Effect of Lysergic Acid Diethylamide on Effective Connectivity of Functionally Anticorrelated Networks

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ABSTRACT

BACKGROUND: Classic psychedelic-induced ego dissolution involves a shift in the sense of self and a blurring of the boundary between the self and the world. A similar phenomenon is identified in psychopathology and is associated with the balance of anticorrelated activity between the default mode network, which directs attention inward, and the salience network, which recruits the dorsal attention network to direct attention outward.

METHODS: To test whether changes in anticorrelated networks underlie the peak effects of lysergic acid diethylamide (LSD), we applied dynamic causal modeling to infer effective connectivity of resting-state functional magnetic resonance imaging scans from a study of 25 healthy adults who were administered 100 mg of LSD or placebo.

RESULTS: We found that inhibitory effective connectivity from the salience network to the default mode network became excitatory, and inhibitory effective connectivity from the default mode network to the dorsal attention network decreased under the peak effect of LSD.

CONCLUSIONS: The effective connectivity changes we identified may reflect diminution of the functional anticorrelation between resting-state networks that may be a key neural mechanism of LSD and underlie ego dissolution. Our findings suggest that changes to the sense of self and subject-object boundaries across different states of consciousness may depend upon the organized balance of effective connectivity of resting-state networks.

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Classic psychedelics are powerful substances with low toxicity that can temporarily alter brain activity and produce profound changes to consciousness (1–5). Their mind-altering effects, which are undergoing translation into modern clinical therapies, may constitute a crucial component of their therapeutic efficacy (6,7). The subjective effects of classic psychedelics are characterized by ego dissolution (3,8), described as a shift in the sense of self and a loss of boundary between the subjective and the objective worlds (9–13). Ego dissolution is suggested as a valid construct (9,10,14) and is thought to involve changes to resting-state network (RSN) activity (6,15,16).

Functional magnetic resonance imaging (fMRI) investigations indicate that activity across the brain is functionally integrated and forms multiple RSNs (17). RSNs are associated with mental activity, and the balance of connectivity between them is associated with the direction of conscious attention (18–20). The default mode network (DMN), which is composed of the medial prefrontal cortex, posterior cingulate cortex, and (bilateral) angular gyrus, is an RSN that activates primarily in the absence of immediate, external, goal-directed attention (21). Its function in self-focused thinking and attention suggests its close relationship to the ego (22). In contrast, the dorsal attention network (DAN) is an RSN that is activated during external-focused task-driven attention (23,24) and is usually considered to be composed of the frontal eye field and the intraparietal sulcus bilaterally. The activity of the DMN and the DAN are identified as anticorrelated and predictably alternate with the inward or outward switching of attention (20). The DMN-DAN anticorrelation can be hypothesized to be a mechanism maintaining the boundary between the subject (observer) and object (observation) that is altered during experiences of psychedelic ego dissolution.

A third RSN, the salience network (SN), acts as the switching mechanism coordinating the direction of attention between internal and external stimuli (25,26) and recruits neural activity in response to stimuli. The SN’s cardinal regions are the dorsal anterior cingulate cortex (dACC) and the anterior insula (AI). The dACC and the AI are consistently coactivated across cognitive tasks (27). However, the dACC is more involved in response selection and conflict monitoring (28,29), while the AI receives greater multimodal sensory input (30,31), detects behaviorally relevant stimuli (32), coordinates responses to stimuli [for example, anxiety (33)], and coordinates the dynamic interactions of anticorrelated networks (34,35).

Coordinated interactions between these networks produce important biopsychological functions. The SN coactivation with the DAN coincides with the detection of bottom-up
features in the visual environment that are infrequent or biologically significant (36–38) and also enables the detection of resources relevant to higher-order goals (32). Furthermore, anticorrelated function between the SN and DMN is a biomarker of efficient cognition (39,40). Trauma to the white matter tracts within the SN that connect the right AI (rAI) and the dACC predicts dysregulated DMN function (41). Importantly, abnormality of the SN connectivity and its anticorrelated interactions is indicative of schizophrenia (42), psychosis (43,44), and internalizing disorders (45) [see Menon (29,32) for a review of associations of SN with psychopathology].

The DMN and SN have previously been investigated in relation to unique senses of self. The SN has been suggested to be involved in an aspect of self, defined as the basic sense of being rooted within a body, termed the minimal or embodied self (12,46,47). This association is supported by changes to the SN documented in psychopathology (48), meditation (49,50), and psychedelic-induced ego dissolution (12) (see Table S1 for a subset of psychedelic findings related to networks and regions of interest). The prereflective qualities that define the minimal self have also been suggested as antecedents of the narrative aspect of self (51,52). The narrative aspect of self is believed to be under the control of the DMN and describes self-related mental activity and personal identity (53,54). For example, the DMN encodes the detail of ongoing experience and performs mental simulation (55,56). These parallels have led to exploratory investigations of the DMN under psychedelic-induced ego dissolution that indicate a general pattern of reduced connectivity (57–60).

Reduced connectivity in the DMN is a feature of improved mental health and has also been identified in meditation (61–64). Seeking cessation of the self in the practice of meditation resembles psychedelic ego dissolution and aligns with an early interpretation of psychedelics noted in filtration theory, which suggests that psychedelics disinhibit cognitive defenses (63–66). Meditation has also demonstrated clinical utility that reflects reports of reduced symptoms of patients experiencing internalizing mental health disorders following psychedelic therapy (60,67–69). Altered self-boundaries may be important to these therapeutic outcomes (6,70,71). For example, an altered relationship between self and other induced by meditation practice that encourages selflessness suggests a neuropsychological mechanism of altered self-boundaries that can enhance well-being (72). Pertinently, a form of meditation termed nondual awareness meditation reduces the anticorrelation of extrinsic and intrinsic activated brain regions (73). Altered subject-object boundaries suggest anticorrelated networks under the control of the SN as a neural mechanism of ego dissolution.

Anticorrelation between the DMN and task-positive networks under the serotonergic psychedelic psilocybin has previously been investigated, with the findings demonstrating reduced anticorrelation when participants experienced ego dissolution under psilocybin (intravenous infusion, 2 mg dissolved in 10 mL saline) (74). However, a similar investigation under the serotonergic psychedelic ayahuasca (oral brew, 2.2 mL/kg body weight, containing 0.8 mg/mL DMT and 0.21 mg/mL harmine) failed to identify anticorrelation changes (75). The inability of functional connectivity analyses to determine the direction of connectivity between networks in these studies suggests the value of adopting mechanistic approaches to determine changes in effective connectivity of networks under psychedelics. Dynamic causal modeling (DCM) is a Bayesian method of inference based on task-based or resting-state fMRI time-series activity of brain regions (76,77). DCM can disentangle hierarchical RSN and regional interactions by determination of the directionality of connectivity. DCM has previously been applied to investigate thalamic connectivity to the cortex under lysergic acid diethylamide (LSD) (78), and DCM has also indicated that the SN is at the apex of the DMN and DAN triple network hierarchy (79). The SN’s position in this hierarchy and its mediating role in controlling the switching of DAN and DMN activity suggests that change to the SN by psychedelics may influence their patterns of anticorrelated activity. The SN and DMN share associations with aspects of self, and the importance of their connectivity in psychopathology suggests that change in their connectivity may be a mechanism of ego dissolution that underlies a shift in the sense of self (80,81).

Therefore, to understand the neural mechanisms of psychedelics that may underlie ego dissolution and inform the biological basis of the subject-object relationship, the directed changes to these networks under 100 μg of the classic psychedelic LSD were investigated. LSD effects were examined across placebo (2 weeks apart from LSD administration), peak effects at 75 minutes, and later effects at 300 minutes post-LSD administration using DCM analysis to reveal regional and network connectivity changes. Ego dissolution (quantified as oceanic boundlessness) was measured using the 5-Dimensional Altered States of Consciousness Scale (5D-ASC) (see the Supplement) (10). Based on previous research that associated the networks under investigation to self and subject-object boundaries, we hypothesized that the association between effective connectivity would change during the peak effects of LSD and ego dissolution. DMN-DAN change may relate to subject-object boundaries, and SN-DMN change may relate to the self. However, the direction of excitatory-inhibitory connectivity change remained exploratory. Moreover, the moderate dose of LSD provided to study participants, whose experience of ego dissolution undoubtedly varied, limits our ability to measure ego dissolution. Therefore, we quantified the results as a measure of LSD-induced connectivity changes that may effectuate ego dissolution. In addition, we measured connectivity of regions composing the networks of interest and the efferent-afferent (hierarchical) connectivity strength between networks.

**METHODS AND MATERIALS**

**Design**

A double-blind, randomized, placebo-controlled crossover study was performed. Testing days occurred 2 weeks apart, and participants were orally administered either LSD after pretreatment with 179-mg mannitol and 1-mg Aerosil (LSD condition), or 179-mg mannitol and 1-mg Aerosil after pretreatment with 179-mg mannitol and 1-mg Aerosil (placebo condition). Resting-state scans (10 minutes each) were taken 75 minutes and 300 minutes following administration. See the Supplement for participant, MRI, and preprocessing details.
Extraction of Region Coordinates Across Subjects

Group independent component analysis of fMRI Toolbox (http://mialab.mrn.org/software/gift) (82) was used to identify the 3 resting-state networks of interest from placebo scans. Preprocessed resting-state fMRI data were spatially sorted into 20 components (83–85) and spatially matched with pre-existing network templates (84).

Networks were composed of cardinal regions constituting a core part of the DMN (86,87), which reliably show anticorrelation with the DAN and SN (87–91) and followed the selection of regions in a related investigation by Zhou et al. (79). Identification of cardinal nodes within each intrinsic network, averaged across our subjects, was located using peak RSN activity of clusters within networks (p = .05) visualized using xjView toolbox (https://www.alivelearn.net/xjview). Associations between peak coordinates and cardinal nodes of network regions of interest (ROIs) were determined by expert visual inspection. The Montreal Neurological Institute coordinates of the selected ROIs are listed in Table 1.

A general linear model was used to regress 6 head motion parameters (3 translation and 3 rotational), white matter signals, and cerebrospinal fluid signals from preprocessed data. One subject was excluded from the analysis because no activation was found in one or more ROIs. We also used global signal regression allowed us to observe anticorrelation in most study participants and was therefore considered appropriate for this study. The time series for each ROI was computed as the principal component of the voxel activity within a 6-mm sphere centered on the ROI coordinates (as listed in Table 1). See Figure S1 for anticorrelation functional connectivity validation.

Specification and Inversion of DCM

A fully connected DCM was specified using the 11 ROIs defined in Table 1, without any exogenous inputs. The DCM for each subject was then inverted using spectral DCM (77,92) to infer the effective connectivity that best explained the observed cross-spectral density for each subject. This procedure was repeated for each of the 3 testing conditions. The DCM fitted the data very well, and the amount of explained variance was more than 85% across all subjects and averaged 91%.

Second-Level Analysis Using the Parametric Empirical Bayes Method

The effective connectivity inferred by spectral DCM for each subject was taken to the second (group) level to test hypotheses about between-subjects effects. A general linear model was used to decompose individual differences in effective connectivity into hypothesized group-average connection strengths plus unexplained noise. Hypotheses on the group-level parameters were tested within the parametric empirical Bayes framework (93), where both the expected values and the covariance of the parameters are taken into account. That is, precise parameter estimates influence the group-level result more strongly than uncertain estimates, which are downweighted. Bayesian model reduction was used as an efficient form of Bayesian model selection (93).

Network-Level Effective Connectivity and Hierarchical Organization

The expected network-level connectivity was computed as the sum of the expected effective connectivity values between the corresponding ROIs. Then, following Zhou et al. (79), the hierarchical connectivity strength of each network was obtained by computing the difference between its averaged efficent and afferent connections (i.e., absolute values) (see the Supplement). A similar approach was used for analyzing hierarchical projections in the monkey brain (94) and prefrontal cortex hierarchical organization in humans (79,95). For clarity, we refer to hierarchical change as afferent and efficent connectivity differences.

RESULTS

Acute Effects

Between-Network Changes in Effective Connectivity. The first resting-state fMRI scan was acquired 75 minutes after administration of LSD, which is during the peak effects of LSD. The connectivity strength between networks was computed as the difference between averaged and unsigned efficent and afferent connection parameters between networks (see Methods and Materials for further details) (79). As shown in Figure 1, at this time, group-level, between-network effective connectivity increased from the SN to the DMN, causing the directed connection to become excitatory. A similar change was observed in the excitatory connectivity from the DMN to the DAN, which resulted in reduced inhibitory connectivity. SN to DMN and DMN to DAN changes from placebo were greatest during the peak effects at 75 minutes and were reduced in the later effects at 300 minutes (Figure 1). These changes show increased afferent connections of the SN and increased efficent connections of the DMN and the DAN.
Effective Connectivity of LSD

**Figure 1.** Network effective connectivity change under peak effects of LSD. (A) Highlighted connections show changes in effective connectivity compared with placebo signifying peak effect. (B) Network effective connectivity change graphed across placebo, peak effects, and later effects. Same data as panels (A) and (B) but plotted as a line graph for better visualization. Values display effect sizes (posterior expectations) of connections in hertz. All displayed connections are for posterior probability > .99. DAN, dorsal attention network; DMN, default mode network; SN, salience network.

**Lasting Effects**

**Between-Network Changes in Effective Connectivity.** LSD effects are also distinguished by changes from placebo that last across time under LSD. Increased DAN to DMN and decreased DMN to SN effective connectivity at 75 minutes remained evident 300 minutes after LSD administration (Figure 1; see Figure S3 for effect size and posterior probabilities). See the Supplement and Figure 2 for between-region changes in effective connectivity for lasting effects.

**Behavioral Associations to Ego Dissolution.** The oceanic boundlessness (ego dissolution) dimension of the 5D-ASC was assessed 720 minutes after the administration of LSD. Effective connectivity changes 75 minutes after LSD administration that were associated with ego dissolution are outlined in the Supplement and presented in Figure S4. We also computed effective connectivity behavioral associations with the global mean scores on the 5D-ASC 720 minutes after the administration of LSD. Effective connections with positive association to ego dissolution overlapped all effective connections with positive association to the global score of subjective effects and accounted for 13 of 15 connections identified (see Figure S4). We used the statistical threshold of posterior probability > .99 for these analyses, which amounts to very strong evidence.

The results demonstrated increased effective connectivity of the DMN to the DAN and of the SN to the DMN during the peak effects of LSD. These changes corresponded with reduced SN increased afferent connections and coincided with a fading of the functional anticorrelation (see Figure S1 for functional connectivity results). Moreover, behavioral associations with effective connectivity suggest that measuring ego dissolution associated with the RSNs captured the overall subjective effects of LSD (see Figure S4).

**DISCUSSION**

This investigation seeks to understand how effective connectivity between anticorrelated large-scale brain networks is related to serotonergic psychedelics and ego dissolution. Our analysis revealed between-network effective connectivity changes that occurred with a diminution of the pattern of anticorrelation under the peak effects of LSD. Bidirectional changes in effective connectivity between the DMN and the DAN were investigated for their hypothesized relationship to subject-object boundaries. We identified reduced inhibition of the DMN to the DAN under the peak effects of LSD. The reduced inhibition is largely lost in the later effects, when ego dissolution dissipates. This indicates reduced inhibition of the DMN to the DAN as a feature of peak LSD effects that may relate to the fading of the functional anticorrelation between these networks. Reduced DMN to DAN inhibition may also represent increased transmission and connection of the narrative self to the sense of object. For instance, the sense of identity may be more readily ascribed to task focus and may, for example, add a quality of identity to the meaning of precepts. Coupling between the DAN and the DMN has also been related to distractibility (96,97). Under psychedelics, distractibility may relate to context sensitivity and confound environmental stimulus from internal stimulus. For example, inhibition of alpha band oscillations under psychedelics may reduce the excitation elicited by external visual stimuli (98). Reduced alpha oscillations have been identified in the DMN (99,100) and may blur the DMN’s capacity for mental simulation with DAN.
breakdown of subpersonal processes underlying the minimal dissolution has previously been suggested to involve the anticorrelation between the DMN and the DAN. Moreover, ego posited function in basic conscious awareness also integrity (12) in occurrences of ego dissolution and its hierarchy during peak effects of LSD when ego dissolution of the boundary between the subject and the object. The opposite effective connectivity from the DAN to object under psychedelics. See the Supplement for region-level changes in DMN-DAN effective connectivity.

Moreover, hierarchical organization and strength of networks were calculated using efferent versus afferent connections (79). The DMN and the DAN showed increased efferent connectivity strength during the peak effects of LSD and segregate from the SN under the peak effects of LSD (see the Supplement). The increase in efferent connectivity strength of the DMN and the DAN reinforces evidence of their fading anticorrelation, which underlies psychadelic subjective effects (see Figure S4) and may contribute to the dissolution of the boundary between the subject and the object. The opposite effective connectivity from the DAN to the DMN also displays reduced inhibition under LSD. However, this change remains over the course of time, suggesting that it is not a primary mechanism of the reduced functional anticorrelation between them or the peak effects of LSD.

Inclusion of the SN in this analysis enabled measurement of its effective connectivity to the DMN and the DAN under LSD. The change to the coordinated balance of networks under the control of the SN by LSD may be an important but overlooked neural mechanism of ego dissolution suggested by the superiority of the SN in this hierarchy of triple networks (79). Previous reports of reduced anticorrelation (74) and reduced SN integrity (12) in occurrences of ego dissolution and its hypothesized function in basic conscious awareness also indicate the value of measuring SN connectivity in the anticorrelation between the DMN and the DAN. Moreover, ego dissolution has previously been suggested to involve the breakdown of subpersonal processes underlying the minimal self, a suggestion that is consistent with Bayesian models of phenomenal selfhood in which the subjective structure of conscious experience is determined from the optimization of prediction in perception and action (54,101,102). The change in the SN effective connectivity under the peak effects of LSD is our most pronounced finding. SN connectivity to the DMN changes from inhibitory to excitatory before returning to inhibitory in the later effects. This flip of valence suggests that SN connectivity change to the DMN is mechanistic in the peak effects of LSD and may indirectly influence the DMN-DAN interactions. The opposite connection, the DMN to the SN, shows an inverse pattern of change from placebo, suggesting reduced DMN influence over the SN, which lasts over time. The SN to DMN connectivity change may therefore be a more likely mechanism of ego dissolution representing a quietening of narrative self in the peak effects of LSD that reduces in the later effects. SN to DMN change is accompanied by increased SN afferent connections and increased DMN efferent connections. We demonstrated that the divergence of SN and DMN efferent-afferent strength under the peak effects of LSD shifts the hierarchical order of the SN beneath the DMN. See the Supplement for region-level changes in SN-DMN effective connectivity.

Taken together, under the peak effects of LSD, a strong increase in change of effective connectivity, and a widening of the gap between the efferent-afferent connectivity strength of the SN compared with the DMN and the DAN shifts in a direction antithetical to normal hierarchical organization (79). This may be said to resemble a collapse—or flattening—of the hierarchy during peak effects of LSD when ego dissolution occurs (Figure 1; Supplement). Similar results that express hierarchical flattening have been identified as the reduced differentiation between global functional integration between cortical regions and decreased modularity between various
brain networks (103–105). Effective connectivity explains this effect as increased excitatory connectivity from the SN to the DMN and increased inhibition from the DMN to the SN. These directed connection changes and the efferent–afferent changes underlie the effects of 100 µg of LSD across our group of participants and may function to alter the relationship between the minimal and narrative senses of self. Although more precise measurement of ego dissolution is required to confirm this hypothesis, the direction of this change suggests that the influence of the minimal self traverses over the narrative self and may relate to the shift in sense of self described under ego dissolution.

Modeling the connectivity of ego dissolution can provide a means to determine the neural mechanisms that underlie the perception of inner and outer reality. This research establishes important steps to identify the change in network interactions associated with the dichotomy of the subject-object relationship under LSD. Understanding network changes that induce psychedelic subjective effects informs the neural mechanisms of psychedelic ego dissolution and advances our understanding of connectivity associated with the sense of self and the sense of separation between the self and the world. The networks involved in this interaction are important in cognitive function and mental well-being, suggesting that understanding the change in networks occurring due to psychedelics may help elucidate mechanisms of psychedelic clinical therapy. Consideration of practical and theoretical challenges may aid future research directed to study ego dissolution and the anticorrelation between brain networks.

Our relatively small sample size (n = 20) is clearly a limitation. Sample size and processing pipeline strongly affect the reliability of results. Small sample size may also account for unexpected placebo effective connectivity in our study participants. A second practical limitation is the large variance of participant subjective responses to a standard dose of LSD (100 µg). Averaging the connectivity of participants experiencing highly variable subjective shifts in consciousness may dilute the effective connectivity representing subjective effects of LSD. An alternative to increased sample size may be pre-determining participant dose response and including only participants with high subjective responses in the analysis, although score variance can benefit the analysis of behavioral associations. Moreover, in this analysis, we did not ascertain to what degree ego dissolution was felt during the acquired scans. Future analyses should pay closer attention to the level of ego dissolution at the time of imaging. See the Supplement for further discussion and limitations.

Future work to extend the current scope of analysis to include connectivity dynamics of additional task-positive networks anticorrelated to the DMN and under control of the SN is required. For example, nonpsychdelic research involving the central executive network, also known as the frontoparietal central executive network, has been conducted to investigate schizophrenia (29,106), meditation (49), and control of attention (23). Its importance is further signified by investigations of large-scale network interactions and anticorrelations with the DMN (22,107,108). Inclusion of the central executive network in anticorrelation investigations may provide a more complete account of anticorrelated network changes associated with ego dissolution.

The between-network balance of anticorrelated activity of specific RSNs depends on subtle adjustments to network activation. Mental well-being and efficient cognition rely on the balance of these interactions. LSD appears to shift the balance of network activation and diminish the anticorrelation between brain networks responsible for internal and external modes of perception. These findings suggest the effective connectivity of anticorrelated network interactions as a network-level neural mechanism of ego dissolution. Observed increases in effective connectivity from the DMN to the DAN and altered network efferent–afferent differences under peak effects may account for the blurring of the boundary between subject and object experienced in ego dissolution. Ego dissolution also involves a shift in the sense of self that may be explained by changes to the interactions between the SN and the DMN. These networks are related to distinct aspects of self. Increased effective connectivity from the SN to the DMN was our most notable finding that emphasized increased salience functions reaching the DMN under the peak effects of LSD. Future research is recommended to relate micro- and meso-level dynamics to identified network effective connectivity changes and to investigate therapeutic associations between subject-object and self-other relationships affected by ego dissolution. This association may help identify network connectivity changes that support psychedelic therapeutic outcomes and help explain the psychological association between ego dissolution and well-being. The neuroscientific study of psychedelic-induced ego dissolution reminds us that constructs and representations of self and internal and external reality exist in connectivity dynamics. This intriguing understanding may inspire future investigations of sentience and consciousness to learn how normal brain function mechanisms contribute to the subject-object relationship and frame our perspective of reality.

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All data are available in the main text, Supplement, or by request to the corresponding author.

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Effective Connectivity of LSD

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