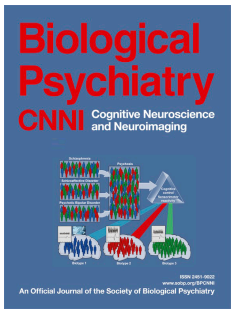

Characterizing thalamocortical (dys)connectivity following d-amphetamine, LSD, and MDMA administration

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Title: Characterizing thalamocortical (dys)connectivity following d-amphetamine, LSD, and MDMA administration

Short title: Substance-induced thalamocortical dysconnectivity

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Abstract

Background

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

Methods

We administrated LSD, d-amphetamine, and 3,4-methylenedioxymethamphetamine (MDMA) in 28 healthy volunteers and investigated their effects on thalamic iFC with two brain networks (auditory-sensorimotor (ASM) and salience (SAL) – corresponding to sensorimotor and prefrontal-limbic cortices, respectively), using a double-blind, placebo-controlled, cross-over design.

Results

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

Conclusions

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

Introduction

Early theories on schizophrenia hypothesized a "dysconnection" syndrome, mainly involving disturbances in cortico-striato-pallido-thalamocortical-circuits (1, 2). Animal studies demonstrated that these circuits are organized topographically – e.g., prefrontal cortices preferentially connect to mediodorsal thalamic nuclei, while sensorimotor areas connect to lateral/posterior thalamic nuclei (3). Findings from *in vivo* investigations in healthy volunteers with resting-state functional magnetic resonance imaging (rs-fMRI) support this topographical organization. Specifically, patterns of intrinsic functional connectivity (iFC – i.e., statistical correlations between signal time-courses of distinct (sets of) brain regions) were identified between thalamic nuclei and cortical areas, consistent with the largely parallel sub-circuits of thalamocortical connections (4). Consistent with the "dysconnection" theories, altered thalamocortical-iFC is one of the most robust large-scale *in vivo* brain imaging findings in schizophrenia (5). Two patterns of thalamocortical dysconnectivity (i.e., reflecting both increased and decreased iFC, not to be confused with "disconnectivity", which denotes a decrease in function only (6)) have been identified consistently: compared to healthy controls, patients exhibit (i) increased iFC (hyperconnectivity) between primary-sensory/motor cortices and the (e.g., posterior/ventrolateral) thalamus and (ii) decreased iFC (hypoconnectivity) between prefrontal-limbic cortices and the (e.g., anterior/mediodorsal) thalamus.

Thalamocortical dysconnectivity has been reported in patients with established schizophrenia (7-9), bipolar disorder (10, 11), first-episode psychosis (12), and individuals at-risk for psychosis (13), suggesting a ubiquitous phenomenon across psychotic disorders. The mechanism underlying thalamocortical dysconnectivity remains unclear but may be related to alterations in neurotransmission, as these appear to modulate iFC (e.g., changes in dopamine transmission modify iFC strength (14)). Therefore, experimental manipulations of neurotransmission could inform on mechanisms underlying thalamocortical dysconnectivity in psychotic disorders.

Research in psychiatry has utilized substance-induced phenomena to model aspects of psychosis (15). For instance, amphetamine has a long-standing tradition as model for psychosis (16), based on two lines of evidence. First, amphetamine increases dopaminergic tone by interacting with the dopamine transporter (DAT) and releasing dopamine (17). This elevation in dopaminergic transmission mirrors increased dopamine levels reported in patients with psychosis (18, 19). Second, amphetamine can induce psychotic states and exacerbate psychotic symptoms in patients with schizophrenia (20, 21). At lower doses, however, psychotic phenomena

are not common (22). It is unclear whether amphetamine induces thalamocortical dysconnectivity, as fMRI reports are scarce.

While current models of psychosis are dominated by dopaminergic and glutamatergic hypotheses (23), the first substance-induced model of psychosis was motivated by LSD-induced effects (24). Typical effects may include altered visual and auditory perceptions, audiovisual synesthesia, derealization, and depersonalization (25, 26). Similar to other classic psychedelics, LSD acts as a partial agonist at the serotonergic 5-hydroxytryptamine 2A (5-HT_{2A}) receptor (25, 27, 28). The apparent similarities between some of the LSD-induced effects and psychotic symptoms catalyzed the serotonergic hypothesis of schizophrenia (15). Certain aspects of this hypothesis may still be relevant today, as psychedelic-induced experiences seem to mimic (some of) the mental phenomena apparent in emerging psychosis (15, 29). We recently argued that thalamocortical-hyperconnectivity with sensorimotor regions may underlie altered perception, as this pattern is consistently reported both in psychedelic-induced and psychotic states (30). Furthermore, thalamocortical-hyperconnectivity is associated with subjective changes in perception following LSD (31) and with psychotic symptoms in schizophrenia (32). A neurobiological mechanism underlying such shared phenomena has been suggested in the form of altered thalamic gating (33, 34). The disrupted thalamic filter model postulates that endogenous or exogenous alterations in neurotransmission (e.g., dopaminergic, serotonergic) potentially disrupt thalamic gating (e.g., via thalamic disinhibition), resulting in cortical sensory flooding, potentially leading to altered mental phenomena. In support, altered dopaminergic transmission (i.e., dopamine synthesis capacity) correlates with thalamocortical dysconnectivity in schizophrenia (9) and psychedelics, which induce alterations in serotonergic transmission, evoke thalamocortical-hyperconnectivity (31, 35, 36). It is unclear whether LSD also induces thalamocortical-hypoconnectivity with prefrontal-limbic cortices. Preller and colleagues (36) found LSD-induced thalamic hypoconnectivity with prefrontal-limbic areas and demonstrated that this effect was depended upon 5-HT_{2A} receptor signaling. Notably, this result was affected by global signal regression (GSR). Using a similar approach without GSR, Müller and colleagues (31) demonstrated an overall increase in thalamocortical-iFC, including to prefrontal-limbic areas and, in another study, increased iFC between several resting-state networks (RSN) covering prefrontal areas and the thalamus (37).

A special case is to be made for 3,4-methylenedioxymethamphetamine (MDMA), the active compound in the recreational drug “ecstasy,” which combines amphetamine-like and LSD-like properties, and may therefore inform on mechanisms of action that are neither amphetamine- nor psychedelic-specific. MDMA is an

amphetamine that elicits its effects mainly via serotonergic rather than dopaminergic neurotransmission (22, 26), and partly also via 5-HT_{2A} receptors (38). MDMA typically induces mild alterations in perception, along with increased feelings of well-being (39). Although not typically used to model psychosis, MDMA can induce psychotic symptoms (40, 41), including delusions, hallucinations, and conceptual disorganization (42). In line with its serotonergic mode of action, evidence indicates that MDMA-induced effects are akin to some LSD-induced neural effects (43), but it remains to be determined whether thalamocortical dysconnectivity is also elicited.

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

Materials and methods

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

Participants and study design

Twenty-eight healthy volunteers were recruited for the study (14 women, mean age 28 ± 4 years). See Supplementary methods and (26) for detailed participant description and study procedures.

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

Assessment of subjective and autonomic effects

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

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

Resting-state functional MRI: data acquisition and preprocessing

For all conditions, structural and functional-MRI data were acquired using a 3-Tesla MRI system (Magnetom Prisma, Siemens Healthcare, Erlangen, Germany), with a 20-channel phased-array radiofrequency head coil. See Supplementary methods for imaging parameters.

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

Seed-based correlation analysis

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

Statistical analyses

Voxel-wise group statistics were performed by applying one-way repeated-measures ANOVAs to the thalamocortical-iFC parameter maps using SPM12 (www.fil.ion.ucl.ac.uk/spm/). A flexible full factorial design was configured using “participants” as between-participant factor and “condition” as within-participant factor (levels: d-amphetamine, LSD, MDMA, and placebo). Statistical testing was limited to voxels contained in the thalamus mask used as target-region for the seed-based analysis. Significant differences were based on

a family wise error (FWE) rate of $p<0.05$ at the cluster level (height-threshold $p=0.001$). The outcomes of interest were thalamocortical-iFC changes induced by the active conditions (d-amphetamine, LSD, MDMA) versus placebo. Thalamic sub-regions were labelled according to the automated anatomical labeling (AAL) atlas (49). IFC values from the thalamic clusters showing substance-induced hypo-/hyperconnectivity (i.e., versus placebo) were extracted, averaged, and correlated with the subscales of the 5D-ASC with Pearson correlation analyses. P-values were Bonferroni adjusted to account for multiple testing.

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

As all three active substances can modify the PP acquired for this study (26), which could in turn bias rs-fMRI results (50), we computed several control analyses to evaluate the influence of PP (see Supplementary methods).

Results

The final sample used for the fMRI data analysis included 25 subjects (mean age 28.2 ± 4.35, range 25-45 years, 12 females). Results regarding substance-induced subjective and autonomic effects have been fully reported elsewhere (26). For the smaller imaging sample (n=25) see Supplementary results and Figures S1 and S2. Repeated-measures ANOVAs demonstrated that experimental sessions did not differ from placebo or each other in FD-based head motion ($F_{3,72}$=1.80, p=0.15) or number of censored volumes ($F_{3,72}$=0.75, p=0.52). Notably, the active conditions differed in the overall strength of the drug effect ($F_{2,48}$=52.9, p<0.001), with LSD eliciting a stronger effect than both d-amphetamine (t(48)=10.17, p<0.001) and MDMA (t(48)=6.39, p<0.001). MDMA elicited a stronger drug effect than d-amphetamine (t(48)=3.78, p<0.001).

Thalamocortical-hyperconnectivity with ASM

Thalamocortical-iFC followed the expected patterns under physiological conditions (i.e., placebo, see Supplementary results; Figures S3).

Compared to placebo, each active substance elicited ASM-thalamic-hyperconnectivity (Figure 1). D-amphetamine elicited hyperconnectivity in one cluster, mainly covering ventrolateral nuclei (Table 1). LSD-induced hyperconnectivity was found in three clusters, covering ventral lateral, and posterolateral nuclei. MDMA evoked hyperconnectivity in one cluster mainly covering the ventral lateral nuclei.

Next, we used a ROI-based approach to test whether the active substances differed in ASM-thalamic-iFC by contrasting them with each other. A repeated-measures ANOVA demonstrated that ASM-thalamic-hyperconnectivity did not differ significantly between substances ($F_{2,48}$=0.85, p=0.43), indicating similar substance-induced changes. Controlling for the overall strength of the drug effects (i.e., including these as covariates-of-no-interest in the ANOVA) did not influence the results ($F_{2,42}$=0.31, p=0.73).

Controlling for PP in the repeated-measures ANOVA did not affect the hyperconnectivity results (Figure S4). Furthermore, ASM-thalamic-hyperconnectivity did not correlate with ΔPP for any of the substances (Table S1), nor with the overall strength of the drug effect (d-amphetamine: r=0.22, p=0.28; LSD: r=0.17, p=0.40; MDMA: r=-0.12, p=0.54).

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

Distinct thalamocortical connectivity patterns with SAL

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

Using a ROI-based approach, we show that SAL-thalamic dysconnectivity differed significantly between substances ($F_{2,48}$=6.73, p=0.003), with LSD eliciting higher iFC values in the whole thalamus than both d-amphetamine (t(48)=2.97, p=0.01) and MDMA (t(48)=3.34, p=0.004), which did not differ from one another (t(48)=0.37, p=0.92). This effect was influenced by the overall strength of the drug effect, i.e., the differences were no longer significant after including these effects as covariates-of-no-interest in the ANOVA ($F_{2,42}$=0.43, p=0.64).

Control analyses demonstrated that PP did not influence substance-induced SAL-thalamic-iFC alterations (Figure S4). SAL-thalamic hypo-/hyperconnectivity did not correlate with ΔPP for any of the substances (Table S1), nor with the overall strength of the drug effects (d-amphetamine: r=-0.22 p=0.28; r=0.36 p=0.07; MDMA: r=-0.11 p=0.59).

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

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

Associations between thalamocortical connectivity and subjective effects

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

D-amphetamine-and MDMA-induced thalamocortical dysconnectivity did not correlate with any of the 5D-ASC subscales (Table S2 and Figure S7). In contrast, LSD-induced ASM-thalamic-hyperconnectivity positively correlated with "blissful state" (r=0.44, p=0.02), "insightfulness" (r=0.49, p=0.01), "audio-visual synesthesia" (r=0.48, p=0.01), and "changed meaning of percepts" (r=0.58, p=0.002) (Figure 2). Only the latter remained significant after adjusting for multiple comparisons (i.e., corrected to p=0.004 (0.05/11)). Similarly, SAL-thalamic-hyperconnectivity also correlated with "audio-visual synesthesia" (r=0.44, p=0.02) and "changed meaning of percepts" (r=0.50, p=0.01), but did not survive correction for multiple comparisons.

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

Discussion

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

Substance-induced ASM-thalamic-hyperconnectivity

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

Consistent with our findings, several studies report LSD-induced thalamocortical-hyperconnectivity with sensorimotor cortices (31, 36, 51). Such effects may be induced by stimulation of 5-HT_{2A} receptors both increasing the activity of pyramidal neurons in the cortex and of cortical and subcortical (i.e., basal ganglia) interneurons, which project to the thalamus, putatively leading to thalamic disinhibition (34). We are not aware of any studies directly investing the effects of d-amphetamine or MDMA on thalamic connectivity with cortical regions/RSNs. However, similar findings have been reported for methamphetamine and methylphenidate. For instance, increased iFC between the thalamus and postcentral cortices was reported in healthy volunteers following methamphetamine (52). Methylphenidate, which binds to DAT and blocks dopamine reuptake, thereby increasing dopamine concentration in the synaptic cleft, similar to d-amphetamine (53), induced hyperconnectivity between a sensorimotor network and a thalamic network (54). Psychostimulant-induced ASM-thalamic-hyperconnectivity may reflect an elevation in dopaminergic transmission, putatively increasing

the activity of striatal medium spiny neurons, which inhibit the pallidal neurons that control thalamic activity, thereby leading to thalamic disinhibition (55, 56). Taken together, these findings provide support for the disrupted thalamic filter model (33), as this model predicts an increase in thalamocortical interactions. ASM-thalamic-hyperconnectivity mainly covered thalamic sensorimotor nuclei (i.e., ventrolateral and posterior thalamic nuclei) for all substances (Table 1). Dysconnectivity peaks differed between substances, possibly due to distinct pharmacological actions or dopaminergic and serotonergic receptor distribution. It is worth noting that the thalamus is not a unitary structure and that thalamic nuclei express distinct dopaminergic D_2-like (57) and 5-HT_{2A} receptor densities (58), which directly affect thalamic function. Therefore, regional differences in receptor distribution may influence changes in thalamocortical-iFC. However, specific receptor-related effects may be difficult to disentangle, due to D_2-like and 5-HT_{2A} receptor overlap in some nuclei (e.g., mediodorsal nucleus, pulvinar) and several other sources that also modulate activity in thalamic nuclei (e.g., striato-pallidal) (see Supplementary discussion).

Importantly, hyperconnectivity between the ASM and thalamic sensorimotor nuclei mirrors previous findings in psychotic disorders (8, 12). The link between alterations in dopaminergic transmission and sensorimotor-thalamic hyperconnectivity is in line with several models of psychosis (2, 55, 59). Additionally, there is also evidence of altered serotonergic transmission in schizophrenia (60). A recent postmortem study using [^{3}H]LSD as radiotracer, demonstrated increased 5-HT_{2A} receptor density in the prefrontal cortex of antipsychotic-naïve patients with schizophrenia, possibly indicating a higher functional sensitivity for this receptor in schizophrenia (61). Furthermore, there is considerable overlap between serotonergic and dopaminergic innervations (e.g., in the striatum) and evidence for serotonergic modulation (i.e., via psilocybin) of dopamine release in the striatum of healthy participants (62). It is unclear whether changes in only one neurotransmitter system are sufficient to drive ASM-thalamic-hyperconnectivity. Notably, patients with schizophrenia receiving antipsychotic medication (i.e., having antagonistic effects at the D_2 receptor) still present ASM-thalamic-hyperconnectivity (9). However, LSD-induced thalamic hyperconnectivity with posterior associative cortices appears dependent upon the 5-HT_{2A} receptor, but some striatal-thalamic interactions do not (63). Interestingly, some atypical antipsychotics (e.g., clozapine, olanzapine) also block 5-HT_{2A} receptors (64), but it is unknown whether patients treated with these medications show ASM-thalamic-hyperconnectivity.

Substance-induced SAL-thalamic dysconnectivity

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

In contrast to our hypothesis regarding SAL-thalamic-iFC, we found the neural effects of d-amphetamine and MDMA similar, despite their predominantly different pharmacological actions (26). However, d-amphetamine and MDMA are structurally related and both stimulate norepinephrine release (65). Furthermore, the neurotransmitter systems have complex interactions at different levels, which might explain the similar neural response (66). Previous findings support d-amphetamine and MDMA-induced SAL-thalamic-hypoconnectivity. For example, a study reported decreased iFC between the anterior cingulum and a cortico-striato-thalamic network following d-amphetamine (44). Similarly, methylphenidate was reported to reduce iFC between SAL and a thalamic network in healthy volunteers (54). Reduced iFC between the thalamus and prefrontal areas was also reported following MDMA administration (67). Interestingly, SAL-thalamic-hypoconnectivity mainly covered ventrolateral nuclei (Table 1). This finding indicates a functional decoupling between the SAL and sensorimotor thalamic nuclei. We speculate that the decoupling between associative cortical and sensorimotor thalamic regions indicates an attenuation of putative sources of noise in the regulation of other cognitive processes (e.g., attentional for d-amphetamine, prosocial for MDMA). In support, methylphenidate also leads to a decoupling between the prefrontal cortices and sensorimotor thalamic nuclei, while sparing other thalamic functional subdivisions (68). Interestingly, the location of the main effects in sensorimotor thalamic nuclei contrasts with findings in patients with psychotic disorders. Specifically, in patients SAL-thalamic-hypoconnectivity was reported in associative thalamic nuclei, especially the mediodorsal nucleus (8, 12, 69). Indeed, there is consistent evidence that this nucleus is involved in the pathophysiology of schizophrenia and that it may play a major role in the patients' cognitive difficulties (70, 71).

Regarding LSD, we observed an increase in functional coupling between association nuclei in the thalamus and prefrontal-limbic areas. Specifically, LSD-induced hyperconnectivity with SAL mainly covered the pulvinar and peaked in the pulvinar, mediodorsal nucleus, and medial geniculate. This finding is in line with

previous reports of increased iFC between distinct associative regions following LSD. For instance, increased iFC between the ventromedial PFC and several other prefrontal regions has been reported (72), as well as increased iFC between several brain networks covering associative cortices (e.g., SAL and default mode network (DMN)) and between these and the thalamus (37, 72). However, in contrast to our finding, Preller and colleagues (36) reported LSD-induced hypoconnectivity with prefrontal-limbic areas. We note that this result was, however, affected by GSR. We detected a somewhat similar effect herein, namely SAL-thalamic-hyperconnectivity was no longer significant after the inclusion of GSR (see Supplementary discussion). Finally, LSD-induced SAL hyperconnectivity with thalamic association nuclei contrasts with SAL-mediodorsal hypoconnectivity reported in psychotic disorders (8, 12), suggesting distinct neural phenomena.

We note that despite the disrupted thalamic filter model predictions (i.e., cortical flooding) we did not observe undifferentiated increases in thalamocortical-iFC. Indeed, SAL-thalamic-hypoconnectivity findings reported for d-amphetamine and MDMA depict functional decoupling rather than an increase in thalamocortical interactions. However, iFC does not allow for the quantification of directionality and it is unclear whether the thalamus drove the SAL-thalamic-hypoconnectivity. Nor is it clear that the thalamus caused hyperconnectivity with sensorimotor areas. These issues may be clarified by employing effective connectivity to assess the potentially causal role of the thalamus in thalamocortical dysconnectivity.

Associations between LSD-induced ASM-thalamic-hyperconnectivity and subjective effects

D-amphetamine and MDMA-induced changes in thalamocortical-iFC were not associated with drug-induced subjective effects. Notably, d-amphetamine and MDMA-induced subjective effects were very mild, and with one exception (i.e., “blissful state” for MDMA) did not differ significantly from placebo (Figure S1). While some studies indicate stronger effects on 5D-ASC following MDMA compared to placebo, including LSD in the study appears to minimize such differences, for detailed discussion see (26). Furthermore, we note that brain-behavior relations are in general difficult to map (73). It is possible that the subjective effects elicited by these substances were too weak to allow for correlations with iFC, indicating an issue with the overall strength of the drug effect (i.e., much weaker effect than LSD) but possibly also the higher specificity of 5D-ASC for psychedelic phenomena, i.e., classic psychedelics elicit in general stronger effects on the 5D-ASC than d-amphetamine or MDMA (26, 74).

LSD elicited typical subjective psychedelic effects (45). Remarkably, ASM-thalamic-hyperconnectivity correlated with several subscales of the 5D-ASC (Figure 2). Such associations are supported by a previous study, which reported significant correlations between subjective changes in visual and auditory perception and thalamocortical-hyperconnectivity following LSD (31). The strongest correlation found in the current study was between ASM-thalamic-hyperconnectivity and the item "changed meaning of percepts". This association remained significant after controlling for the effects of PP and multiple comparisons. Based on the 5D-ASC items covered by this subscale, it is pertinent to assume that both changes in perception and the interpretation of such changes are assessed, and these are partially reflected in some of the iFC changes identified in this study (see Supplementary discussion). Therefore, this subscale may be relevant for psychotic disorders as changes in the interpretation of a precept may explain (some) psychotic symptoms (e.g., delusions)(29).

Strengths and limitations

To our knowledge this is the first study that investigated the neural effects of prototypical psychedelics (LSD), empathogens (MDMA), and psychostimulants (d-amphetamine) in the same participants with a within-subject design. Our results replicate several disparate findings for LSD (31, 36, 51), MDMA (67), and psychostimulants with a similar pharmacological action as d-amphetamine (54). This study also has some limitations. First, we found that the overall strength in drug effect differed considerably between substances. While trying to match the qualitative character of these compounds is not feasible, we note that the between-substance differences in SAL-thalamic-iFC may have been driven by differences in the overall strength of the drug effects. This indicates that beyond pharmacological effects the overall strength of the drug effect may also influence thalamocortical-iFC. Second, subjective effects (i.e., 5D-ASC) were evaluated retrospectively in this study (after ca. 11h), however, evidence indicates that the timing of the assessment (during peak effects or the next day) does not have a big impact on the ratings (75). Third, while LSD-induced changes in thalamocortical-iFC are in line with the a priori expectations of functional manipulations in thalamic nuclei expressing 5-HT_{2A} receptors, the localization of dopaminergic and serotonergic receptors alone did not accurately explain thalamocortical dysconnectivity induced by d-amphetamine or MDMA. Nevertheless, other sources may also modulate iFC in these regions. Forth, it is possible that substance-induced thalamocortical dysconnectivity was secondary to within-network iFC changes, following wide-spread changes in cortico-

cortical iFC. However, control analyses demonstrated that within-network iFC was similarly affected by all substances, despite distinct thalamocortical effects (see Supplementary Results and Figure S8).

Conclusions

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

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Tables

Table 1: Thalamocortical connectivity peaks for the active substances compared to placebo

	Auditory-sensorimotor Network			Salience Network		
Thalamus	**D-Amphetamine**	**LSD**	**MDMA**	**D-Amphetamine**	**LSD**	**MDMA**
IFC changes vs. placebo	increase	increase	increase	decrease	increase	decrease
FC Peak & Cluster size	MDm R x=3 y=-9 z=12 174 voxels	VL_L x=-9 y=-6 z=15 32 voxels VA_R x=9 y=0 z=9 22 voxels VPL_L x=-15 y=-21 z=12 12 voxels	MDm R x=0 y=-6 z=9 117 voxels	VA_L x=-9 y=-6 z=6 5 voxels VL_R x=15 y=-15 z=9 6 voxels	PuM R x=18 y=-27 z=9 17 voxels MDm L x=-3 y=-9 z=15 7 voxels MGN L x=-15 y=-27 z=-3 11 voxels	VL_R x=12 y=-12 z=3 23 voxels VL_L x=-12 y=-15 z=12 17 voxels
Cluster label	VL_L 16.09% VL_R 12.64%	VL_L 46.88% VA_L 21.88% VA_R 18.18% VL_R 13.64% VPL_L 83.33% PUL_L 16.67%	VL_L 13.68% VL_R 11.11%	VL_L 40.00% VA_L 40.00% IL_L 20.00% VL_R 100.00%	PuM R 29.41% VPL-R 29.41% PuL_R 11.76% AV_L 14.29% PuI L 27.27% VPL_L 18.18%	VL_R 91.30% VL_R 64.71% IL_L 11.76% VPL_L 11.76%

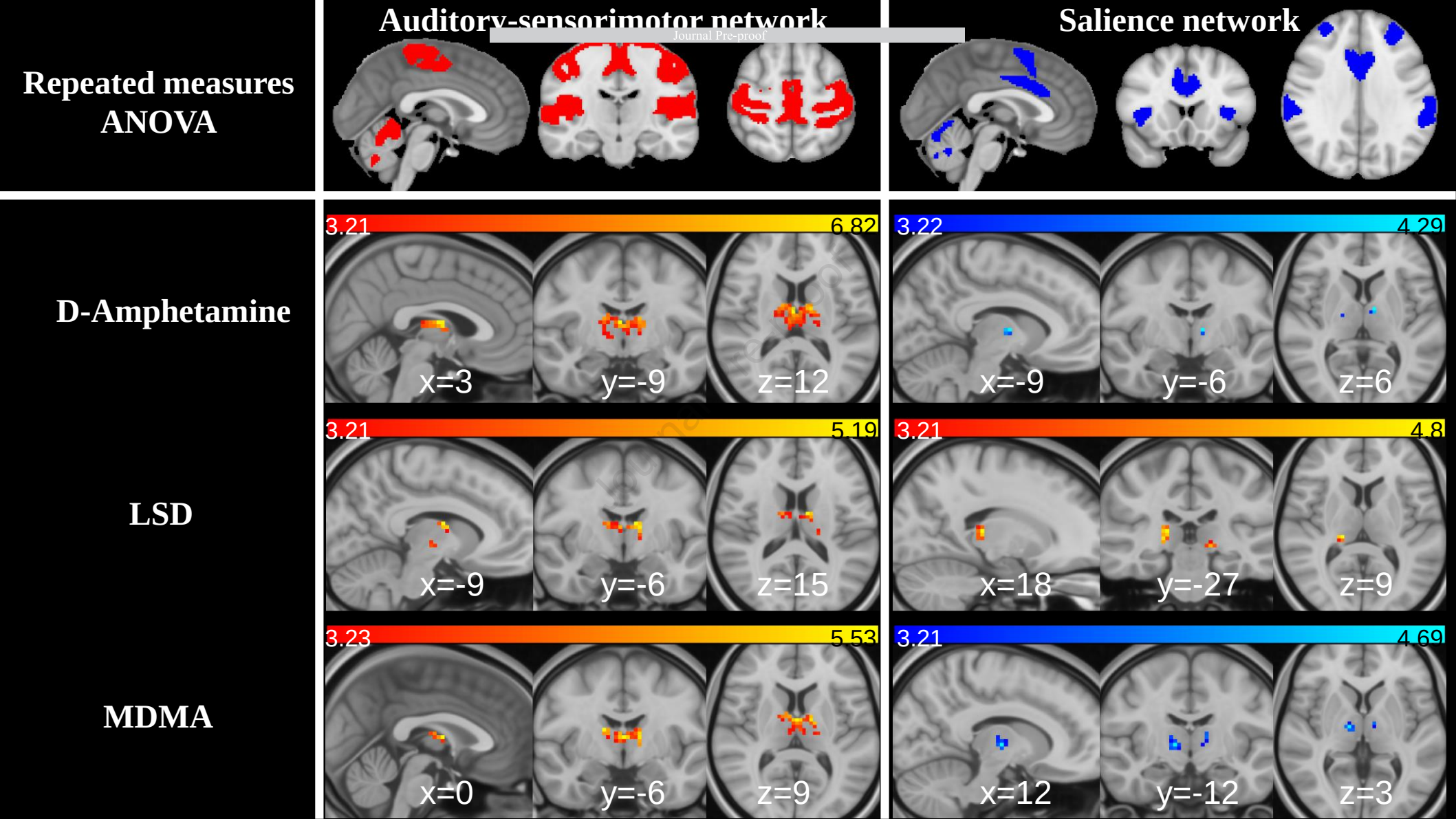
Table 1 depicts functional connectivity cluster peaks with the corresponding MNI coordinates (upper row) and cluster labels (lower row). The percentages (%) shown for the cluster labels reflect the percentage of overlap between a given iFC cluster and the corresponding thalamic nuclei from the AAL. Abbreviations: MDm - mediodorsal medial magnocellular nucleus, VL - ventral lateral nucleus, VA – ventral anterior nucleus, VPL - ventral posterolateral nucleus, IL – intralaminar nucleus, PuM – pulvinar medial, PuL – pulvinar lateral, MGN – medial geniculate, AV – anteroventral nucleus, R – right, L- left.

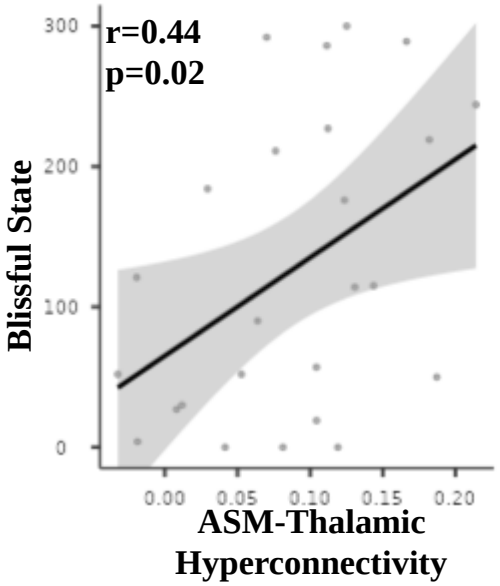
634 **Figure legends**

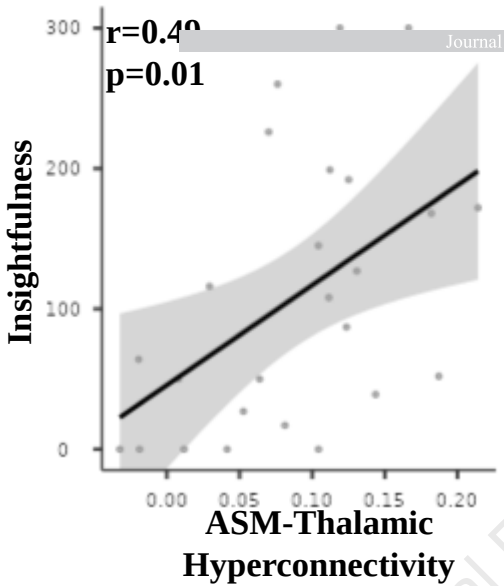
635 **Figure 1.** Depicted are voxel-wise repeated-measures ANOVA parametric maps reflecting contrasts between
636 the active substances and placebo for iFC between the thalamus and the auditory-sensorimotor network (ASM)
637 and salience network (SAL), respectively. All three substances elicited ASM-thalamic-hyperconnectivity
638 compared to placebo (shown in yellow/red). While d-amphetamine and MDMA elicited SAL-thalamic-
639 hypoconnectivity compared to placebo (shown in blue), LSD elicited hyperconnectivity. Color bars reflecting
640 t-values are shown for each contrast. The analyses were computed in SPM12 ($p<0.001$, cluster level corrected
641 $p_{FWE}<0.05$), x, y, and z indicate MNI coordinates.

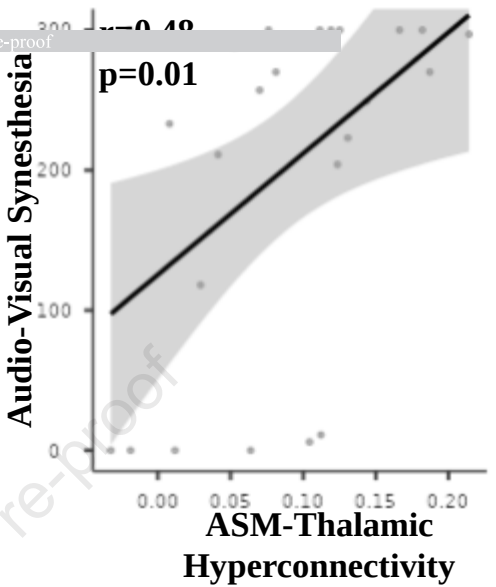
642

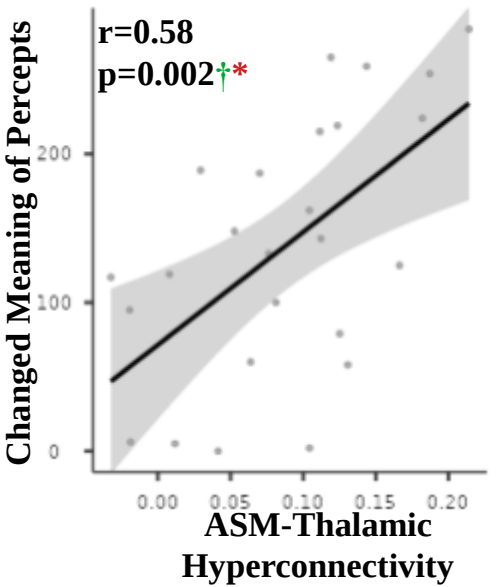
643 **Figure 2.** Correlations between LSD-induced thalamocortical-hyperconnectivity and 5D-ASC measures. *Top:*
644 correlations for LSD-induced ASM-thalamic-hyperconnectivity. *Bottom:* correlations for LSD-induced SAL-
645 thalamic-hyperconnectivity. Abbreviations: ASM – auditory-sensorimotor network, SAL – salience network.

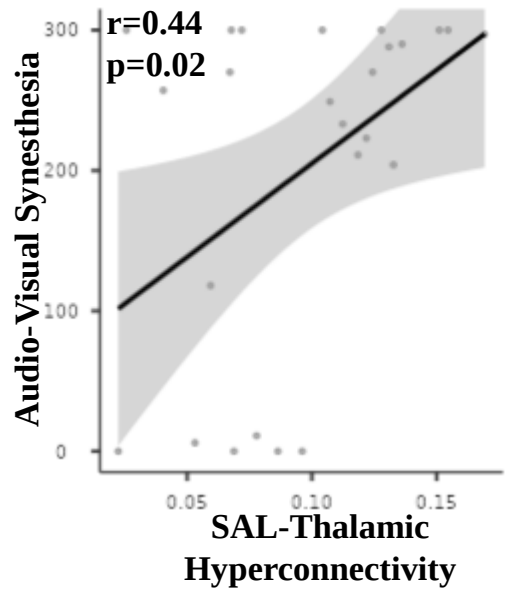


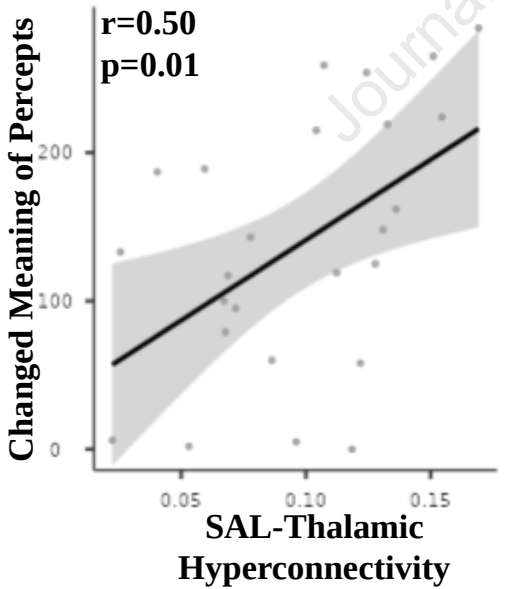












* significant after correcting for multiple comparisons

† significant after controlling the physiological parameters systolic and diastolic blood pressure, heart rate, temperature, and multiple comparisons