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LSD-induced changes in the functional connectivity of distinct thalamic nuclei

Stefano Delli Pizzi [a,c], Piero Chiacchiaretta [b], Carlo Sestieri [a,d], Antonio Ferretti [a,d,e], Maria Giulia Tullo [a], Stefania Della Penna [a,d], Giovanni Martinotti [a], Marco Onofrj [a], Leor Roseman [f], Christopher Timmermann [f], David J. Nutt [f], Robin L. Carhart-Harris [f,g], Stefano L. Sensi [a,c,d,*]

[a] Department of Neuroscience, Imaging, and Clinical Sciences, University "G. d'Annunzio" of Chieti-Pescara, Italy
[b] Department of Innovative Technologies in Medicine and Dentistry, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy
[c] Molecular Neurology Unit, Center for Advanced Studies and Technology (CAST), University "G. d'Annunzio" of Chieti-Pescara, Italy
[d] Institute for Advanced Biomedical Technologies (ITAB), "G. d'Annunzio" University, Chieti-Pescara, Italy
[e] UdA-TechLab, Research Center, University "G. d'Annunzio" of Chieti-Pescara, 66100 Chieti, Italy
[f] Centre for Psychedelic Research, Faculty of Medicine, Imperial College London, London, United Kingdom
[g] Psychedelics Division, Neuroscape, Neurology, University of California San Francisco

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ABSTRACT

The role of the thalamus in mediating the effects of lysergic acid diethylamide (LSD) was recently proposed in a model of communication and corroborated by imaging studies. However, a detailed analysis of LSD effects on nuclei-resolved thalamocortical connectivity is still missing. Here, in a group of healthy volunteers, we evaluated whether LSD intake alters the thalamocortical coupling in a nucleus-specific manner. Structural and resting-state functional Magnetic Resonance Imaging (MRI) data were acquired in a placebo-controlled study on subjects exposed to acute LSD administration. Structural MRI was used to parcel the thalamus into its constituent nuclei based on individual anatomy. Nucleus-specific changes of resting-state functional MRI (rs-fMRI) connectivity were mapped using a seed-based approach. LSD intake selectively increased the thalamocortical functional connectivity (FC) of the ventral complex, pulvinar, and non-specific nuclei. Functional coupling was increased between these nuclei and sensory cortices that include the somatosensory and auditory networks. The ventral and pulvinar nuclei also exhibited increased FC with parts of the associative cortex that are dense in serotonin type 2A receptors. These areas are hyperactive and hyper-connected upon LSD intake. At subcortical levels, LSD increased the functional coupling among the thalamus's ventral, pulvinar, and non-specific nuclei, but decreased the striatal-thalamic connectivity. These findings unravel some LSD effects on the modulation of subcortical-cortical circuits and associated behavioral outputs.

Abbreviations: ANT, anterior thalamic group; ASC, Altered States of Consciousness; AV, antero-ventral nucleus; CeM, centromedian nucleus; CL, central lateral nucleus; CM, central medial nucleus; CON-A, Control network A; CON-B, Control network B; CON-C, Control network C; CSTC, cortico-striatal thalamo-cortical; DAN-A, Dorsal Attention A; DAN-B, Dorsal Attention B; DMN, default mode network; DMN-A, Default Mode network A; DMN-B, Default Mode network B; DMN-C, Default Mode network C; FC, functional connectivity; fMRI, functional Magnetic Resonance Imaging; L, left; L-SG, limitans; LD, laterodorsal; LGN, lateral geniculate nucleus; LMBN-A, Limbic network A; LMBN-B, Limbic network B; LP, lateroposterior nucleus; LSD, Lysergic acid diethylamide; MD, mediodorsal; MDm, magnocellular mediodorsal; MDl, parvocellular mediodorsal; MGN, medial geniculate nucleus; Met, Metathalamus; MRI, Magnetic Resonance Imaging; MV-re, Reuniens; NS, Non-specific; Pc, paracentral nucleus; Pf, parafascicular; PuA, Anterior or oral pulvinar; PuI, Inferior pulvinar; PuL, Lateral pulvinar; PuM, Medial pulvinar; R, right; rs, resting-state; SMN-A, Somato-motor A; SMN-B, Somato-motor B; SVAN-A, Salience/Ventral Attention A; SVAN-B, Salience/Ventral Attention B; TPN, Temporo-parietal network; VA, Ventro-anterior; VAm, ventral-anterior nucleus; VAmc, ventro-anterior magnocellular nucleus; VCN, Visual central network; VL, ventrolateral; VLa, anterior ventro-lateral nucleus; VLp, ventro-lateral posterior nucleus; VM, ventro-medial nucleus; VP, Ventro-posterior; VPN, Visual peripheral network; VPL, ventral-postero-lateral nucleus.

* Corresponding author.
E-mail addresses: ssensi@uci.edu, stefano.sensi@unich.it (S.L. Sensi).

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1. Introduction

Lysergic acid diethylamide (LSD) is a psychoactive drug that alters perception and consciousness (Preller and Vollenweider, 2018). The usefulness of LSD in psychotherapy was first recognized in the 50 s, but concerns about its uncontrolled recreational use overshadowed research on the compound. In recent years, LSD has regained attention (Nutt et al., 2020) as a way to investigate the neural bases of perception, cognition, and consciousness (Avram et al., 2021) and as a supplementary tool for the treatment for a range of psychiatric disorders, like treatment-resistant depression and end-of-life and cancer-related anxiety (Carhart-Harris et al., 2021; Daws et al., 2022; Rucker et al., 2018).

As far as the compound's neural effects, recent experimental data indicate that subcortical structures play a synergic role with the neocortex in mediating the psychedelic experience (Avram et al., 2021; Doss et al., 2022; Gaddis et al., 2022; Stoliker et al., 2022). One view proposes that, within the cortico-striatal-thalamo-cortical (CSTC) loop, psychedelic drugs, including LSD, modulate the descending glutamatergic projections that connect the prefrontal cortex (PFC) to the striatum, thereby affecting the striate-thalamic loop. This, in turn, would result in the alteration of the thalamic filtering of sensory inputs and, ultimately, perception dissonance (Vollenweider, 2001; Vollenweider and Preller, 2020). Furthermore, resting-state functional Magnetic Resonance Imaging (rs-fMRI) studies support the notion that LSD alters the functional connectivity (FC) between the thalamus and primary sensory cortices, including the sensorimotor, auditory, and visual networks (Tagliazucchi et al., 2016; Muller et al., 2017). Using dynamic causal modeling to assess the effective connectivity between the brain structures that form the CSTC loop, a recent study also found that LSD decreases the strength of inhibitory connections that run from the ventral striatum to the thalamus and enhances the strength of excitatory thalamocortical projections to the sensory and posterior parietal cortices (Preller et al., 2019).

One limitation affecting the study of thalamocortical connectivity is that the thalamus contains several highly interconnected nuclei of first- and high-order (Ward et al., 2013). First-order thalamic nuclei (e.g., the geniculate and ventral nuclei) receive sensorimotor inputs from peripheral or other subcortical structures and act as a relay station for transferring afferent information to the primary cortices (Halassa et al., 2017; Moustafa et al., 2017). High-order nuclei (e.g., pulvinar and mediodorsal nuclei), instead, simultaneously send/receive inputs from/to multiple brain regions, thereby shaping the cortico-cortical communication flows (Halassa et al., 2017). Finally, although the intralaminar (IT) complex is considered among the high-order nuclei (Saalmann, 2014) based on evidence for its modulatory activity on the cortico-cortical network involved in consciousness and arousal, this set of nuclei shares some functional properties with the first-order nuclei as it also modulates sensory integration (Bartlett, 2013). This view is supported by evidence for its direct connectivity with the striatum (Smith et al., 2004), the main recipient of the 5-HT2A upregulation. However, considering this functional heterogeneity, it is currently not clear if the effect of LSD on thalamocortical connectivity is widespread or specific for particular nuclei.

A recent study has attempted to address this outstanding issue (Avram et al., 2022). The authors conducted a seed-based analysis starting from two cortical seeds from the 7-network parcellation proposed by Yeo and colleagues (Yeo et al., 2011). Seeds were selected based on studies investigating thalamocortical dysconnectivity in schizophrenia (Avram et al., 2018; 2020): the auditory/sensorimotor and the salience network. The modulation of the connectivity between these networks and each voxel in the thalamus was assessed upon the administration of different compounds (d-amphetamine, LSD, MDMA) versus baseline. LSD was found to increase the auditory/sensorimotor-thalamic connectivity with the ventral thalamic nuclei (and partially with the pulvinar). The compound also enhanced the salience-thalamic connectivity with the ventral nuclei, the pulvinar, and the mediodorsal (MD) nucleus. However, a comprehensive analysis of the effects triggered by LSD on the whole pattern of thalamocortical connectivity is still missing.

The present study uses a whole-brain approach to test whether acute LSD administration alters the functional thalamocortical coupling, in a nucleus-specific manner. A first prediction about functional specificity derives from the empirical work of Avram and colleagues (2022) and focuses on the activity of ventral nuclei, the pulvinar, and the MD nucleus. Whereas the ventral nuclei are expected to modulate their connectivity with sensory networks in psychedelic states (Muller et al., 2017), the MD might change its pattern of connectivity not only with the salience network but also with the Default Mode Network (DMN, Raichle, 2001), as the latter network is hyperactivated by LSD (Delli Pizzi et al., 2023) and functionally and anatomically connected with the MD nucleus (Harrison et al., 2022). Another prediction stems from the CSTC model (Vollenweider and Preller, 2020), which proposes that psychedelics have a predominant effect not only on ventral nuclei but also on the IT complex, as the latter participate in filtering the flux of peripheral information to sensory networks.

To test these predictions, we used structural and functional Magnetic Resonance Imaging (MRI) data from a placebo-controlled study on fifteen healthy volunteers undergoing LSD acute administration. Structural MR images were processed using a probabilistic method and a-priori information from ex-vivo MRI and histology to generate an accurate parcellation of the human thalamic nuclei based on subject-specific anatomy (Iglesias et al., 2018). Functional images were analyzed using a seed-based approach to identify the pattern of nuclei-specific modulations of thalamocortical connectivity with the main resting-state cortical networks, according to the 17-network classification proposed by Yeo and colleagues (Yeo et al., 2011). Analogously, at the subcortical level, we measured resting-state FC between different thalamic nuclei, and between thalamic nuclei and the striatum. The aim was to identify those nuclei that exhibited changes in subcortical connectivity induced by LSD.

2. Materials and methods

2.1. Ethics statement

The current study moves from a re-analysis of previously published data (Carhart-Harris et al., 2016; Tagliazucchi et al., 2015; Luppi et al., 2021). However, the novelty of the paper relates to the role played by a distinct subset of thalamic nuclei. Here, we restate that the current study was approved by the National Research Ethics Service Committee London-West London and was conducted following the revised Declaration of Helsinki, the International Committee on Harmonization Good Clinical Practice guidelines, and the National Health Service Research Governance Framework. Imperial College London sponsored the research conducted under a Home Office license for research with Schedule 1 drugs.

2.2. Experimental design and MRI protocol

The data acquisition protocol and subjective effect rating are described in detail by Carhart-Harris et al. (2016). Twenty healthy volunteers with previous experience using psychedelic drugs underwent two 3T MRI scans, 14 days apart, in which they received a placebo (10-mL sal10 mL or an active dose of LSD (75 μg of LSD in 10-mL saline). The infusion (drug/placebo) was administered over 2 min and occurred 115 min before the resting-state scans were initiated. The MRI protocol consists of anatomical images (3D fast spoiled gradient echo scans in an axial orientation, field of view=256 × 256 × 192; repetition time/echo time=7.9/3.0 ms; inversion time=450 ms; flip angle=20) and three fMRI scans acquired at resting-state with eyes-closed (gradient echo planer imaging sequence, repetition time/echo time=2000/35 ms, field of view=220 mm, 64 × 64 acquisition matrix, parallel acceleration

factor=2; 220 vol; 3.4 mm isotropic voxels). Of the three rs-fMRI scans, we used only the first one acquired without music stimulation. After the scan, visual analogue scale (VAS) ratings were performed in the scanner via a response box. At the end of scanning days, participants also completed the Altered States of Consciousness (ASC) scale (Dittrich et al., 1998), providing retrospective subjective evaluations on the peak of the experience (i.e., during fMRI scanning) (Carhart-Harris et al., 2016)

One subject aborted the experiment due to anxiety and four others we excluded for excessive head motion in the scanner (defined as >15 % of volumes with mean frame-wise displacement (FD)>0.5 (Carhart-Harris et al., 2016), leaving 15 subjects for analysis.

2.3. MRI data analysis

For each subject, T_1-weighted images were processed with FreeSurfer 7.3 using the "recon-all -all" command line. The tool provided automated reconstruction and labeling of cortical and subcortical regions. The segmentThalamicNuclei.sh script was subsequently used to compute the thalamus parcellation (Iglesias et al., 2017). FreeSurfer-Functional Analysis Stream (http://surfer.nmr.mgh.harvard.edu/fswiki/FsFastFunctionalConnectivityWalkthrough) was used to perform a seed-based FC analysis mapping the interactions between each thalamic region and the rest of the brain. The first four rs-fMRI volumes were discarded from the analysis to allow T1 equilibration of the MR signal. First, motion and slice timing corrections were performed according to the standard preprocessing pipeline in FS-FAST (https://surfer.nmr.mgh.harvard.edu/fswiki/preproc-sess). The ICA-based Automatic Removal Of Motion Artifacts (ICA-AROMA) procedure was then applied to identify and remove further motion artifacts from fMRI data (Pruim et al., 2015). To remove physiological noise and other confounds, we regressed out cerebrospinal fluid and white matter signals (Behzadi et al., 2007). In detail, the EPI average time courses within the ventricle mask and the WM mask (considering the top 5 principal components) were regressed out from the EPI time series, whereas global signal regression was not performed. Although applying global signal regression can remove the spurious inflation of connectivity values caused by the above confounds, the procedure also introduces artifactual negative correlations (Murphy and Fox, 2017). Additional preprocessing included temporal band-pass filtering (0.01<Hz<0.1) and volume censoring (i.e., scrubbing). Specifically, volumes for which the frame-wise displacement value (FD) was larger than 0.5 mm were removed (Power et al., 2012). Furthermore, since head motion (mean frame-wise displacement, FD) was slightly higher in the LSD than the placebo condition (mean±SD, placebo: 0.04±0.02; LSD: 0.06±0.03; $p = 0.02$), for the functional connectivity modulations which survived the correction for multiple comparisons, we also checked for potential residual confounding effects of head motion by estimating the linear regression between FC changes and the mean FD across subjects (Supplementary Figure 1). Final data preprocessing included the creation of a binary mask of the brain from an input functional volume (masking), registration to the structural image, sampling to the surface, and no surface smoothing. The surface sampling was done onto the surface of the left and right hemispheres of fsaverage. The cortical time series data were sampled onto fsaverage, whereas the timeseries of the thalamic nuclei and striatum were derived from individual subcortical volumes. The "selxavg3-sess" command line performed the first-level analysis (single-subject analysis) including the computation of the Pearson correlation coefficient (R-value) between the time series within the seed and the time series at each voxel. The obtained correlation maps were then transformed into z-score, and its average was computed for each of the seventeen Yeo's networks (Yeo et al., 2011), which are adapted to individual anatomy. At the subcortical level, the averaged time series from each thalamic and striatal region (i.e., the nucleus accumbens, caudate nucleus, and putamen) were extracted and correlated subject-by-subject.

2.4. Statistical analysis

All the reported statistical tests are two-tailed. LSD effects were estimated from FC differences between the two conditions (LSD-PCB). For the analyses examining the connectivity of the thalamic seeds with the cortical networks, one-sample ANOVAs were used to assess the presence of a significant effect of LSD for each thalamic region. Considering the inclusion of thirty-four cortical targets in the model, the Bonferroni correction was applied to account for multiple comparisons. We also performed an exploratory analysis to assess the effect of LSD on subcortical interactions. To increase statistical power, we performed a reduction of the search space by subdividing the thalami into two clusters based on the results of the previous analysis [thalamic regions that changed (A) or did not change (B) their connectivity with the cortex]. A within-thalamus analysis assessed the presence of a significant effect of LSD on within-cluster (A, B) and between-cluster (A-B) connectivity, using one-sample repeated-measures ANOVAs. A thalamo-striatal analysis assessed the presence of a significant effect of LSD between the two thalamic clusters (A, B) and the striatum, using one-sample ANOVAs.

3. Results

3.1. Thalamic nuclei segmentation

Using anatomical images, the thalamus of each subject was parceled in fifty nuclei (twenty-five nuclei for each hemisphere, Supplementary Fig. 1, upper panel). Given that some of the nuclei were too small in size to be used as seeds in rs-fMRI FC analysis, the parceled nuclei were merged in thirteen thalamic subfields (Supplementary Fig. 2, lower panel): 1. the anterior group including the anteroventral nucleus and the dorsal lateral nucleus; 2. the MDm and MDl nuclei; 3. the PuA; the medial pulvinar (PuM); the lateral pulvinar (PuL); the inferior pulvinar (PuI); 4. the lateral geniculate nucleus (LGN); 5. the ventral-anterior group (VA) group (encompassing the ventral-anterior and ventro-anterior magnocellular nuclei); the ventrolateral (VL) complex, divided into anterior (VLa) and posterior subdivisions (VLp), as they receive main afferents from the pallidum and cerebellum, respectively (Mai and Majtanik, 2017); the ventral-posterior (VP) group [including the ventral-postero-lateral and ventro-medial nuclei]; 6. the intralaminar nuclei (IT), including the central medial, central lateral, paracentral, centromedian, and parafascicular nuclei). The structural features of each nucleus and rs-fMRI seed are reported in Supplementary Table 1.

3.2. Thalamocortical functional connectivity

Under placebo, the MDm and MDl nuclei displayed, respectively, positive FC with the DMN and sensorimotor networks ($p \leq 0.001$; Supplementary Tables 2–3). The VLa complex exhibited positive functional connections with the DMN (component A) and frontoparietal networks ($p = 0.001$; Supplementary Table 4). The VLp complex showed positive functional coupling with the salience network ($p = 0.001$; Supplementary Table 5). The VP complex showed positive functional connections with the salience/ventral attention (component A, $p = 0.001$) and sensorimotor (component A, $p = 0.001$; component B, $p<0.001$) networks (Supplementary Table 6). The IT complex showed positive functional connections with the sensorimotor network (component B, $p = 0.001$; Supplementary Table 7). The PuA nucleus was positively coupled with the dorsal attention (component B, $p<0.001$), salience/ventral attention (component A, $p<0.001$), and sensorimotor (component B, $p \leq 0.001$) networks (Supplementary Table 8). The PuL showed positive functional connections with the dorsal and salience/ventral attention networks ($p<0.001$; Supplementary Table 9). The PuM and LGN, respectively, exhibited positive functional coupling with the DMN ($p<0.001$; Supplementary Table 10) and visual peripheral ($p = 0.001$;

Supplementary Table 11) networks.

LSD selectively modified the cortical FC of four thalamic subfields (extended results in Supplementary Tables 12–24). The process involved the two first-order nuclei encompassing the VLa (Fig. 1, Supplementary Fig. 3, and Supplementary Table 12) and the VP complex (Fig. 2, Supplementary Fig. 4, and Supplementary Table 13) as well as the IT complex (Fig. 3, Supplementary Fig. 5, and Supplementary Table 14) and the high-order PuA nucleus (Fig. 4, Supplementary Fig. 6, and Supplementary Table 16). Specifically, the VLa complex showed increased FC with the sensorimotor network (corrected $p = 0.001$). Instead, the VP complex and IT nuclei displayed increased FC with the auditory network ($p = 0.001$). The PuA nucleus showed an FC disconnection with the auditory network ($p = 0.001$). In addition, some relevant trends toward further significant increases in thalamocortical FC were observed. The VLa complex exhibited enhanced FC with the DMN ($p = 0.025$) and changes in polarity in the auditory network ($p = 0.034$). The VP complex showed increased FC with the DMN ($p = 0.02$) and changes in polarity in the auditory network ($p = 0.034$). The IT and PuA nuclei showed altered FC with the limbic networks ($p = 0.050$). Interestingly, the PuL nucleus showed increased FC with the DMN ($p = 0.004$) and with the auditory network (left: $p = 0.004$; right: $p = 0.008$) as well as decreased FC with the frontoparietal control network (Supplementary Figure 7). Finally, the MDm nucleus showed increased functional coupling with the auditory cortex ($p = 0.002$), but not a significant change of FC with the DMN. Notably, for all the significant FC modulations, the linear regression with FD across subjects was far from being significant, implying that these modulations were not driven by motion artifacts (see Supplementary Figure 7).

3.3. Sub-cortical functional connectivity

The administration of LSD, compared to the placebo, also altered the subcortical FC within the thalamus (i.e., between thalamic nuclei) and between thalamic nuclei and the striatum. In particular, LSD significantly enhanced the FC strength within the set of thalamic subfields that exhibit a significant modulation of thalamocortical FC (Clusters A, mean ± SD: 0.64±0.32, $p<0.001$) but also within the set of subfields whose cortical connectivity was unaffected (Cluster B, mean ± SD: 0,49±0.19, $p<0.001$) and between these two sets (mean ± SD: 0,31±0.21, $p<0.001$). However, the increase of within-cluster FC in cluster A was significantly higher than for cluster B ($p = 0.002$) and showed a tendency for a significant difference also compared to the inter-cluster connectivity ($p = 0.09$), again supporting a spatially specific effect of LSD.

Similarly, while LSD reduced the connectivity between the striatum and both thalamic clusters (Cluster A: mean ± SD: −0.56±0.17, t_{14}=12.958, $p<0.001$; Cluster B: mean ± SD: −0.44±0.16, t_{14}=10.414, $p<0.001$), a greater effect was observed for the cluster of nuclei that exhibited a significant modulation of thalamocortical FC (t_{14}=−6.671, $p<0.001$).

4. Discussion

In the present study, we conducted a comprehensive analysis of the spatial modulation of thalamocortical connectivity induced by LSD, through the parcellation of thalamic nuclei based on individual anatomy and the assessment of nucleus-specific connectivity with cortical resting-state networks. Upon placebo, the overall pattern of thalamocortical connectivity was in line with previous studies that assessed the functional connections of thalamic subregions with the cortex (Kumar et al. 2021; Lambert et al., 2017; Li et al., 2022). We found that LSD modifies the connectivity of the first-order VLa and VP complex, the high-order PuA nucleus, and the IT complex. While the VLa complex enhanced FC with the sensorimotor network, the three other nuclei displayed altered FC with the auditory network. The administration of LSD also resulted in increased subcortical FC within the thalamus and a reduction of FC between the thalamus and the striatum. These effects were stronger for the nuclei that also exhibited a modulation of thalamocortical connectivity.

The present findings are partially consistent with the results of a recent study that has attempted to disentangle the effect of LSD on different thalamic nuclei. Our study differs as we did not limit the analysis to interactions that involve only two cortical networks (Avram et al., 2022). By expanding the analysis to all the main resting-state networks and evaluating anatomically defined thalamic seeds, we also revealed LSD effects on the functional connectivity between the ventral

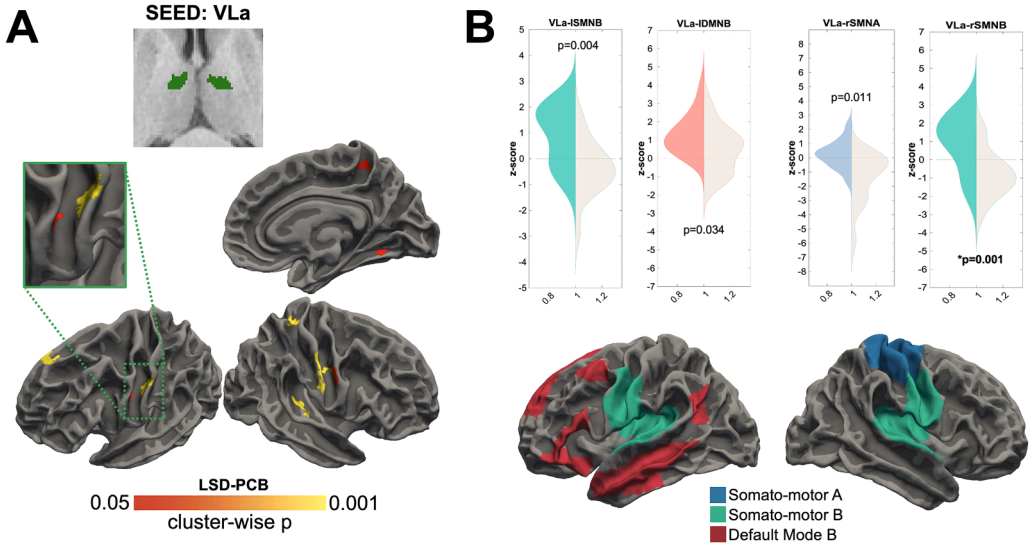

Fig. 1. LSD-induced changes on functional connectivity (FC) of the VLa nuclei. The left panel displays, by performing a vertex-wise analysis, statistically thresholded maps illustrating the FC of the VLa nucleus with the rest of the brain in LSD-PCB condition. Clusters changing from red to yellow indicate increased connectivity. The figure depicts regions with a cluster-wise probability below the corrected p-value of 0.05 and voxelwise (cluster-forming) threshold at corrected $p<0.01$. The right panel shows, by a seed-to-cortical analysis and color-based labeling,Yeo's networks which show significant changes in the VLa FC under LSD. The violin plots report the distribution of z-score values expressing the connection strength between VLa nuclei and Yeo's networks for each condition (i.e., placebo, LSD). The networks are labeled as follows: DMNB=Default Mode Network, component B; SMNA=Sensori-Motor Network, component A; SMNB=Sensori-Motor Network, component B; TPN=Temporal Parietal/Auditory Network (TPN); *l*=left; *r*=right.

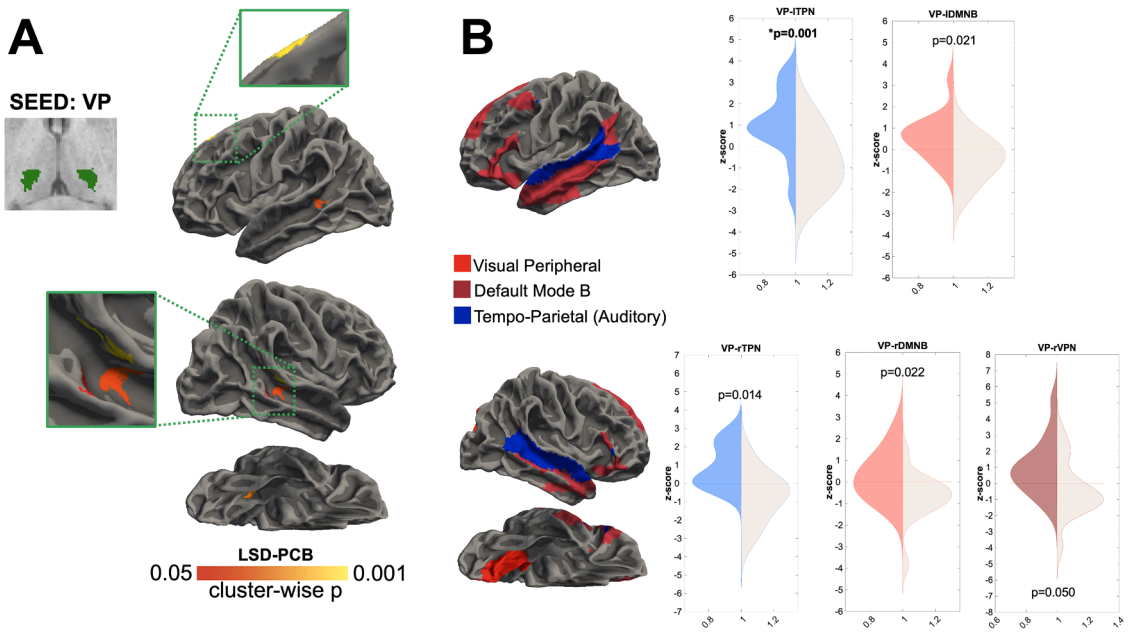

Fig. 2. LSD-induced changes on functional connectivity (FC) of the VP nuclei. The left panel displays, by performing a vertex-wise analysis, statistically thresholded maps illustrating the FC of the VP nucleus with the rest of the brain in LSD-PCB condition. Clusters changing from red to yellow indicate increased connectivity. The figure depicts regions with a cluster-wise probability below the corrected p-value of 0.05 and voxelwise (cluster-forming) threshold at corrected $p<0.01$. The right panel shows, by a seed-to-cortical analysis and by color-based labeling,Yeo's networks which show significant changes in the VP FC under LSD. The violin plots report the distribution of z-score values expressing the connection strength between VP nuclei and Yeo's networks for each condition (i.e., placebo, LSD). The networks are labeled as follows: DMNB=Default Mode Network, component B; TPN=Temporal Parietal/Auditory Network; VPN=Visual Peripheral Network; *l*=left; *r*=right.

thalamic nuclei and auditory-somatomotor networks. However, unlike the work by Avram and colleagues (Avram et al., 2022), we found a modulation of the anterior, rather than medial, pulvinar FC. We also failed to see a statistically significant modulation of FC involving the mediodorsal nucleus. While this latter result might reflect the use of a more stringent statistical threshold, uncorrected results indicate that the MD nucleus modulates its connectivity with the auditory cortex, rather than with the salience or the DMN, as might have been expected. The present study also provides evidence for the involvement of the IT nuclei. This result fits better with the prediction of the CSTC model, according to which these nuclei are responsible, along with the ventral nuclei, for the altered filtering of peripheral information caused by LSD. Overall, the present findings are consistent with the idea that psychedelics affect thalamocortical connectivity by altering the thalamic gating of sensory inputs (Vollenweider and Preller, 2020). On the other hand, our results do not provide much support for the crucial involvement of high-order nuclei (i.e., the MD and the medial pulvinar) in the shaping of associative cortical–cortical interactions. We, therefore, propose that the widespread effect of LSD on the connectivity of the DMN and fronto-parietal networks, indicated by previous studies (Carhart-Harris et al., 2016; Delli Pizzi et al., 2023), is the likely consequence of a direct LSD influence on cortical serotonin receptors located in these cortical regions (Delli Pizzi et al., 2023). This idea is also consistent with the limited expression of serotonin receptors in subcortical compared to cortical structures. This suggests that the thalamus is indirectly affected by LSD through top-down cortico-thalamic connections.

The most straightforward result of the present study is the altered FC modulation between first-order VLa (FC increase) and VP (polarity changes) complexes with the sensorimotor and auditory networks. On the one hand, lesion studies (Beauchamp and Ro, 2008; Ro et al., 2007) indicate that the VL complex is not only involved in motor control (Ward, 2013) but also in sensory processing (Wijesinghe et al., 2015). Specifically, small lesions restricted to the VL region cause a reorganization of thalamocortical connectivity that enhances excitatory connections between the auditory and somatosensory cortex. The process generates synesthesia and sensory input overflow to the cortex (Beauchamp and Ro, 2008; Ro et al., 2007; 2013). On the other hand, the VP complex is part of the somatosensory system and has been defined as the "sensory thalamus" (Mai and Majtanik, 2017). Of note, the inferior VP portion, via projections to the primary vestibular cortex, relays vestibule-cortical information (Mai and Majtanik, 2017, Deecke et al., 1974). Both lines of evidence support the hypothesis that altered FC of the ventral nuclei contributes to the perceptual effects of psychedelics, through a process leading to erroneous multisensory integration and processing by the primary cortex, which, in turn, becomes flooded with unfiltered inputs originated by the thalamus (Vollenweider and Preller, 2020).

Another result that fits with the prediction stemming from the CSTC model is the significant modulation of connectivity patterns of the IT complex. The IT nuclei, long thought to be a non-specific arousing system in the brain (Benarroch et al., 2008), have been more recently also associated with sensory processing (Bartlett, 2013). The paraventricular thalamic nucleus, in particular, is implicated in awareness of viscerosensory stimuli (Bhatnagar and Dallman 1999; Van der Werf et al., 2002) while the centromedian-parafascicular (CM/Pf) complex exhibits reciprocal connections with the superior temporal area involved in auditory processing (Karnath, 2001). Specifically, the CM-Pf receives inputs from the auditory cortex and sends outputs back to the cortex, suggesting an involvement in the integration of auditory stimuli in the processing of multimodal sensory information (Karnath, 2001). These anatomical connections mirror the positive functional coupling that we observed, under a placebo, between the IT complex and both the sensorimotor and auditory networks. Herein, we found a significant increase in IT complex FC with the auditory network and a trend toward a significant disconnection with the limbic system. While the former effect could be considered as further evidence to disentangle the sensorial misperception under psychedelic experience, the altered FC with the limbic network could be relevant in the context of mood disorders (Flagel, 2021). In that respect, the IT complex, and especially the paraventricular nucleus, has been found to receive inputs from regions closely implicated in arousal and emotional processing (Barson et al., 2020). Thus, the LSD-induced modulation of IT connectivity could offer

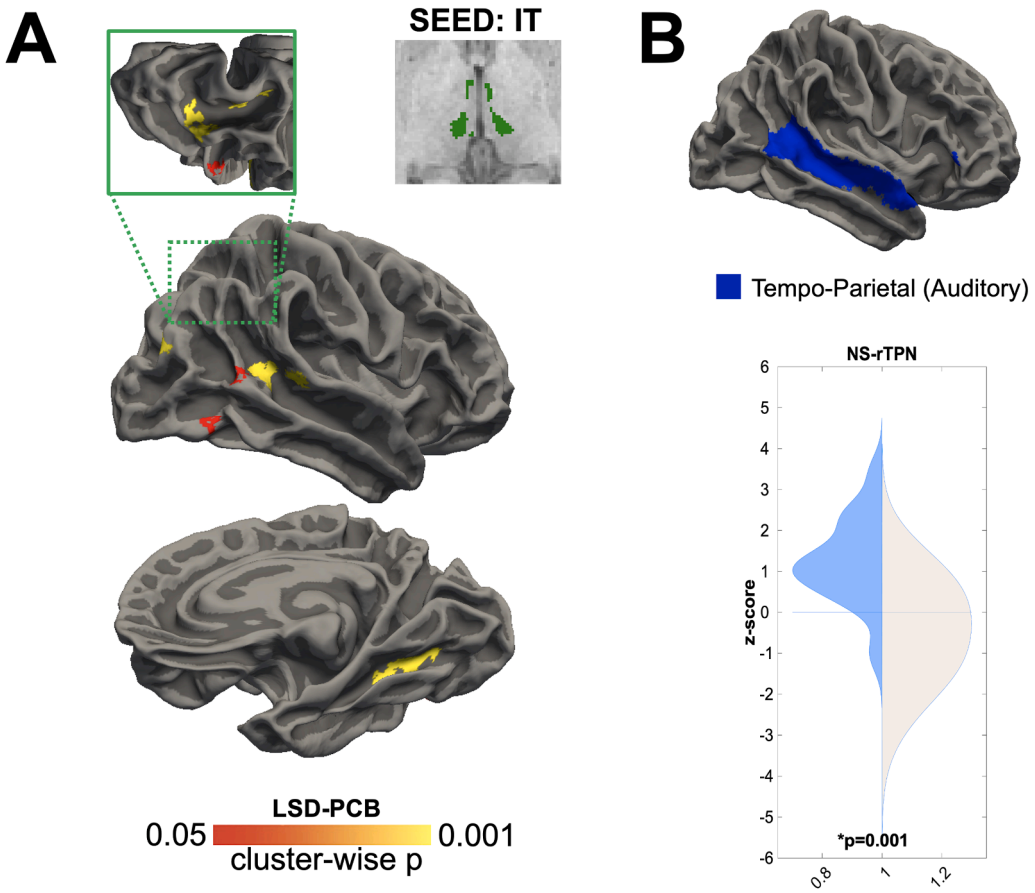

Fig. 3. LSD-induced changes on functional connectivity (FC) of the IT nuclei. The left panel displays, by performing a vertex-wise analysis, statistically thresholded maps illustrating the FC of the IT nucleus with the rest of the brain in LSD-PCB condition. Clusters changing from red to yellow indicate increased connectivity. The figure depicts regions with a cluster-wise probability below the corrected p-value of 0.05 and voxelwise (cluster-forming) threshold at corrected $p<0.01$. The right panel shows, by a seed-to-cortical analysis and by color-based labeling,Yeo's networks which show significant changes in the IT FC under LSD. The violin plots report the distribution of z-score values expressing the connection strength between IT nuclei and Yeo's networks for each condition (i.e., placebo, LSD). The networks are labeled as follows: LMBB=Limbic Network, component B; TPN=Temporal Parietal/Auditory Network; *l*=left; *r*=right.

promising options for the treatment of mood disorders (Flagel, 2021).

An additional finding of the present study concerns the effect of LSD on the FC modulation of the PuA nucleus. This nucleus is critically involved in somatosensory processing and proprioception (Delhaye et al., 2018). The PuA exhibits anatomical connections with the primary somatosensory areas (Padberg et al., 2009), the superior (area 5) and inferior (area 7b) somatosensory association cortices (Yeterian and Pandya, 1985; Friedman and Murray, 1986; Pearson et al., 1978; Weber and Yin, 1984), and the lateral parietal cortex (Burton, 1984). In line with these structural data, we have shown that, under placebo intake, the PuA nucleus displays functional connections with the somatosensory/parietal components of associative cortices (i.e., the dorsal attention, salience/ventral attention, and sensorimotor networks). While these connections remain stable under LSD, we found an FC disconnection of the PuA nucleus with the auditory cortex. Neuro-anatomical tracer studies indicated that labeled cells from auditory cortex injections are commonly found within the PuA (Hackett et al., 2007). Moreover, the altered FC of PuA with the auditory cortex could have a behavioral relevance. Recent studies indicated that a correlation between atrophy of the PuA and persistent auditory hallucinations occurs in persons with schizophrenia (Perez-Rando et al., 2022).

The cortical targets of LSD-driven increased thalamocortical FC are areas that mainly include the sensorimotor and auditory networks. Behavioral investigations have demonstrated physiological perceptual interactions between the auditory and somatosensory modalities (Halpern et al., 1986; Yau et al., 2010). Likewise, MRI studies have proposed the existence of highly tuned multisensory integration processes for gathering coherent somatosensory and auditory stimuli from the environment. These studies have also revealed the activation of the secondary somatosensory cortex in response to sound (Ro et al., 2013). To explain this phenomenon, it has been hypothesized that auditory stimuli first evoke activity in the auditory cortex, and the activity then spreads via cortico-cortical connections to the somatosensory cortex (Ro et al., 2013). Notably, the sensory cortices are specific targets of LSD-driven functional hyper-connectivity with the whole thalamus (Muller et al., 2017). Moreover, the alteration of these thalamocortical connections is associated with subjective visual and auditory misperceptions (Muller et al., 2017; Ramsay et al., 2019). Finally, LSD, via direct modulation of $5HT_{2A}$ receptors, increases the sensitivity to auditory stimuli from the dorsal cochlear nucleus (Tang and Trussell 2015) along the primary auditory pathway (Hurley 2006; Hurley and Sullivan 2012) to the primary auditory cortex (Luo et al., 2016; Riga et al., 2016). LSD also alters intrinsic FC in primary auditory areas and attenuates the top-down suppression of prediction errors in response to auditory stimuli (Timmerman et al., 2018).

At the subcortical level, LSD increased the functional coupling between VLa/VP, PuA, and non-specific thalamic nuclei but decreased striatal-thalamic connectivity. The ventral nuclei also showed increased connectivity with parts of the associative cortex that are rich in $5\text{-}HT_{2A}$ receptors as well as hyperactive and hyper-connected upon LSD intake (Delli Pizzi et al., 2023). From a physiological standpoint, the thalamic filtering of incoming external/internal stimuli is regulated through 5-

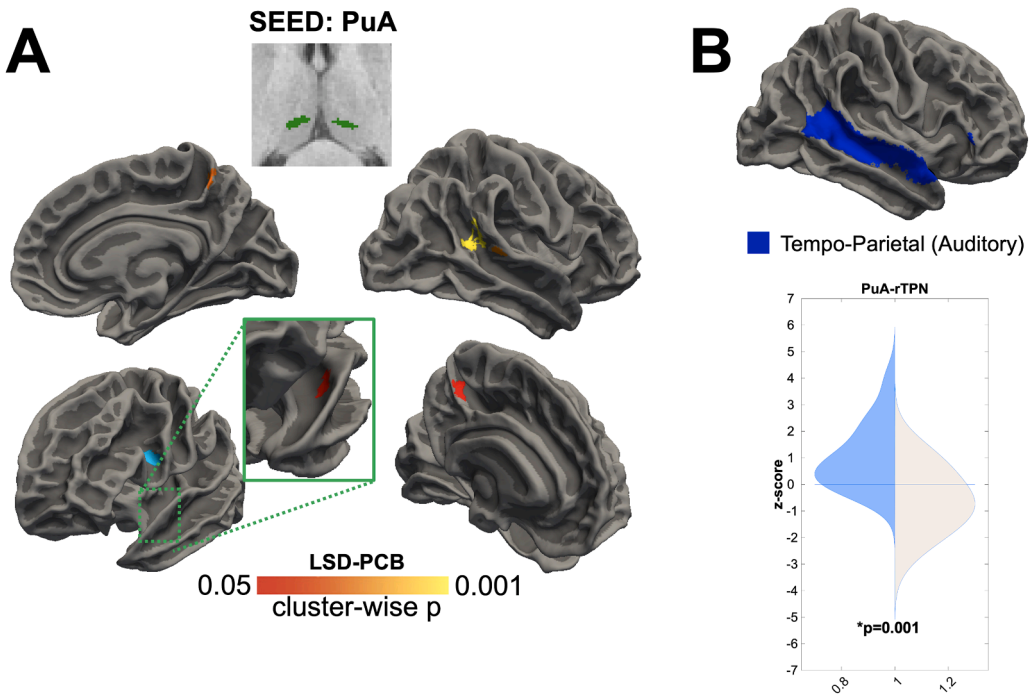

Fig. 4. LSD-induced changes on functional connectivity (FC) of the PuA nuclei. The left panel displays, by performing a vertex-wise analysis, statistically thresholded maps illustrating the FC of the PuA nucleus with the rest of the brain in LSD-PCB condition. Clusters changing from red to yellow and from blue to dark blue indicate, respectively, increased and decreased connectivity. The figure depicts regions with a cluster-wise probability below the corrected p-value of 0.05 and voxelwise (cluster-forming) threshold at corrected $p<0.01$. The right panel shows, by a seed-to-cortical analysis and by color-based labeling,Yeo's networks which show significant changes in the PuA FC under LSD. The violin plots report the distribution of z-score values expressing the connection strength between PuA nuclei and Yeo's networks for each condition (i.e., placebo, LSD). The networks are labeled as follows: LMBB=Limbic Network, component B; TPN=Temporal Parietal/Auditory Network; *l*=left; *r*=right.

HT_{2A} receptors within the dorsal raphe and prefrontal regions (Fig. 5, panel A). Specifically, ascending serotoninergic projection from the dorsal raphe and descending glutamatergic projections from the prefrontal associative areas regulate, directly (Vollenweider and Preller, 2020) or through the striatum, the activity of ventral and non-specific thalamic nuclei (Bennarroch et al., 2008; Draganski et al., 2008; Karnath, 2001; Sadikot and Rymar, 2009). While the ventral and IT nuclei selectively target the primary sensory cortex, the IT complex also exerts a feedback modulation of the striatum (Bennarroch et al., 2008; Sadikot and Rymar, 2009). In particular, several studies have reported that the CM nucleus modulates the sensorimotor striatum (i.e., putamen), whereas the Pf regulates the limbic/associative striatum (i.e., the nucleus accumbens, caudate) and pallidum (Bennarroch et al., 2008; Sadikot and Rymar, 2009; Vollenweider and Preller, 2020).

Therefore, we propose that, under LSD, the binding on 5-HT_{2A} promotes increased excitatory neurotransmission along the prefrontal striatum and dorsal raphe-striatum projections (Fig. 5, panel B). This process, besides activating glutamatergic neurons that directly descend to the thalamus, also triggers the activity of GABA-ergic interneurons connecting the ventral/dorsal striatum to the pallidum and the pallidum to the ventral and non-specific thalamic nuclei. The process generates a downregulation of thalamic filtering and an overflow of sensory stimuli to the cortex.

Our results contribute to understanding the neurobiological processes occurring upon the production of psychotic symptoms. Indeed, although thalamocortical dysrhythmia has been proposed as a key factor promoting psychosis in neurological and psychiatric disorders (Avram et al., 2022; Onofrj et al., 2019), the individual contribution of different thalamic nuclei to these processes is still poorly understood. Notably, the present data did not find a major effect of LSD on LGN activity (Foote et al., 1982), a phenomenon associated with hallucinations (Lee et al., 2016). However, we observed an interesting trend toward a significant increased FC between the PuL nucleus and the DMN, thereby suggesting a possible involvement of aberrant connectivity along this pathway in the generation of visual hallucinations. The PuL, together with the PuI, constitutes the "visual pulvinar", an associative thalamic complex that actively relays and critically integrates the flux of visual stimuli to multimodal areas (Grieve et al., 2000; Benarroch, 2015). Structural alterations of the visual pulvinar and its projections to the posterior cortical areas have also been associated with the presence of visual hallucinations in dementia with Lewy bodies (Delli Pizzi et al., 2014; Onofrj et al., 2019). On the other hand, increased FC within the DMN has been associated with the occurrence of visual hallucinations in Parkinson's disease (Franciotti et al., 2015) and during psychedelic experiences induced by LSD intake (Delli Pizzi et al., 2023).

Our study presents some limitations. First, the sample size is relatively small, and our findings must be confirmed with larger datasets. This issue reflects the difficulty of collecting data from healthy subjects undergoing LSD administration because the protocol requires rigid inclusion/exclusion criteria and complex management of the data collection. Second, the investigation of whether LSD modulates the thalamocortical FC of the medial geniculate nucleus (MGN), a portion of the auditory thalamus acting as a relay station between the inferior colliculus and the auditory cortex is not allowed due to intrinsic limitation of the resolution of the MRI data (Bartlett et al., 2013). The MGN is too small in size to be covered by a sufficient number of rs-fMRI voxels in a seed-based approach and higher resolution information will be needed for further studies. Third, we recognize that the spatial resolution of the rs-fMRI images acquired with a 3T scanner inherently constrains the measure of thalamocortical functional connections and that the time series from adjacent nuclear regions may impinge on our results. However, the smaller seeds used for the FC analyses consist of at least 6 fMRI voxels. Moreover, we would also highlight the good correspondence between the known anatomic connections of thalamic

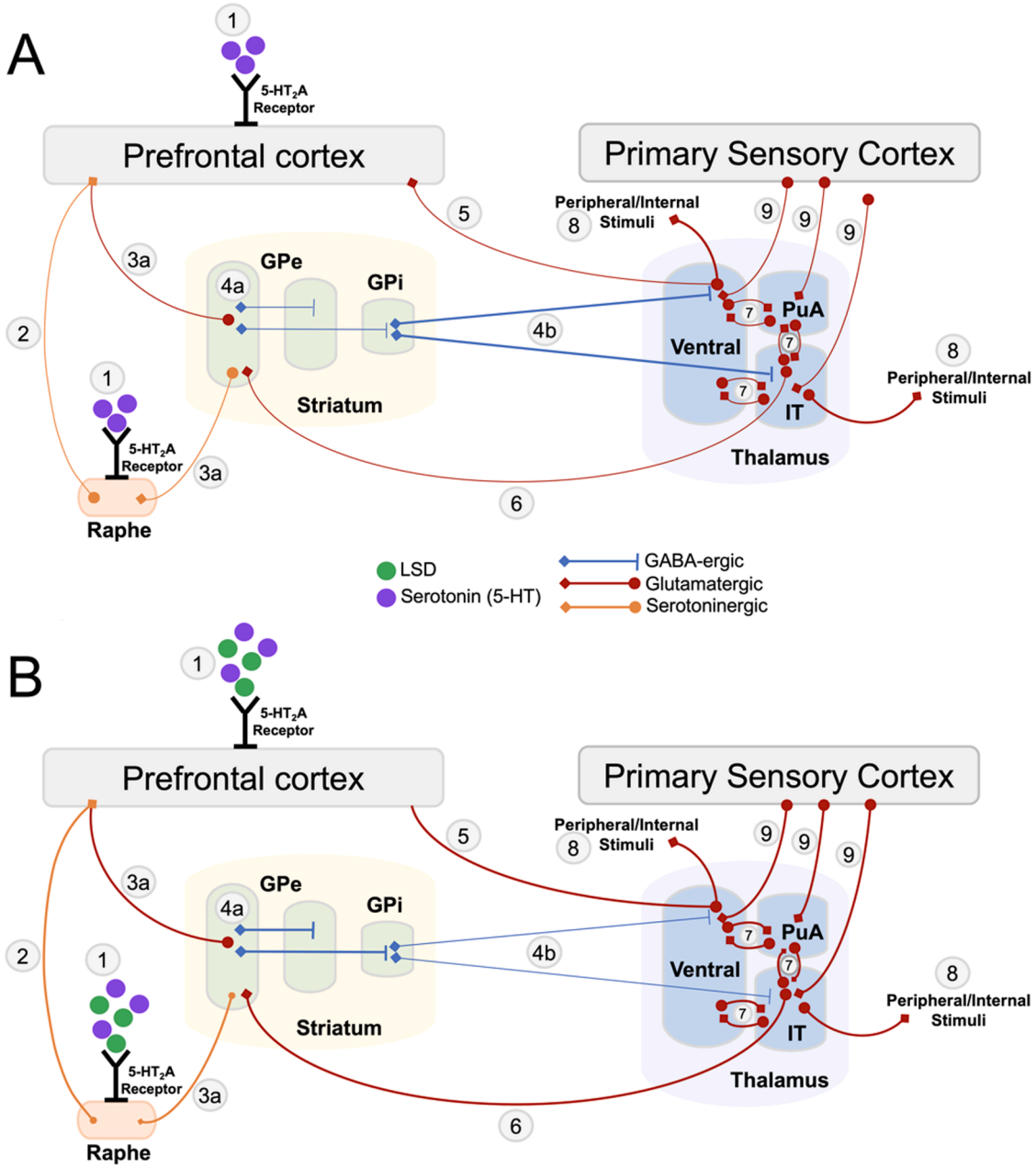

Fig. 5. Proposed model for corticothalamic and thalamocortical modulation under LSD. Panel A: In the placebo condition, thalamic filtering is regulated through the physiological synaptic release of serotonin (5-HT) that binds the 5-HT_{2A} receptors, mainly expressed within the dorsal raphe and prefrontal associative areas (1). When activated, the dorsal raphe also potentiates the prefrontal cortex activation (2). Descending glutamatergic projections from the prefrontal regions (3a) and ascending serotoninergic projection from the dorsal raphe (3b) regulate, through the striatum (3–4) or directly (5), the activity of ventral and non-specific thalamic nuclei. The IT complex, in addition, exerts a feedback modulation of the striatum (6). The ventral and IT nuclei, which are closely interconnected (7), shape the flow of incoming external/internal stimuli (8) to the primary sensory cortex (9). Panel B: LDS, synergically with the 5-HT synaptic release, binds the 5-HT_{2A} receptors (1) and then, as compared with placebo, promotes a greater increased excitatory neurotransmission along the prefrontal striatum and dorsal raphe-striatum projections (2). This process over-activates GABA-ergic interneurons connecting the ventral/dorsal striatum to the pallidum (3), inhibits the interneuron from the pallidum to the thalamus (3–4), and increases the activity of glutamatergic connections between the prefrontal areas and ventral thalamus (5) and between the IT nuclei and the striatum (6). The process generates a consistent increase of intra-thalamic connectivity (7), a downregulation of thalamic filtering (8), and an overflow of sensory stimuli to the cortex (9).

nuclei (Benarroch et al., 2015; Ward, 2013) and the functional coupling of seeds with the cortex that we observed under the placebo condition. Consistent with our prediction, in the placebo condition, the medi-odorsal nuclei displayed positive functional coupling with the DMN. The inferior/lateral pulvinar nuclei were positively coupled with the attention and sensory networks. The medial pulvinar and LGN, respectively, exhibited positive functional coupling with the DMN and visual network.

5. Conclusion

The current study provides new insights into the effects of LSD on subcortical-cortical circuits. It also identifies specific thalamic nuclei that modulate thalamocortical FC associated with the psychedelic experience. Further investigations will clarify whether these processes are common to other psychedelic drugs and how they may impact the treatment of neuropsychiatric disorders.

Data and code availability statement

Functional MRI data from the original study are available from OpenNeuro: https://openneuro.org/datasets/ds003059/versions/1.0.0. Freesurfer toolbox is freely available online (https://freesurfer.net; https://web.conn-toolbox.org). All codes used in the analyses are part of the default toolbox pipelines.

Declaration of Competing Interest

Robin Carhart-Harris is a scientific advisor to TRYP, Mydecine, Usona Institute, Synthesis Institute, Journey Collab', Journey Space, Osmind, Maya Health, Beckley Psytech, Anuma, MindState, Entheos Labs. The authors declare no conflict of interest.

Data availability

Data will be made available on request.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2023.120414.

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