Increased thalamic resting-state connectivity as a core driver of LSD-induced hallucinations

Müller F, Lenz C, Dolder P, Lang U, Schmidt A, Liechti M, Borgwardt S. Increased thalamic resting-state connectivity as a core driver of LSD-induced hallucinations.

**Objective:** It has been proposed that the thalamocortical system is an important site of action of hallucinogenic drugs and an essential component of the neural correlates of consciousness. Hallucinogenic drugs such as LSD can be used to induce profoundly altered states of consciousness, and it is thus of interest to test the effects of these drugs on this system.

**Method:** 100 μg LSD was administrated orally to 20 healthy participants prior to fMRI assessment. Whole brain thalamic functional connectivity was measured using ROI-to-ROI and ROI-to-voxel approaches. Correlation analyses were used to explore relationships between thalamic connectivity to regions involved in auditory and visual hallucinations and subjective ratings on auditory and visual drug effects.

**Results:** LSD caused significant alterations in all dimensions of the 5D-ASC scale and significantly increased thalamic functional connectivity to various cortical regions. Furthermore, LSD-induced functional connectivity measures between the thalamus and the right fusiform gyrus and insula correlated significantly with subjective auditory and visual drug effects.

**Conclusion:** Hallucinogenic drug effects might be provoked by facilitations of cortical excitability via thalamocortical interactions. Our findings have implications for the understanding of the mechanism of action of hallucinogenic drugs and provide further insight into the role of the 5-HT₂A-receptor in altered states of consciousness.

**Significant outcomes**

- This fMRI study demonstrated widespread increases in functional connectivity after the administration of LSD to healthy subjects
- These alterations correlated with characteristic auditory and visual drug effects
- Whole brain voxel-wise global correlation analysis revealed LSD-induced increases in functional connectivity in thalamus and striatum

**Limitations**

- Relatively small sample size
- No dose-response data provided
- Ratings on subjective drug effects did not correspond to the duration of the MRI scan exclusively
Substances known as hallucinogenic drugs are of interest for their specific effects on the mind (1, 2), as well as their potential therapeutic use (e.g. 3–5). These substances alter the human psyche in a profound way, including alterations in cognition, emotions and perception, which are unique among psychoactive drugs (1, 2, 6). Investigations of the neural correlates of these altered states of consciousness might provide insight into the mechanisms underlying these distinctive effects. For empirical and theoretical reasons, it has been proposed that the thalamus is an important site of action for hallucinogenic drugs (7). An important model suggested that hallucinogens disrupt thalamic gating of external and internal signals, leading to increased passage of information across the cortex (8). Several neuroimaging studies indicated that hallucinogenic drugs affect thalamic glucose metabolism and blood flow (9–12), while other evidence reveals that hallucinogens, which mainly act as 5HT2A receptor agonists (13, 14), induce cortical activation via binding on thalamic 5HT2A-receptors with consecutive release of glutamate in the cortex (15–17). Features of increased thalamocortical resting-state functional connectivity (rFC) after the administration of psilocybin (18) and LSD (19) have been reported, but not yet investigated in detail.

The thalamocortical system has also been closely associated with consciousness. Along with the reticular formation, the thalamus seems to be the only region in the brain where small lesions can lead to loss of consciousness (20). Neuroimaging studies found reduced thalamocortical rFC in patients in vegetative states, and this was restored after recovery (21). The thalamus was also found to be the common site of action of at least eight different anaesthetics (22). More specifically, it has been shown that unconsciousness induced by the anaesthetic dexmedetomidine was associated with decreased rFC between the thalamus and the default mode network (23). It is particularly interesting that, after recovery from unconsciousness, thalamocortical connectivity was the only measure that was restored. Moreover, reduced rFC between the thalamus and various cortical regions was reported after administration of the anaesthetic propofol; again, connectivity was restored after recovery (24). Similar results were found in a PET study using two other anaesthetics (25). These observations (and other reasons) have given rise to several theories stating that the thalamocortical system is an essential component for regulating consciousness (22, 26, 27). Hallucinogens such as LSD can be used to induce profoundly altered states of consciousness, and it is thus of interest to test the effects of these drugs on a system that has been so closely associated with consciousness.

Aims of the study

This study sought to investigate the acute brain effects of LSD in healthy participants, using a placebo-controlled design. Resting-state fMRI was used to investigate the effects of 100 μg orally administered LSD on thalamic rFC. We further tested the relationship between thalamic rFC measures and subjective LSD effects on ratings of visual and auditory changes. Our hypothesis was that LSD would increase thalamocortical connectivity relative to placebo and that this effect would be associated with the subjective LSD-induced visual and auditory alterations.

Material and methods

We used a randomised, placebo-controlled, double-blind cross-over design and a washout period of at least 7 days between the two study sessions. Each participant completed two study sessions. The study was approved by the Ethics Committee for Northwest/Central Switzerland (EKNZ) and by the Federal Office of Public Health. Experiments were undertaken with the understanding and written consent of each subject. The study was registered at clinicaltrials.gov prior to study start (NCT02308969). Placebo and LSD were administered orally at 9:00 am. The MRI scan took place at 11:30 am (starting 2.5 h after administration of placebo and LSD), taking into account the time to peak effects of oral LSD (1, 6, 28).

Participants

Twenty-four participants completed the study. Due to our quality assurance criteria (cumulative head motion of >2 mm translation or ≥2° rotation or considerable MRI image artefacts), we had to exclude four subjects, resulting in a final sample of 20 participants (10 male, 10 female; mean age 32.4 ± 10.9 years; range: 25–60 years, all right-handed and all but one with university education). The lifetime drug use of the 20 included subjects is shown in Table S1. None of the participants tested positive for any drug (including tetrahydrocannabinol) in the screening or test session. No serious adverse reactions or events occurred during the whole period of the study in any of the participants.
Assessments of subjective drug effects and plasma levels

Subjective effects of LSD were measured 3 h after administration of placebo or LSD, using the five dimensions of altered states of consciousness (5D-ASC) scale. The 5D-ASC was designed to measure altered states of consciousness via visual analogue scales and is well validated (29). Subjects were asked to retrospectively rate subjective effects as the administration of LSD and placebo. Blood was collected into lithium heparin tubes 2 and 3 h after administration of LSD and placebo respectively. Blood samples were immediately centrifuged, and plasma was rapidly stored at −20°C until analysis. LSD concentrations in plasma were determined using a validated liquid chromatography–tandem mass spectrometry method (28).

Image acquisition and preprocessing

Scanning was conducted on a three Tesla MRI system (Magnetom Prisma, Siemens Healthcare, Erlangen, Germany), using a 20-channel phased array radio frequency head coil. Functional MRI acquisition was based on an interleaved T2*-weighted echo planar imaging sequence, with 35 axial slices with a slice thickness of 3.5 mm, a 0.5-mm interslice gap, a field-of-view of 224 × 224 cm² and an in-plane image matrix size of 64 × 64 – resulting in 3.5 × 3.5 × 3.5 mm³ resolution. To restrict motion, each participants head was fixed using two foam wedges. The corresponding repetition time was 1.8 s, echo time 28 ms and bandwidth = 2442 Hz/pixel. Subjects were asked to close their eyes and not to fall asleep. In total, 300 volumes were acquired (including five dummy scan volumes to ensure signal stabilisation).

Processing was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) and the CONN functional connectivity toolbox 16.0 (http://www.nitrc.org/projects/conn) (30). Five dummy scans were excluded from any further processing, and the remaining volumes were quality checked for severe head motion and image artefacts. Subjects with cumulative head motion of >2 mm translation or >2° rotation were excluded. We further tested for differences in head motion between drug and placebo sessions. Mean composite motion (a measure for scan-to-scan movement) was 0.15 ± 0.07 mm (mean ± SD) for the LSD condition and 0.13 ± 0.07 mm (mean ± SD) for the placebo condition. There were no significant differences between conditions (t = 1.10, P = 0.29; paired t test, two tailed). Additionally, mean and maximum movement was aggregated across all six motion parameters and compared between conditions.

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Again, no significant differences were found (mean movement: t = −0.85, P = 0.42; maximal movement: t = 1.60, P = 0.13; paired t test, two tailed).

All volumes were slice time corrected, realigned, co-registered to the preprocessed T₁-weighted structural volume, normalised into a standard stereotactic space (Montreal Neurological Institute) and smoothed with a 5 mm full width at half maximum Gaussian kernel. Noise correction included scrubbing (31) with a global signal threshold of z > 3 and a composite subject motion threshold of >0.5 mm using ART as implemented in CONN, linear regression of the six motion parameters, of the effects of each condition, and the white matter and cerebrospinal fluid signals, using individual tissue masks obtained from the T₁-weighted structural images. The resulting functional images were band-pass filtered (0.008 < f < 0.09 Hz).

Thalamic resting-state functional connectivity analysis

Three functional connectivity analyses were performed: (i) an ROI-to-ROI (region of interest) analysis using the left and right thalamus as separate sources and ROIs covering the whole brain as targets, (ii) a ROI-to-voxel analysis using the combined ROIs of the the left and right thalamus as the source and voxels covering the whole brain as targets, (iii) lastly, global rFC was assessed by a global correlation analysis. Global correlation is a data-driven, whole brain measure for network centrality, calculated by the averaged correlation coefficients of each voxel to each other voxel of the brain (30).

For all analysis, structural ROIs were defined according to areas of the Harvard–Oxford atlas for cortical and subcortical structures and the automated anatomical labelling atlas for the cerebellum. For analysis i), rFC was assessed using separate ROIs for the left and the right thalamus; for analysis ii), a combined ROI for the left and right thalamus was used. Targets of analysis i) were a set of 130 ROIs covering the whole brain as targets (see Supporting Information for more details). Time courses were compared using bivariate correlations. Effects of the drug and the placebo condition were estimated using two-tailed one-sample t tests. Differences between conditions were assessed using two-tailed paired t tests. Results were corrected for multiple comparisons across all ROI pairs (2 × 130), and all voxels, respectively, using false discovery rate (FDR) procedures. Results were considered significant at a threshold of P < 0.05 (FDR) for ROI-to-ROI-analysis. For voxel-based analysis ii) and iii), cluster
size correction ($P < 0.05$, FDR) based on a cluster-forming threshold of $P < 0.05$, FDR was applied.

Relation with drug plasma concentrations and subjective effect ratings and connectivity

Subsequently, individual plasma levels of LSD, individual subjective ratings on visual and auditory hallucinations and levels of vigilance were correlated (Pearson’s $r$) with individual FC measures for the contrast LSD > placebo.

Ratings on the 5-ASC major dimensions ‘visionary restructuralization’ and ‘auditory alterations’ (the main scales for sensory alterations) were correlated with rFC measures between the thalamus and regions known to be involved in auditory and visual hallucinations respectively (32). Masks were defined according to the Harvard–Oxford atlas for cortical and subcortical structures and the automated anatomical labelling atlas for the cerebellum. Masks of these meta-analytically (32) identified regions (for visual hallucinations: right and left lingual gyrus, right cuneus, right cerebellum, right middle occipital gyrus and right fusiform gyrus; for auditory hallucinations: right and left superior temporal gyrus, right and left insula, right inferior frontal gyrus and right precentral gyrus) were used to extract significant clusters obtained in analysis ii) (cluster size corrected at $P < 0.05$, FDR, based on a cluster-forming threshold of $P < 0.05$, FDR). RFC measures between the bilateral thalamus and ROIs (six for the analysis of visual drug effects and six for the analysis of auditory drug effects) were correlated with individual ratings on the 5-ASC major dimensions ‘visionary restructuralization’ and ‘auditory alterations’ respectively. Results of each analysis were corrected for multiple comparisons (FDR). Statistical significance was assumed at $P < 0.05$, FDR (two tailed).

Furthermore, rFC measures obtained in analysis ii) (mean of all significant voxels) were correlated with plasma levels of LSD obtained directly before the MRI scan (2 h after administration), because resting-state measures were the first sequence in our protocol. Plasma levels were also correlated with rFC measures between the thalamus and ROIs found to be significantly associated with subjective drugs. Statistical significance was assumed at $P < 0.05$ (two tailed).

As alterations in thalamocortical rFC between conditions might be due to differences in vigilance between conditions (33–35), results of rFC analyses (mean connectivity across all significant voxels in ROI-to-voxel analysis, mean of all significant voxels in global correlation analysis, rFC between thalamus and right insula/fusiform gyrus) for the LSD > placebo contrast were correlated with ratings on the item ‘I felt sleepy’ of the 5D-ASC (tenth item of the questionnaire) assessed under both conditions (placebo condition: mean 12 ± SD 20.7%; LSD condition: mean 21.3 ± SD 29.1%).

Calculations were performed using spss version 23.00 (IBM). Additional Methods and Materials are provided in the Supporting Information.

Results

Plasma levels and subjective drug effects

Plasma concentrations of LSD were $0.0 ± 0.0$ ng/ml (mean ± SD) at baseline, $1.3 ± 0.6$ ng/ml (mean ± SD) at 2 h after administration (directly before the MRI scan) and $1.1 ± 0.5$ ng/ml (mean ± SD) at 3 h after administration. Plasma concentrations of LSD after administration of placebo were $0.0 ± 0.0$ ng/ml (mean ± SD) at all time points. LSD caused subjective alterations in all lower-order scales of the 5D-ASC measured 3 h after administration, directly after the MRI scan (see Fig. 1). All ratings were significantly increased compared with placebo ($P < 0.01$).

Functional connectivity analysis

ROI-to-ROI analysis showed significantly increased rFC between the thalamus and regions distributed across the whole brain under LSD,
relative to placebo (all $P < 0.05$, FDR). Overall rFC between the left and right thalamus and 104 of 130 investigated regions was increased. Decreased connectivity was found in one case between the left thalamus and vermis 10 (see Fig. 2a). For detailed results, see Table S2. Similar patterns were observed for the right and the left thalamus (see Figure S1).

The results obtained in the ROI-to-ROI analysis were further investigated using a ROI-to-voxel approach with the bilateral thalamus as the region of interest. Under the placebo condition, we observed connectivity patterns which were consistent with previous findings (23). LSD significantly increased rFC relative to placebo across various regions, with pronounced clusters in the occipital lobe. The results are shown in Fig. 2b; for detailed results, see Table S3.

Global correlation analysis showed increased network centrality in a cluster (841 voxels, $P < 0.000001$, FDR) comprising the left and the right thalamus (266 voxels, and 262 voxels respectively), the left and right caudate (103 and 2 voxels respectively) and the right putamen (41 voxels). A second cluster (186 voxels, $P < 0.000001$, FDR) comprised the left caudate (58 voxels), the left putamen (48 voxels) and the left pallidum (8 voxels). Results are shown in Fig. 3.

**Relation of thalamocortical connectivity to drug plasma levels and subjective effect ratings**

Plasma levels of LSD did not significantly correlate with thalamocortical rFC measures derived in ROI-to-voxel analysis ii) ($r = 0.19$, $P = 0.42$).

RFC measures between the thalamus and the right fusiform gyrus correlated significantly with ratings on the ‘visionary restructurization’ scale ($r = 0.66$, $P = 0.008$, FDR) and connectivity measures between the thalamus and the right insula

![Fig. 2.](image)

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$LSD > Placebo$
correlated significantly with ratings on the ‘auditory alterations’ scale \( r = 0.60, P = 0.021, \text{FDR} \). Results are shown in Fig. 4. No significant correlations were found between these rFC measures and plasma levels of LSD (thalamus-right fusiform gyrus: \( r = 0.42, P = 0.07 \); thalamus-right insula: \( r = 0.16, P = 0.49 \)).

The 5D-ASC item ‘I felt sleepy’ obtained under the drug and the placebo condition did not significantly correlate with any of the investigated rFC measures (see Table S4).

**Discussion**

In this study, we have investigated the acute effect of LSD on thalamic resting-state FC in healthy subjects. Our key finding was that LSD induced globally increased thalamocortical rFC compared with placebo. Subjective drug effect ratings on ‘visionary restructuralization’ and ‘auditory alterations’ correlated significantly with rFC measures between the thalamus and the right fusiform gyrus and insula, two regions known to be involved in visual and auditory hallucinations respectively (32). No significant correlations were found between these measures and LSD plasma levels, which is in line with previous findings on correlations of LSD plasma exposure with subjective drug effects (see 36 and discussion therein). Global correlation analysis indicated that the bilateral thalamus and parts of the basal ganglia showed significantly increased network centrality after LSD administration compared with placebo.

The notion that the thalamus might be a crucial site of action of hallucinogens has been under debate for years (7, 8). One important model proposed that hallucinogenic drugs disrupt thalamic gating and thalamocortical functioning, which was compared with alterations in psychosis (8). In this notion, both states are characterised by a deficit in filter or gate internal and external stimuli, leading to increased input to the cortex. Previous neuroimaging studies reported diverging effects of psilocybin, mesca-line and DMT on the thalamus. Using different imaging modalities, such as SPECT, PET and fMRI, glucose metabolism and blood flow were found to be decreased (9–11), unchanged (37, 38) or increased (12) in this studies. Consistently with our findings, a recent fMRI study reported increased global functional connectivity of thalamic subdivisions after the administration of LSD (19). In contrast with our results, this study additionally reported increased global functional connectivity of several cortical regions. As these authors used a ROI-to-ROI approach, they might be capable to detect alterations in rFC

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**Fig. 3.** Voxel-to-voxel global correlation analysis \( (P < 0.05, \text{cluster size FDR-corrected on the basis of a voxel-threshold of } 0.05 \text{ FDR-corrected}) \). Right is right side of the brain.

**Fig. 4.** Correlations between acute LSD-induced thalamic rFC measures and subjective ratings on the (a) ‘visionary restructuralization’ (VR) and (b) ‘auditory alterations’ (AA) scales.
more sensitively than our approach (using an ROI-to-voxel approach in combination with a conservative threshold).

Functional significance of increased thalamocortical connectivity

The classical notion of the thalamus as a mere relay for sensory information has been revised. The cortex and thalamus form a complex system of extensive and reciprocal connections, capable of generating oscillatory rhythms (39). Corticothalamic pathways are thought to serve integration and transfer of information between cortical regions, possibly via synchronisation (40). Activities of the thalamocortical system are also reflected in rFC measured with rsfMRI. Thalamocortical rFC was shown to be in relatively good agreement with the known anatomy (41), and specific connectivity was observed between the thalamic subdivisions and known resting-state networks (42). Although some links have been described, the relationship between electrophysiological measures and rsfMRI connectivity is still a matter of debate. Associations between connectivity measured by local field potentials and BOLD rFC have been described for a visual thalamocortical network (43), with the highest association between BOLD connectivity and fluctuations in low frequencies (<20 Hz), particularly pronounced for the alpha band. The same study also found that low-frequency oscillations, especially alpha bands, modulated gamma activity within regions of the network, a phenomenon known as cross-frequency coupling. Cross-frequency coupling (CFC; i.e. the modulation of a frequency band by another frequency band) is a relatively new field of interest, and is thought to be important for large-scale integration of local activity via regulation of local high-frequency activity (44). CFC has also been described for frontal (45) and parietal (46) thalamocortical systems. A recent causality analysis reported that thalamic activity drives CFC within the thalamocortical system (47). As regards function, thalamocortical interactions via CFC have been implicated in memory formation (48) and memory retrieval (49). Once again, one of those studies found that the thalamus was the source of the signal (49).

Potential mechanisms of increased thalamocortical rFC under LSD exposure and relationship to subjective drug effects

Taken together, the available electrophysiological data suggest that thalamocortical resting-state FC best corresponds to fluctuations in low frequencies. While slow frequencies are thought to serve large-scale interactions, gamma frequencies represent local processing (50). The observed increase in thalamocortical rFC under LSD exposure might thus represent large-scale interactions via slow frequencies changes, which might facilitate local cortical excitability, possibly via CFC. It can be speculated that this mechanism is actually driven by signals of thalamic origin (47). This model could explain correlations between thalamocortical connectivity and auditory and visual alterations observed in our study. Interestingly, it has already been proposed that synchronised thalamocortical oscillations independent of sensory input may underlie hallucinations (51). Our findings could potentially explain various other effects induced by LSD, some of which have also been proposed to be associated with dysfunction of the thalamocortical system, including synesthesia via coupling of qualitatively different sensory regions (52) or dream-like states (53). However, we restricted our analysis to auditory and visual drug effects, to limit multiple comparisons.

A specific site of action for the observed effects of LSD on thalamocortical connectivity might lie in the reticular nucleus, a thin shell of inhibitory, GABAergic neurons surrounding the dorsal thalamus. The reticular nucleus has also already been proposed as a key element in the action of hallucinogenic drugs (7) and in neural correlates of consciousness (22, 26). LSD mainly acts by activation of serotonin 5-HT₂A-receptors (7), which are expressed in all nuclei of the thalamus (54), including the reticular nucleus (55). Several studies have indicated that 5-HT₂A-receptors often activate inhibitory GABA neurons (7), and this has also been specifically shown for the reticular nucleus (55). The reticular nucleus is known to be involved in thalamic oscillations and manipulation of this system might probably alter synchronised thalamic activity (56). The thalamus is also part of the cortico-basal-ganglia-thalamo-cortical circuitry. Besides its involvement in motor function, this circuitry has also been implicated in other functions like emotions and cognition. The striatum (comprised of caudate and putamen) is the main input structure of the basal ganglia and receives afferents from various cortical regions (57). Output nuclei of the basal ganglia mainly project to the thalamus which then projects back to the cortex (57). Like in the thalamus, 5HT₂A-receptors are expressed in the basal ganglia (54) and involvement of this circuitry in the mechanism of action of hallucinogenic drugs has already been suspected (8). Global correlation analysis in this study revealed significantly increased global rFC of the striatum after the administration of LSD. This observation could suggest that the whole cortico-basal-ganglia-
thalamo-cortical circuitry is involved in changes in rFC induced by LSD.

The thalamus and the thalamocortical system have been proposed as an important neural correlate of consciousness (22, 26, 27), a view that is supported by various empirical findings (see Introduction and Ward, 2011, for an overview). What is critical to these models is the capacity of the thalamocortical system to integrate information via its ubiquitous connections and its ability to exhibit synchronised activity. These features are believed to serve the integration of different sensations (such as perception and memory) within one unified experience, which is one of the phenomenological core features of consciousness. One prominent model, the dynamic core theory, was formulated by Edelman and Tonini (27). The dynamic core represents a cluster of coherent neural activity that integrates fractured activity of cortical regions via synchronisation, but which changes over time, corresponding to different states of consciousness. Although not necessarily restricted to it, the dynamic core essentially involves the thalamocortical system. A second and more detailed model in terms of neurophysiology was introduced by Llinás et al. (26). According to this model, consciousness experience is based on coherent oscillations (∼40 Hz) in the thalamocortical system. Thalamocortical loops arising from specific thalamic nuclei are thereby thought to carry the ‘content’ (e.g. sensory information), while the interaction with non-specific loops allows fusion into a single consciousness experience. It is remarkable that we found widespread alterations caused by a drug known for its potency to alter consciousness in a system that has been closely linked to consciousness itself. Given the framework of the models referred to, our findings might be interpreted as recruitment of data that is usually suppressed data, which enters consciousness by re-entry into the thalamocortical system.

Our study has several limitations. We do not provide dose-response data and used a moderate dose of 100 µg LSD in a relatively small sample of 20 subjects. The treatment assignment was unavoidably unblinded due to the obvious psychoactive effects of LSD. Moreover, the MRI environment might have influenced the subjective drug effects. We do not provide a causality analysis of the thalamocortical interaction and restricted our analysis to auditory and visual drug effects, to limit multiple comparisons. Thalamocortical connectivity was investigated for both thalamic hemispheres; however, it should be kept in mind that the time courses of these structures are also correlated. Furthermore, 5D-ASC major dimensions ‘visionary restructurization’ and ‘auditory alterations’ are not specific for hallucinations, but also comprise other drug effects. Ratings on the 5D-ASC did not cover the whole period as administration of placebo and LSD and thus did not correspond to the duration of the MRI scan exclusively. We did not specifically assess sleepiness during the fMRI but used an item of the 5D-ASC which covered the whole period since administration of placebo and LSD. In comparison with previous investigations of thalamocortical connectivity after administration of a hallucinogenic drug (18, 19), the strengths of our study are the documentation of plasma LSD concentrations, the absence of significant differences in head movement between conditions and a larger, sex-balanced and almost hallucinogen-naïve sample (only two subjects had had used a hallucinogen before, both on only one occasion).

Acknowledgement

The authors would like to express their thanks to Sarah Longhi MD for helpful comments on the manuscript. This work was supported by the Swiss National Science Foundation (grant no. 320030_170249 to ML).

Declaration of interest

The authors declare no competing interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Connectome ring showing the results of the ROI-to-ROI-analysis using the right (a) and left (b) thalamus as sources and ROIs covering the whole brain as targets (see Table S2 for ROI labels). Results are corrected for multiple comparisons across all ROI-pairs (P < 0.05, FDR). The colour bar represents the t value.

**Table S1.** Cumulative lifetime use by the included subjects of legal and illicit drugs.

**Table S2.** Results of the ROI-to-ROI analysis using the right and left thalamus as seeds and ROIs covering the whole brain as targets. Results are corrected for multiple comparisons across all ROI-pairs (2 × 130, P < 0.05, FDR).

**Table S3.** Results of the ROI-to-voxel using the bilateral thalamus as seed (cluster-size corrected (P < 0.05, FDR) on the basis of a cluster-forming threshold of P < 0.05, FDR).

**Table S4.** Correlation between functional connectivity measures and the tenth item (“I felt sleepy”) of the 5D-ASC.