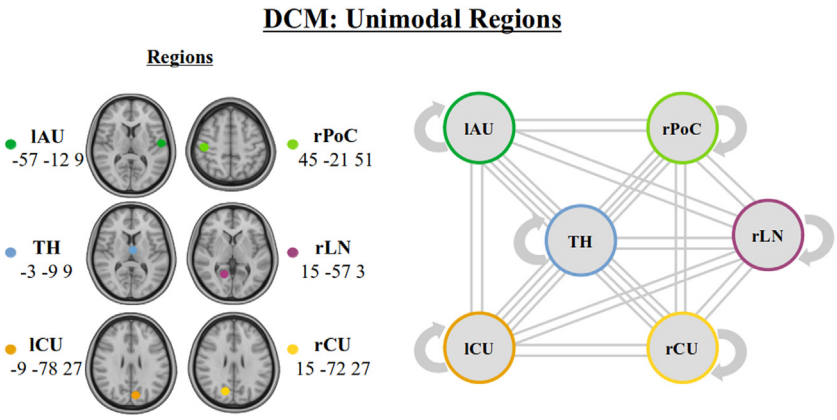

Figure 1. Depicted on the left are axial slices containing the nodes of the DCM model that was used to investigate substance-induced effective connectivity changes between the thalamus and unimodal cortices. Shown on the right are all possible connections between the DCM nodes in light gray. Self-connections are depicted as circular arrows around each region. DCM, dynamic causal modeling; lAU, left auditory cortex; lCU, left cuneus; rCU, right cuneus; rLN, right lingual gyrus; rPoC, right postcentral cortex; TH, thalamus.

peak differences in SAL-thalamic iFC generated by the 3 substances against placebo.

For both models, we masked the ROIs with spheres of 8-mm radius. All ROI time series were computed as the first principal component of the voxel activity within these spheres. The ROI time series were corrected for head motion (6 parameters) and physiological noise (i.e., signals from cerebrospinal fluid and white matter extracted from a 4-mm sphere of the left ventricle and a 4-mm sphere from the pons, respectively). Low-frequency signal drifts were also filtered out by using a 128-second high-pass filter.

Model Space Selection. The extracted time series were used to specify fully connected DCM models for every subject and compare all possible nested models of interactions between regions. Both models (i.e., unimodal and SAL-transmodal regions) were estimated with spectral DCM in SPM12 (version 7771, DCM12.5), which uses a power law model of endogenous neural fluctuations to fit the cross-spectral density (22). For the unimodal regions, we specified the fully connected DCM using the 6 ROIs (Figure 1) without exogenous inputs. Each participant's DCM was then inverted using spectral DCM to identify the effective connectivity that best explained each subject's observed cross-spectral density. We repeated the procedure for each substance. The amount of mean explained variance after model fitting was high for every condition (d-amphetamine: 89%, LSD: 89%, MDMA: 90%, placebo: 90%), indicating that the DCM explained the data very well. For the transmodal areas, we specified the fully connected DCM using the 6 ROIs covering the SAL and the thalamus (Figure 2). We followed the same procedures as above. Unlike the previous model (i.e., in which all ROIs were involved in all conditions), the placebo condition for the SAL was specific for every contrast. The amount of mean explained variance was also high for this model (d-amphetamine: 89%, $placebo_A$: 91%; LSD: 91%, placebo: 91%; MDMA: 91%, $placebo_M$: 91%). We did not observe any case showing $<75\%$ explained variance.

Group-Level Analyses Using Parametric Empirical Bayes. We estimated between-subject variability by taking the subject-specific effective connectivity values inferred by spectral DCM to a group-level (Bayesian) general linear model implemented in the parametric empirical Bayes framework. Next, Bayesian model reduction was used to perform an

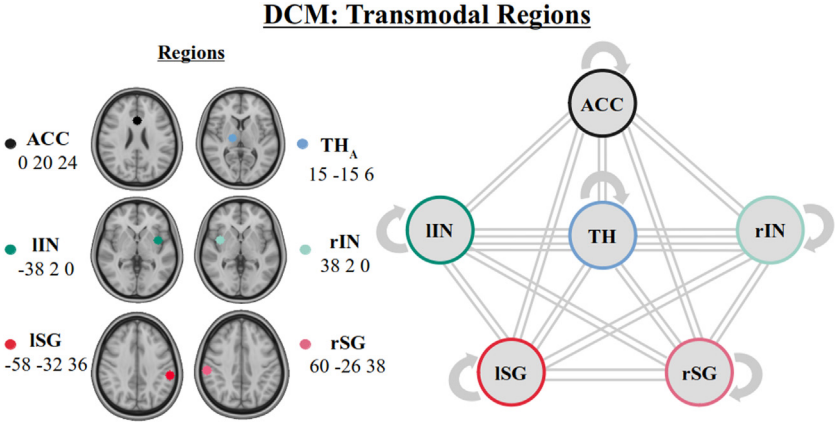

Figure 2. Depicted on the left are axial slices containing the nodes of the DCM model that was used to investigate substance-induced effective connectivity changes between the thalamus and salience network–derived transmodal cortices. Shown on the right are all possible connections between the DCM nodes in light gray. Self-connections are depicted as circular arrows around each region. ACC, anterior cingulate cortex; DCM, dynamic causal modeling; lIN, left insula; lSG, left supramarginal gyrus; rIN, right insula; rSG, right supramarginal gyrus; TH, thalamus; TH_A, thalamus region identified from the contrast d-amphetamine vs. placebo.

automatic search for more plausible reduced models nested within the full model (28). For more details on parametric empirical Bayes, see Supplemental Methods. Based on model evidence, distinct thresholds have been developed (29). For informative reasons, we report connectivity changes reflecting weaker effects (i.e., posterior probability $>$ .5 and effect sizes $<$ 0.1 Hz) in addition to connectivity changes reflecting strong effects (posterior probability of $>$ .99 and effect sizes of $>$ 0.1 Hz). Beyond effective connectivity between regions, we also report self-connections, which are log scaled, reflecting inhibitory activity decay. Reduced self-inhibition is indicated by a negative sign and reflects disinhibition, whereas increased self-inhibition is indicated by a positive sign.

Associations Between Effective Connectivity and Subjective Effects. To determine whether changes in effective connectivity were functionally relevant, we investigated the relationships between VAS items and the inferred DCM coupling parameters. The VAS contained the following items: "any drug effect," "good drug effect," "bad drug effect," "drug liking," "drug high," "stimulated," "ego dissolution," "talkative," "open," "concentration," "sense of time," and "speed of thinking" (27). We used multiple linear regression analysis to examine whether the VAS items, examined separately, were predicted by either cortico-thalamic (i.e., all connections from cortical regions to the thalamus) or thalamocortical (i.e., all connections from the thalamus to cortical regions) effective connectivity showing strong effects for both DCM models. If the main regression model was significant, we further examined the relationship between the corresponding VAS item and every cortico-thalamic/thalamocortical coupling parameter. Because these analyses were exploratory, we did not correct for multiple comparisons.

RESULTS

Effective Connectivity Changes Between the Thalamus and Unimodal Cortices

All substances elicited changes in effective connectivity, mainly between the unimodal regions and the thalamus (Figure 3 and Table 1).

Compared with placebo, both d-amphetamine and MDMA reduced the effective connectivity from the left auditory cortex, right postcentral cortex, and left cuneus (weaker effect for d-amphetamine) and right cuneus to the thalamus. In contrast, the thalamus increased effective connectivity to the left auditory cortex and right lingual gyrus. Both substances elicited increased self-inhibition in the right lingual gyrus, decreased self-inhibition in the right postcentral cortex (weaker effect for MDMA), and decreased effective connectivity from the right postcentral cortex to the left auditory cortex and from the right lingual gyrus to the left auditory cortex (weaker effect for d-amphetamine). In addition, d-amphetamine specifically increased thalamic self-inhibition (weaker effect). MDMA also induced specific but weaker effects, including increased effective connectivity from the thalamus to the right cuneus and right postcentral gyrus and decreased effective connectivity between the left cuneus and the left auditory cortex.

LSD decreased effective connectivity from the left auditory cortex and right postcentral cortex to the thalamus but also increased effective connectivity from the right lingual gyrus to the thalamus. The thalamus increased its self-inhibition and also effective connectivity to the left auditory cortex and the right lingual gyrus, although the latter effects were weaker. Finally, LSD reduced self-inhibition in the right postcentral cortex and, with a weaker effect, also reduced the effective connectivity from the left cuneus to the left auditory cortex.

Taken together, these findings mainly indicate decreased effective connectivity from specific unimodal regions to the

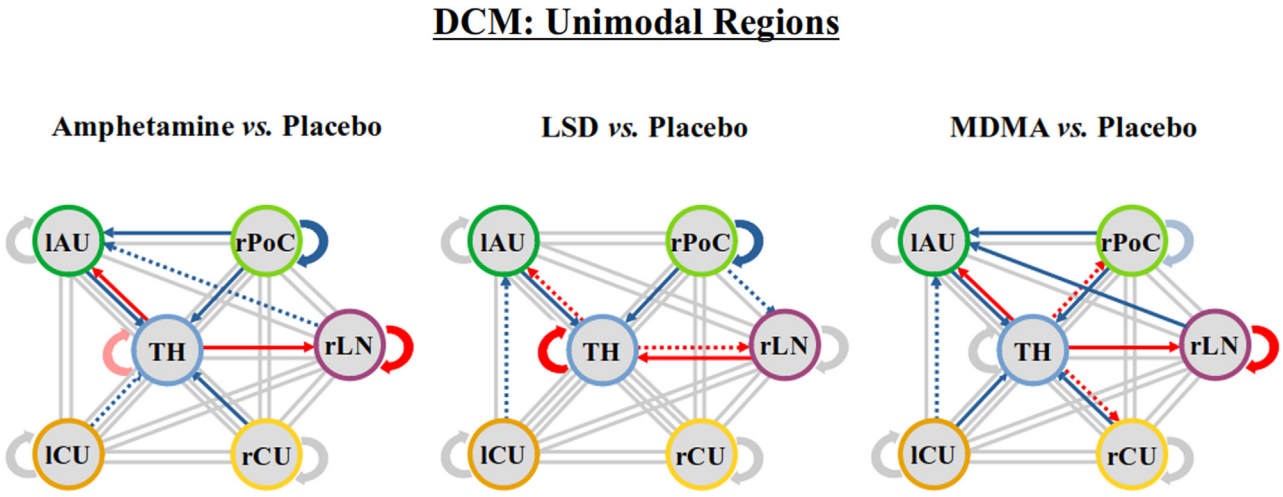

Figure 3. Differences in effective connectivity between the thalamus and unimodal cortices are shown between d-amphetamine, LSD, and MDMA against placebo. Red arrows indicate increased excitatory influence of a substance vs. placebo, whereas blue arrows indicate inhibitory influence. Increased self-inhibition is shown in red circular arrows, and reduced self-inhibition is shown in blue. Gray arrows indicate connections that were not different between substance and placebo. Dashed arrows and transparent circular arrows indicate weaker effects (i.e., surpassing a posterior probability threshold of .5 but $<$ .99 and/or with an effect size of $<$ 0.1 Hz). DCM, dynamic causal modeling; lAU, left auditory cortex; lCU, left cuneus; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; rCU, right cuneus; rLN, right lingual gyrus; rPoC, right postcentral cortex; TH, thalamus.

Table 1. Substance-Induced Effective Connectivity Changes Between the Thalamus and Unimodal Cortices

Connection	Substance-Induced EC Changes	Substance-Induced EC Valence	Effect Size, Hz	Posterior Probability
d-Amphetamine vs. Placebo				
lAU → TH	−	I	0.24	>.99
rLN → lAU	−	I	0.08[a]	.8[a]
rLN → rLN	+	E	0.14	>.99
rCU → TH	−	I	0.15	>.99
lCU → TH	−	I	0.10	.9[a]
rPoC → lAU	−	I	0.13	>.99
rPoC → rPoC	−	I	0.15	>.99
rPoC → TH	−	I	0.24	>.99
TH → lAU	+	E	0.17	>.99
TH → rLN	+	E	0.20	>.99
TH → TH	+	E	0.04[a]	.5[a]
LSD vs. Placebo				
lAU → TH	−	I	0.24	>.99
rLN → TH	+	E	0.12	>.99
lCU → lAU	−	I	0.06[a]	.6[a]
rPoC → rLN	−	I	0.06[a]	.6[a]
rPoC → rPoC	−	I	0.15	>.99
rPoC → TH	−	I	0.13	>.99
TH → lAU	+	E	0.07[a]	.7[a]
TH → rLN	+	E	0.05[a]	.6[a]
TH → TH	+	E	0.12	>.99
MDMA vs. Placebo				
lAU → TH	−	I	0.19	>.99
rLN → lAU	−	I	0.12	>.99
rLN → rLN	+	E	0.12	>.99
rCU → TH	−	I	0.10	>.99
lCU → lAU	−	I	0.06[a]	.7[a]
lCU → TH	−	I	0.12	>.99
rPoC → lAU	−	I	0.15	>.99
rPoC → rPoC	−	I	0.05[a]	.6[a]
rPoC → TH	−	I	0.30	>.99
TH → lAU	+	E	0.11	>.99
TH → rLN	+	E	0.14	>.99
TH → rCU	+	E	0.04[a]	.5[a]
TH → rPoC	+	E	0.04[a]	.5[a]

Connections surpassing a posterior probability threshold of .5 are shown.

−, decreased; +, increased; E, excitatory; EC, effective connectivity; I, inhibitory; lAU, left auditory cortex; lCU, left cuneus; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; rCU, right cuneus; rLN, right lingual gyrus; rPoC, right postcentral cortex; TH, thalamus.

[a]Weak effects (posterior probability < .99 and/or an effect size < 0.1 Hz).

thalamus and increased effective connectivity from the thalamus to some unimodal areas, independent of substance.

Specific Effective Connectivity Changes Between the Thalamus and Unimodal Cortices

Next, we investigated specific substance-induced effects by comparing the substances to one another (Figure 4 and Table 2).

Compared with d-amphetamine, LSD increased effective connectivity from the right postcentral cortex (weaker effect), right lingual gyrus, and right cuneus to the thalamus and reduced effective connectivity from the thalamus to the right lingual gyrus. In addition, LSD reduced the self-inhibition in the right lingual gyrus. Furthermore, the right postcentral cortex and right lingual gyrus increased effective connectivity to the left auditory cortex, although these effects were weaker. Similarly, the right lingual gyrus increased the effective connectivity on the right cuneus.

Compared with MDMA, LSD increased effective connectivity from the right postcentral cortex, right lingual gyrus (weaker effect), and right cuneus (weaker effect) to the thalamus, as for d-amphetamine. In addition, LSD increased effective connectivity from the right postcentral cortex and right lingual gyrus (weaker effect) to the left auditory cortex. Furthermore, LSD reduced the self-inhibition in the right lingual gyrus, as for d-amphetamine.

The differences between d-amphetamine and MDMA were less pronounced. d-Amphetamine increased the self-inhibition in the left auditory cortex, in contrast to MDMA (weaker effect).

Effective Connectivity Changes Between the Thalamus and Transmodal Cortices

All substances elicited changes in effective connectivity between the SAL-derived transmodal cortices and the thalamus (Figure 5 and Table 3). Compared with placebo, d-amphetamine and MDMA increased effective connectivity from the left and right insula (weaker effect for MDMA) and left supramarginal gyrus to the thalamus. Furthermore, both the left and right insula increased effective connectivity to the anterior cingulate cortex (ACC) (weaker effects for both substances) and right supramarginal gyrus (weaker effect for d-amphetamine), while the thalamus decreased effective connectivity to both the left and right insula (weaker effects for the latter). We also observed increased effective connectivity from the left supramarginal gyrus to the ACC (weaker effects for both amphetamines) and greater thalamic self-inhibition (weaker effect for MDMA). Specific d-amphetamine–induced changes included reduced effective connectivity from the thalamus to the left supramarginal gyrus and increased self-inhibition of the left insula, although both effects were weaker. Specific MDMA-induced changes included decreased effective connectivity from the ACC to the left and right insula (weaker effect). Other weaker effects included increased effective connectivity from the right insula to the left supramarginal gyrus and decreased effective connectivity from the left supramarginal gyrus to the left insula.

LSD changes in effective connectivity were restricted to increased effective connectivity from the thalamus to the ACC and left supramarginal gyrus (weaker effect) and right supramarginal gyrus. Thalamus self-inhibition was also increased. No changes in corticothalamic effective connectivity were observed; however, there was a decrease in right insula self-inhibition (weaker effect).

Associations With Subjective Effects

We studied the relationships between effective connectivity changes and VAS items using multiple linear regression

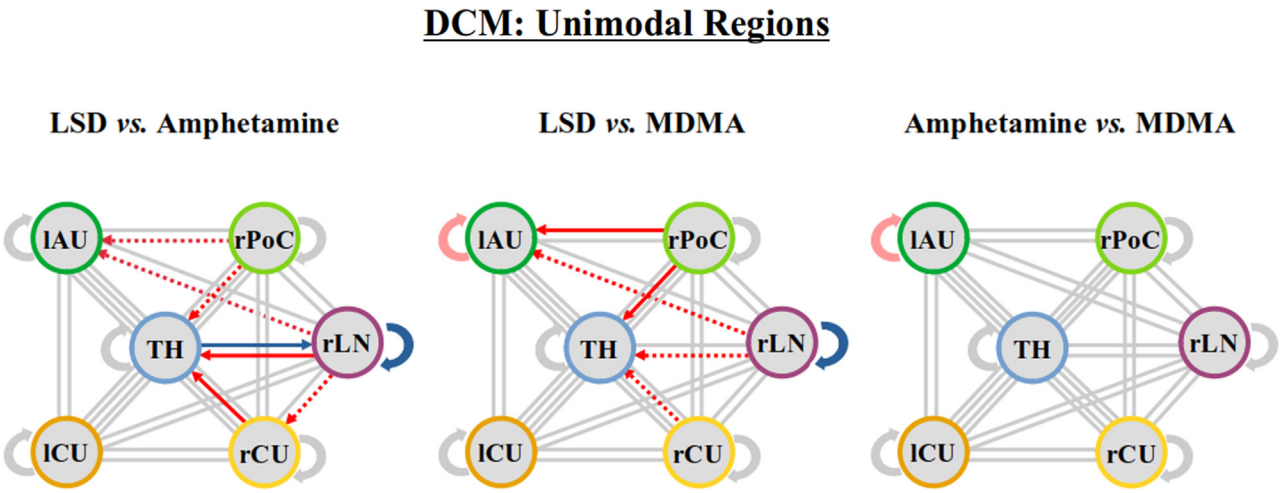

Figure 4. Direct comparisons are shown between d-amphetamine, LSD, and MDMA regarding their effects on effective connectivity between the thalamus and unimodal cortices. Red arrows indicate increased excitatory influence, whereas blue arrows indicate inhibitory influence. Increased self-inhibition is shown in red circular arrows, and reduced self-inhibition is shown in blue. Gray arrows indicate connections that were not different between the substances. Dashed arrows and transparent circular arrows indicate weaker effects (i.e., surpassing a posterior probability threshold of .5 but $<$ .99 and/or with an effect size of $<$ 0.1 Hz). DCM, dynamic causal modeling; lAU, left auditory cortex; lCU, left cuneus; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; rCU, right cuneus; rLN, right lingual gyrus; rPoC, right postcentral cortex; TH, thalamus.

analysis. For details, see Supplemental Results and Figures S2 and S3. Briefly, for unimodal regions, d-amphetamine–induced changes in corticothalamic effective connectivity predicted "speed of thinking" ($F_{3,21}$ = 4.57, p = .01), whereas thalamocortical effective connectivity significantly predicted "good drug effect" ($F_{2,22}$ = 3.96, p = .03) and "drug liking" ($F_{2,22}$ = 5.54, p = .01). Following LSD, corticothalamic effective connectivity predicted the item "concentration" ($F_{3,21}$ = 4.48, p = .01). MDMA-induced effects did not predict any of the VAS items. Furthermore, substance-induced effective connectivity changes concerning transmodal areas did not significantly predict any VAS items. In addition, Pearson correlation analyses were performed to explore relationships between all VAS items and all coupling parameters (Table S2).

DISCUSSION

Thalamocortical interactions are changed in substance-induced altered states of consciousness (15); however, it was unclear how distinct substances, with differential pharmacological modes of action and subjective effects, drive alterations in thalamocortical coupling. We used spectral DCM to characterize thalamocortical and corticothalamic effective connectivity and investigated interactions between the thalamus and data-driven unimodal and, separately, SAL-derived transmodal cortices. First, we found that compared with placebo and LSD, d-amphetamine and MDMA induced relatively consistent changes in effective connectivity between the thalamus and unimodal cortices. Specifically, we found decreased effective connectivity to the thalamus and increased thalamic effective connectivity to some cortical areas, indicating reduced top-down and increased bottom-up processing. Second, we mapped the effective connectivity between the thalamus and transmodal cortices and found that the amphetamines increased the influence of transmodal cortices on the thalamus while reducing the effective connectivity from the thalamus to some of these same cortices, indicating increased top-down and decreased bottom-up processing. In contrast, LSD did not change corticothalamic coupling but increased the effective connectivity from the thalamus to transmodal cortices, suggesting alterations in the hierarchical organization of bottom-up and top-down information flow.

Shared Effective Connectivity Changes Between the Thalamus and Unimodal Cortices

Our first main finding demonstrated increased effective connectivity from the thalamus to the auditory cortex and lingual gyrus for all substances compared with placebo despite predominantly distinct pharmacological and subjective effects (Figure 3). The substance-induced effects are mainly induced via partial 5-HT_{2A} receptor agonism for LSD (30), increased dopaminergic transmission for d-amphetamine (31), and increased serotonergic transmission for MDMA (32). Nevertheless, the pharmacological modes of action are far more complex, including overlapping effects (e.g., agonistic activity at dopamine receptors) (27,33,34) and interactions between the glutamatergic, dopaminergic, and serotonergic systems (35). In contrast to our hypothesis, substance-induced effects did not increase all connections from the thalamus to the investigated unimodal regions. Remarkably, however, the substances increased effective connectivity from the thalamus to the same regions, suggesting a common pathway—perhaps related to direct dopaminergic effects in the striatum. This finding is congruent with TFM (11,12), indicating increased bottom-up information flow. Intriguingly, corticothalamic effective connectivity was decreased (with one exception for LSD, see below), suggesting reduced top-down information flow.

Table 2. Specificity of LSD-Induced Effective Connectivity Changes Compared With d-Amphetamine and MDMA

Connection	Substance-Induced EC Changes	Substance-Induced EC Valence	Effect Size, Hz	Posterior Probability
LSD vs. d-Amphetamine				
rLN → lAU	+	E	0.04[a]	.6[a]
rLN → rLN	−	I	0.17	>.99
rLN → rCU	+	E	0.04[a]	.5[a]
rLN → TH	+	E	0.13	>.99
rCU → TH	+	E	0.14	>.99
rPoC → lAU	+	E	0.06[a]	.7[a]
rPoC → TH	+	E	0.09[a]	.8[a]
TH → rLN	−	I	0.11	>.99
MDMA vs. LSD				
lAU → lAU	+	E	0.06[a]	.6[a]
rLN → lAU	+	E	0.07[a]	.7[a]
rLN → rLN	−	I	0.14	>.99
rLN → TH	+	E	0.04[a]	.5[a]
rCU → TH	+	E	0.06[a]	.7[a]
rPoC → lAU	+	E	0.12	>.99
rPoC → TH	+	E	0.17	>.99
d-Amphetamine vs. MDMA				
lAU → lAU	+	E	0.11	.9[a]

Connections surpassing a posterior probability threshold of .5 are shown. Direct comparisons between substances were only possible for the first model, which quantified the effective connectivity between the thalamus and unimodal cortices.

−, decreased; +, increased; E, excitatory; EC, effective connectivity; I, inhibitory; lAU, left auditory cortex; lCU, left cuneus; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; rCU, right cuneus; rLN, right lingual gyrus; rPoC, right postcentral cortex; TH, thalamus.

[a]Weak effects (posterior probability < .99 and/or an effect size < 0.1 Hz).

Deviating somewhat from these results, LSD increased the effective connectivity from visual areas (i.e., lingual gyrus) to the thalamus. This increase may reflect neurobiological processes underlying visual hallucinations (36). In support of this, psilocybin and LSD increase cerebral blood flow and iFC in the visual cortex while decreasing alpha power (37,38). The increased effective connectivity from the thalamus to the lingual gyrus is also consistent with a recent report that evaluated effects of LSD on whole-brain effective connectivity with a different approach, regression DCM (26). However, effective connectivity from Heschl's gyrus and the planum temporale (roughly corresponding to our left auditory cortex ROI) to the thalamus or from the right postcentral gyrus to the thalamus were not altered in that study, which only reported increased corticothalamic (but also thalamocortical) effective connectivity. These discrepancies may be explained by methodological differences between the 2 studies (e.g., DCM approach, higher variance in the larger sample, ROI definition). For details regarding methodological differences between spectral and regression DCM, see the Supplemental Discussion.

Next, we investigated specific effects by directly comparing the active substances to one another. Compared with the amphetamines, LSD showed increased top-down corticothalamic effective connectivity for both visual and sensorimotor areas. While the former possibly reflects a mechanism underlying alterations in visual processing, we speculate that the increased effective connectivity from the postcentral gyrus likely reflects increased activity of pyramidal neurons in cortical layer V, located in somatosensory areas, known to be highly sensitive to psychedelic action (39). Consistent with the iFC findings from our previous paper (21), we found only minor differences between d-amphetamine- and MDMA-elicited changes, indicating overlapping effects. Such overlap is plausible because the 2 amphetamines are related structurally and also stimulate norepinephrine release, in addition to having shared dopaminergic effects (34); however, we cannot completely rule out the possibility that our study may have been underpowered to detect differences.

Finally, some substance-induced changes in effective connectivity significantly predicted several VAS items. Regarding corticothalamic effective connectivity, d-amphetamine–induced effects were negatively associated with "speed of thinking," indicating that decreased influence of specific unimodal cortices on the thalamus may be relevant for some d-amphetamine–related subjective effects. LSD-induced effects were associated with the item "concentration," i.e., the more reduced the connectivity, the lower the concentration. MDMA-induced changes in corticothalamic effective connectivity did not predict any of the VAS items. Concerning thalamocortical effective connectivity, only d-amphetamine–induced effects were associated with "good drug effect" and "drug liking." These findings indicate that increased thalamocortical effective connectivity, reflecting bottom-up processing, may be relevant for some subjective experiences, presumably processed in transmodal cortices (e.g., processing emotion).

Distinct Effective Connectivity Changes Between the Thalamus and Transmodal Cortices

Our second main finding demonstrated that thalamocortical and corticothalamic effective connectivity with SAL-derived transmodal cortices were distinct for the 3 substances compared with placebo (Figure 5). First, d-amphetamine and MDMA increased the effective connectivity from several cortical areas to the thalamus, indicating increased top-down processing. However, thalamic effective connectivity was reduced to several cortical regions (i.e., more pronounced to the left insula), indicating decreased bottom-up information flow to these areas. The reduced thalamocortical effective connectivity is consistent with our previous reports of SAL-thalamic hypoconnectivity following d-amphetamine and MDMA (21). In addition, the amphetamines increased effective connectivity between distinct cortical regions. MDMA also reduced effective connectivity between several cortical regions (ACC and left supramarginal gyrus to the left and right insula), indicating a more complex pattern of changes compared with d-amphetamine. The constellation of increased corticothalamic but decreased thalamocortical effects may reflect enhanced top-down control over sensorimotor processing (40,41). We speculate that this increased top-down control may be the mechanism underlying enhanced cognitive, emotional, and prosocial processes following d-amphetamine and MDMA (42,43). Second, LSD

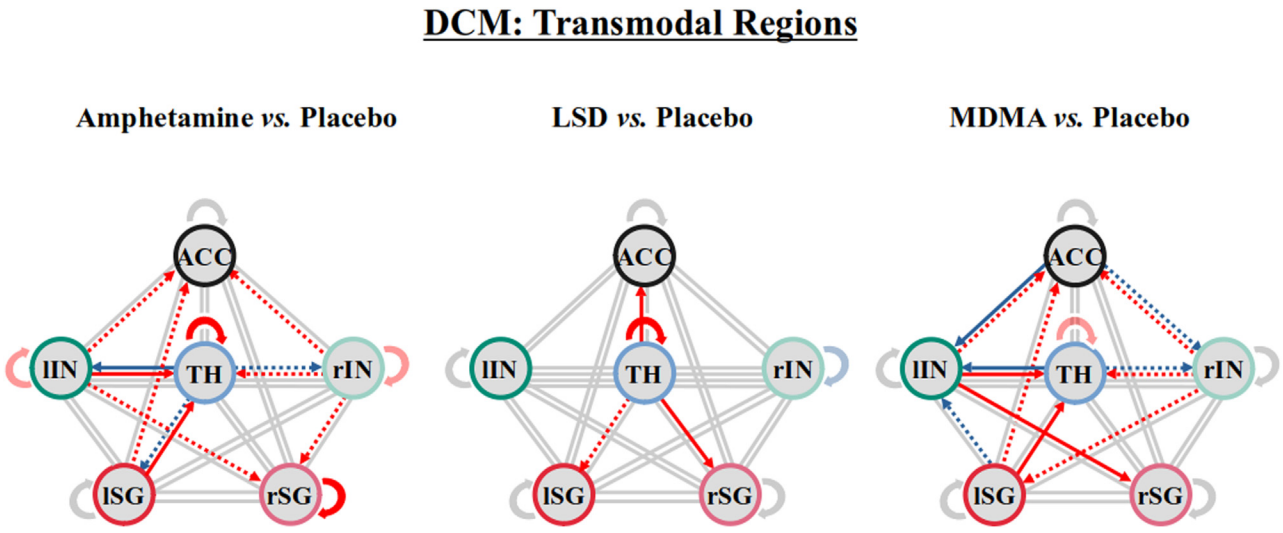

Figure 5. Differences in effective connectivity between the thalamus and salience network–derived transmodal cortices are shown between d-amphetamine, LSD, and MDMA against placebo. Red arrows indicate increased excitatory influence of a substance vs. placebo, whereas blue arrows indicate inhibitory influence. Increased self-inhibition is shown in red circular arrows, and reduced self-inhibition is shown in blue. Gray arrows indicate connections that were not different between substance and placebo. Dashed arrows and transparent circular arrows indicate weaker effects (i.e., surpassing a posterior probability threshold of .5 but $<$ .99 and/or with an effect size of $<$ 0.1 Hz). ACC, anterior cingulate cortex; DCM, dynamic causal modeling; lIN, left insula; LSD, lysergic acid diethylamide; lSG, left supramarginal gyrus; MDMA, 3,4-methylenedioxymethamphetamine; rIN, right insula; rSG, right supramarginal gyrus; TH, thalamus.

did not elicit changes in corticothalamic effective connectivity but increased thalamocortical effective connectivity with several transmodal cortices, indicating increased bottom-up information flow. These findings are consistent with our previous report of SAL-thalamic hyperconnectivity following LSD (21) and are supported by results of animal studies (44). Notably, although covering several thalamic nuclei, the thalamic ROI was centered around a peak in the mediodorsal nucleus, which increases firing following LSD (44). A previous study investigating LSD-induced effects on effective connectivity (13) also reported increased thalamic effective connectivity with some transmodal cortices (posterior cingulate cortex) but not others (superior temporal gyrus). Furthermore, while some corticothalamic connections were not altered by LSD (from the superior temporal gyrus), others were reduced (from the posterior cingulate cortex). While comparing these findings with ours is tempting, key methodological differences between the 2 studies discourage such an attempt. Specifically, Preller *et al.* (13) used an additional condition in which ketanserin (a 5-HT_{2A} receptor antagonist) was administered to the participants, and the LSD and ketanserin conditions were combined to evaluate LSD-induced effects, which were specifically independent of or dependent on 5-HT_{2A} receptors. Stated differently, a direct LSD versus placebo comparison as assessed in the current study was not investigated therein, making direct comparisons difficult. We also note that Bedford *et al.* (26) did not report any reductions in effective connectivity from the thalamus to any transmodal cortices or from any of these cortices to the thalamus. However, not all connections from the thalamus to transmodal cortices were increased, indicating regional specificity. Consistent with Bedford *et al.* (26), we observed that LSD increased the effective connectivity from the thalamus to the ACC and to the right supramarginal gyrus. Furthermore, the effective connectivity from the ACC to the thalamus was not altered. However, in contrast to Bedford *et al.* (26), we did not observe increased effective connectivity from the thalamus to the insula cortices or from the insula and supramarginal cortices to the thalamus. These discrepancies may reflect a power issue in our study (i.e., a smaller participant sample) or a difference in methodology (e.g., regression DCM vs. DCM, employed ROIs). Beyond thalamocortical interactions, Stoliker *et al.* (45) used DCM to examine changes in the relationships between intrinsic brain networks following LSD. They demonstrated that the SAL inversed its effective connectivity to the default mode network from inhibitory to excitatory during peak drug effects, indicating a change in the hierarchical organization of ongoing brain activity.

Altered effective connectivity between SAL-derived transmodal areas and the thalamus did not predict any of the VAS items for any of the investigated substances.

Final Remarks

These results advance our knowledge about the action of psychedelics on brain function and refine current models that aim to explain the underlying neurobiological processes. Specifically, our findings demonstrate that cortical flooding is not specific to psychedelics, which is congruent with TFM (11,12). However, our results expand this model by demonstrating that this effect is 1) specific to some unimodal cortices and 2) accompanied by a decrease in top-down cortical control. Remarkably, this constellation of effects depended on the cortex type. In contrast to unimodal cortices, SAL cortical regions increased their influence on the thalamus and the thalamus weakened its influence on these same areas following d-amphetamine and MDMA, suggesting an alternative, top-down view in which transmodal cortices potentially disrupt

Table 3. Substance-Induced Effective Connectivity Between the Thalamus and Transmodal Cortices

Connection	Substance-Induced EC Changes	Substance-Induced EC Valence	Effect Size, Hz	Posterior Probability
d-Amphetamine vs. Placebo				
lIN → ACC	+	E	0.08[a]	>.99
lIN → lIN	+	E	0.09[a]	>.99
lIN → rSG	+	E	0.09[a]	>.99
lIN → TH	+	E	0.10	>.99
rIN → ACC	+	E	0.04[a]	.6[a]
rIN → rIN	+	E	0.04[a]	.5[a]
rIN → rSG	+	E	0.04[a]	.6[a]
rIN → TH	+	E	0.04[a]	.6[a]
lSG → ACC	+	E	0.09[a]	>.99
lSG → TH	+	E	0.12	>.99
rSG → rSG	+	E	0.11	>.99
TH → lIN	−	I	0.10	>.99
TH → rIN	−	I	0.09[a]	>.99
TH → lSG	−	I	0.03[a]	.5[a]
TH → TH	+	E	0.19	>.99
LSD vs. Placebo				
rIN → rLN	−	I	0.05[a]	.7[a]
TH → ACC	+	E	0.10	>.99
TH → lSG	+	E	0.07[a]	.8[a]
TH → rSG	+	E	0.12	>.99
TH → TH	+	E	0.20	>.99
MDMA vs. Placebo				
ACC → lIN	−	I	0.10	>.99
ACC → rIN	−	I	0.04[a]	.6[a]
lIN → ACC	+	E	0.09[a]	>.99
lIN → rSG	+	E	0.11	>.99
lIN → TH	+	E	0.16	>.99
rIN → ACC	+	E	0.04[a]	.5[a]
rIN → lSG	+	E	0.09[a]	>.99
rIN → TH	+	E	0.04[a]	.6[a]
lSG → ACC	+	E	0.04[a]	.5[a]
lSG → lIN	−	I	0.03[a]	.5[a]
lSG → TH	+	E	0.12	>.99
TH → lIN	−	I	0.15	>.99
TH → rIN	−	I	0.04[a]	.5[a]
TH → TH	+	E	0.05[a]	.6[a]

Connections surpassing a posterior probability threshold of .5 are shown.

−, decreased; +, increased; ACC, anterior cingulate cortex; E, excitatory; EC, effective connectivity; I, inhibitory; lIN, left insula; LSD, lysergic acid diethylamide; lSG, left supramarginal gyrus; MDMA, 3,4-methylenedioxymethamphetamine; rIN, right insula; rSG, right supramarginal gyrus; TH, thalamus.

[a]Weak effects (posterior probability < .99 and/or an effect size < 0.1 Hz).

unimodal sensory processing. Remarkably, LSD led to increased bottom-up information flow independent of cortex type, suggesting an alteration in hierarchical processing potentially reflecting unimodal-transmodal integration. In support of this idea, a recent study demonstrated that LSD and psilocybin flatten the hierarchical organization of ongoing brain activity by reducing the functional differentiation of transmodal and unimodal cortices (46). This flattening of the functional hierarchy may be elicited by greater unimodal-transmodal integration, which would thus disrupt regular functioning—corresponding to functional segregation and integration of low-level sensorimotor to associative information (47).

Limitations

Our study has some limitations that need to be considered. Interestingly, LSD induced weaker thalamocortical effects than the amphetamines in the investigated unimodal regions. However, this pattern was reversed for several transmodal cortices (ACC and supramarginal gyri), suggesting a specific mechanism for LSD. Supporting evidence from Bedford *et al.* (26) indicates that increased effective connectivity between the thalamus and the cortex seems more pronounced for transmodal cortices (e.g., prefrontal, limbic) than unimodal ones (e.g., occipital, sensorimotor), although this has not been quantified directly. Such effects are perhaps driven by higher 5-HT_{2A} receptor density in transmodal than in unimodal cortices (48). Next, we observed some discrepancies between the LSD findings reported herein and those observed in Preller *et al.* (13) and Bedford *et al.* (26) (for a summary table, see Table S3). Although not directly contradictory, these inconsistencies may be attributed to key methodological differences between the studies: 1) Preller *et al.* (13) combined LSD and ketanserin conditions to determine 5-HT_{2A} receptor–related effects, and 2) Bedford *et al.* used regression DCM with an atlas-based ROI definition. Regression DCM has high computational efficiency, making it useful for investigating hundreds of nodes (49). However, when analyzing a small number of nodes (e.g., herein 6 ROIs per model), spectral DCM as applied here is preferred because of its superior neurobiological plausibility. Finally, we only investigated some substance-induced effective connectivity changes in thalamocortical and corticothalamic interactions. While the investigated areas were informed by our previous study, we acknowledge that focusing on only a subset of regions is a limitation—which is however coupled with the higher computational demands of spectral DCM, which are in turn based on the higher neurobiologically accuracy of the model compared with other more computationally efficient DCM variants (49,50).

Conclusions

LSD, d-amphetamine, and MDMA increased the excitatory influence of the thalamus to specific unimodal cortices while reducing the influence of these cortices on the thalamus. Intriguingly, the amphetamines elicited opposing effects with transmodal cortices covering the SAL. However, LSD also increased effective connectivity to these transmodal areas, suggesting a disruption in the hierarchical organization between the thalamus and unimodal and transmodal cortices.

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