Effect of LSD and music on the time-varying brain dynamics

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Abstract

Psychedelics are getting closer to being widely used in clinical treatment. Music is known as a key element of psychedelic-assisted therapy due to its psychological effects, specifically on the emotion, meaning-making and sensory processing. However, there is still a lack of understanding in how psychedelics influence brain activity in experimental settings involving music listening. The main goal of our research is to investigate the effect of music, as a part of "setting", on the brain states dynamics after lysergic acid diethylamide (LSD) intake. We used an open dataset, where a group of 15 participants underwent two scanning sessions under LSD influence and under placebo. Every scanning session contained three runs: two resting-state runs separated by one run with music listening. We applied K-Means clustering to identify the repetitive patterns of brain activity, so-called *brain states.* For further analysis, we calculated states' dwell time, fractional occupancy and transition probability. We found that the brain states' dynamics during the resting-state and listening to music on both LSD and placebo does not differ significantly. Furthermore, we found that the music itself could potentially have a long-term influence on the resting-state, in particular on the states involving task-positive networks. Collectively, these findings suggest that the whole-brain states' dynamics during psychedelic experience and placebo is relatively stable, however, music, as a crucial element of "setting", can potentially have an influence on the subject's resting-state. Further studies should replicate these results on a larger sample size.

Keywords: brain states, clustering, LSD, music, psychedelics, resting-state

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Introduction

Multiple clinical trials are investigating the therapeutic potential of psychedelics in treatment of various psychiatric diseases, such as depression, end-of-life anxiety, post-traumatic stress disorder, and addiction. As we are getting closer to widely approve psychedelics-assisted therapies, there is a necessity to understand the dynamical brain processes that underlie psychedelic experience in various treatment settings. Treatment setup, also known as "set" and "setting", is one of the key factors modulating the effects of psychedelics and contributing to the positive outcomes of psychedelic experience (Carhart-Harris et al. 2018). Here, we investigate how music, as a part of the "setting", affects the brain states' dynamics during the psychedelic experience.

Psychedelics, such as psilocybin, lysergic acid diethylamide (LSD) or MDMA, cause a profound effect on perception (Kometer et al. 2015; Kraehenmann et al. 2017), consciousness (Lebedev et al. 2015; Liechti et al. 2017; Smigielski et al. 2019), mood (Schmid and Liechti 2018; Forstmann et al. 2020), personality (Lebedev et al. 2016), and behavior (Kometer et al. 2012; Griffiths et al. 2018; Schmid and Liechti 2018). There is growing evidence that psychedelic substances can increase openness (MacLean et al. 2011), enhance creative thinking, along with empathy and subjective well-being (Pokorny et al. 2017; Mason et al. 2019). In addition, altered states of consciousness, which contribute to the "mystical-type experiences" phenomena, seem to be one of the most important factors that can cause positive outcomes of the psychedelic experience (Griffiths et al. 2006, 2011, 2018; MacLean et al. 2011; Barrett and Griffiths 2017; Liechti et al. 2017). At present, psychedelic-assisted therapy finds use in treating depression (Carhart-Harris et al. 2016a; Davis et al. 2021), cancer-related psychological distress (Grob et al. 2011; Gasser et al. 2015; Griffiths et al. 2016; Ross et al. 2016), addiction (Johnson et al. 2014; Bogenschutz et al. 2015; Bogenschutz and Johnson 2016) and post-traumatic stress disorder (Ot'alora G et al. 2018; Mithoefer et al. 2019; Varker et al. 2021). The effectiveness of psychedelic-assisted therapies, however, can be potentially increased by understanding the exact mechanisms of their action on the human body, specifically, the brain.

Acting mostly on serotonergic 5-HT_{2A} receptors and, to lesser extent, on dopaminergic and glutamatergic neuromodulatory systems, psychedelics influence the whole-brain activity and network organization. Specifically, psychedelics modulate the exploration of the brain's repertoire of functional network states during resting state (Tagliazucchi et al. 2014; Lord et al. 2019), alter their segregation and integration (Preller et al. 2020; Luppi et al. 2021), increase whole-brain between-network functional connectivity (Mason et al. 2020), decrease modularity of large-scale brain networks (Lebedev et al. 2015) and support formation of new local-range connections (Petri et al. 2014). In terms of specific brain subsystems, studies report an decrease in activity in medial prefrontal cortex (mPFC), a key region in default mode network (DMN) (Carhart-Harris et al. 2012a; Palhano-Fontes et al. 2015), along with decreased functional connectivity within DMN (Carhart-Harris et al. 2012a, 2016b). Recently, (Parker Singleton et al. 2021) showed that the brain manifests recurrent states of brain network activity during resting state. Since the majority of neuroimaging research on psychedelics focused on comparing brain activity or connectivity at rest, we still need research on how psychedelic experience affects the brain dynamics during different experimental settings.

Music has been an inherent part of spiritual ceremonies for centuries (Guerra-Doce 2015) and appears to be the most frequently used stimuli during psychedelic sessions (O'Callaghan et al. 2020). As a part of the "setting" (Eisner 1997), its role is to enhance and influence the sensory and mental effects of psychedelics as well as serve as a "guide" supporting the whole experience (Bonny and Pahnke 1972). Music

can deeply affect human cognition, therefore, its potential to contribute to the positive outcomes of the psychedelic-assisted therapy should not be underestimated (Barrett et al. 2017, 2018b). Indeed, recent studies confirm that music supports the beneficial effect of psychedelics on mental imagery (Kaelen et al. 2016a), emotion processing (Kaelen et al. 2015, 2016b; Carbonaro et al. 2018), meaning making (Preller et al. 2017) and openness (Kaelen et al. 2018). However, most studies focus on the psychological aspect of using music in psychedelic therapy, rather than investigate its impact on the brain architecture. As a result, brain activity under music and psychedelic influence remains poorly understood. An important question remains: how both of these factors facilitate changes in brain architecture? Can we also observe changes in time-varying brain activity during psychedelic experience combined with music listening?

Our goal was to examine the effect of LSD and music on time-varying brain dynamics. The dynamics of time-varying brain activity can be captured by determining *brain states*, that is, repetitive patterns of cortical activity (Meer et al. 2020; Cornblath et al. 2020). In detail, brain states represent the whole-brain activity at a given time point, which occur repeatedly during certain condition and are reproducible across subjects. The major advantage of this method, in comparison to standard brain activation analysis methods based on General Linear Model (Friston et al. 1994), is the ability to get a deep insight into the brain dynamics in the fast-changing environment or under rapid stimuli, which makes it suitable to track changes in brain activity during psychedelic experiences. Here, we applied the K-Means clustering algorithm (Le Cam and Neyman 1967; Lloyd 1982; Goutte et al. 1999; Allen et al. 2014; Cornblath et al. 2020) to identify brain states and to compare their dynamics during resting-state and music listening. We used an open dataset from the intervention study, where a group of 15 participants underwent two scanning sessions under LSD influence and under placebo. Every scanning session contained three runs: two resting-state runs separated by one run with music listening.

First, we compared resting-state without (1st run) and with music (2nd run) stimuli during psychedelic experience and on placebo, to investigate how music affects brain states dynamics. Based on previous studies on music processing (Blood and Zatorre 2001; Koelsch 2011; Vuilleumier and Trost 2015; Chan and Han 2022) we hypothesized that brain states associated with emotions (limbic network), autobiographical memory (default mode network), and music processing (sensory networks) will be more frequent during music listening in comparison to resting-state. As psychedelics enhance sensory (Carhart-Harris et al. 2012a, 2016b; Császár-Nagy et al. 2019; Aday et al. 2021), emotional (Kometer et al. 2012; Kraehenmann et al. 2015; Grimm et al. 2018) and self-related processing (Smigielski et al. 2020) we also expect that the difference will be more pronounced under LSD influence. Second, we investigated the long-term effect of music under LSD by comparing brain states dynamics during resting-state *before* (1st run) and resting-state *after* music listening (3rd run). Since music is an essential element supporting positive outcomes of psychedelic treatments (Barrett et al. 2017; Kaelen et al. 2018), we hypothesized that music listening on psychedelics will have a lasting impact on the time-varying brain activity. Specifically, we expect to observe different patterns of brain states dynamics for the two resting-state runs. Similarly to the previous comparison, the difference will be higher for the LSD condition when compared to the placebo condition.

Methods

Dataset

Data used for analysis was obtained from the OpenNeuro database (OpenNeuro Dataset ds003059) (Carhart-Harris et al. 2016b; 2020). Dataset included preprocessed fMRI scans obtained from 15 participants in two sessions, each consisting of three runs. Detailed recruitment of subjects is described in Carhart-Harris et al. (2016b).

Experimental procedures

Full description of the experimental procedures can be found in Carhart-Harris et al. (2016b). In summary, twenty healthy participants were recruited for two sessions of fMRI scanning. Sessions were separated by at least 14 days. In one of these sessions, subjects received LSD (75 μg in 10 mL saline) and in the other placebo (10 mL saline). Following the post-infusion acclimatization period, fMRI scanning started 115 minutes after the infusion. Each session consisted of three runs, lasting approximately 7.5 minutes. During each scan participants were encouraged to keep their eyes closed and relax. First and third runs were resting-state, while the second involved listening to music (Fig. 1). Two tracks from the album Yearning, made by ambient artist Robert Rich and classical Indian musician Lisa Moskow were chosen for listening during this run. Each participant listened to both tracks, in a balanced order across conditions (Kaelen et al. 2016a). For data analysis we included fMRI images from all runs, as our main goal was to investigate both the effect of LSD and music on brain states' dynamics.

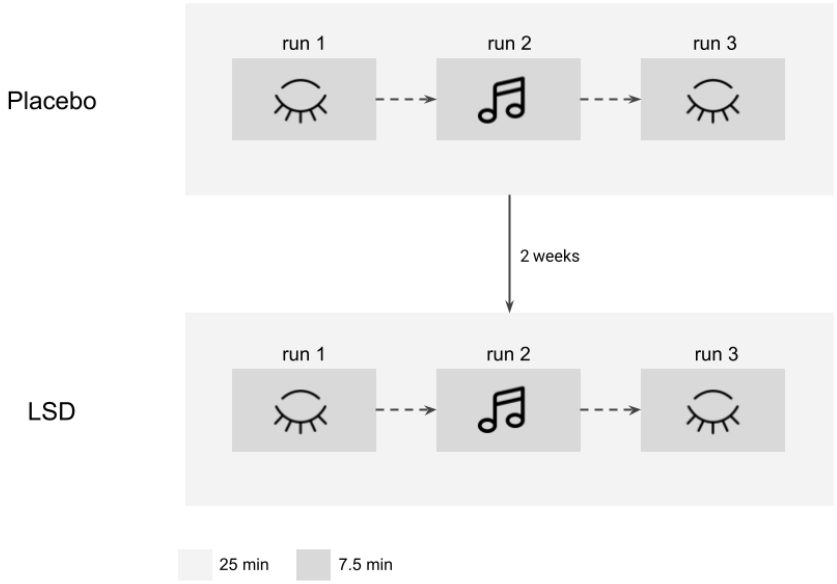

Fig. 1 Study design. Participants underwent two single-blind fMRI sessions in either LSD or placebo condition. The order of conditions was balanced across subjects. Each session included three scans, 1st and 3rd with no stimulation (resting-state) and the 2nd, which involved listening to music. Musical Notes, Closed eye icon by Icons8.

Data acquisition and preprocessing

The detailed overview of data acquisition and preprocessing is described in Carhart-Harris et al. (2016b). In brief, BOLD fMRI data acquisition was performed using a gradient echo planar imaging sequence, with TR

= 2 s, FOV = 220 mm and 64 × 64 acquisition matrix. Preprocessing of the BOLD fMRI data consisted of: 1) removal of the first 3 volumes; 2) despiking (AFNI); 3) slice-time correction (AFNI); 4) motion correction (AFNI); 5) brain extraction (BET, FSL); 6) registration to anatomical scans (FSL, Freesurfer, manual); 7) non-linear registration to 2mm MNI brain (Symmetric Normalization (SyN), ANTS); 8) scrubbing; 9) spatial smoothing (AFNI); 10) band-pass filtering between 0.01 to 0.08 Hz (AFNI); 11) de-trending (AFNI); 12) regression of the nuisance regressors (Symmetric Normalization (SyN). After the preprocessing procedures 15 and 12 participants were included for analysis, from resting state and music runs respectively.

Clustering of BOLD scans using KMeans algorithm

In order to represent brain activity and its fluctuations as so-called brain states (Cornblath et al. 2020) we applied the K-Means clustering algorithm (Le Cam and Neyman 1967; Hartigan and Wong 1979; Lloyd 1982; Goutte et al. 1999; Allen et al. 2014; Cornblath et al. 2020). K-Means is an unsupervised machine learning method that allows to group data points with similar spatial properties with no prior knowledge about the structure of the data. Here, brain states are defined as repeated patterns of brain activity, represented as clusters in the regional activation space. Prior to clustering timeseries into discrete brain states, we concatenated all data points into one $N \times P$ array, where N - number of timepoints, P - number of features (ROIs). The length of N was equal to 18228 (15 subjects × 868 resting-state scans + 12 subjects × 434 music scans). Such a procedure ensures the correspondence of brain states' labels across all subjects, sessions and runs. To determine the most appropriate number of brain states, we applied the K-Means algorithm with Euclidean distance as a measure of similarity. Following Cornblath et al. (2020), we identified the maximum number of k. For both conditions (LSD and placebo) the length of timeseries was equal to 217, therefore to analyze the transitions between states based on the $k \times k$ matrix, k^2 must be < 217. Based on that, we run the K-Means clustering with k ranging from 2 to 14. We repeated this procedure 100 times, with random seed = 42 to ensure reproducibility. For the main criterion for choosing the optimal k, we selected the gain in variance explained for a unit increase in k. Variance explained is defined as the ratio of between-cluster variance (sum of squares) to total variance in the data (within-cluster plus between-cluster sum of squares) (Cornblath et al. 2020). As shown in Supplementary Fig. 2, for $k > 4$ gain in variance explained is equal to less than 1%, therefore we have chosen $k = 4$ as the most optimal number of brain states (Cornblath et al. 2020). These results are consistent with Parker Singleton (2021), who also used the K-Means algorithm to cluster resting-state scans of this dataset and also found $k = 4$ as the most appropriate number of k. Additionally, for each run we calculated the number of absent states, which showed that for $k > 13$ the correspondence of brain states across participants was not maintained (Supplementary Fig. 3).

Correlating brain states with large-scale brain networks and Neurosynth topic maps

After the KMeans clustering, we correlated each brain state with 7 a priori defined brain networks. We used Schaefer 2018 atlas parcellation, with 400 ROIs and 2 mm resolution (Schaefer et al. 2018). The parcellation was downloaded from a publicly available repository (https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal, commit: 703454d). The parcellation was provided together with labels that indicated the membership of each parcel to one of the 7 large-scale networks. As a result, each brain state activity could be associated with positive or negative correlation with each large-scale brain network, as shown on Fig. 2.

Additionally, to get more insight into the brain states' characteristics we correlated each state with several uniformity test maps obtained from the Neurosynth database (https://neurosynth.org/). Uniformity test maps are defined as z-scores from a one-way ANOVA testing whether the proportion of studies that report activation at a given voxel differs from the rate that would be expected if activations were uniformly distributed throughout gray matter. Here, we correlated each brain states' spatial distribution to 11 uniformity test maps which can potentially describe the psychedelic experience: social cognition, attention, music, emotional, somatosensory, happy, pain, reward, language, anxiety and autobiographical memory. This procedure allowed us to describe each state in terms of associated mental states (Fig. 3).

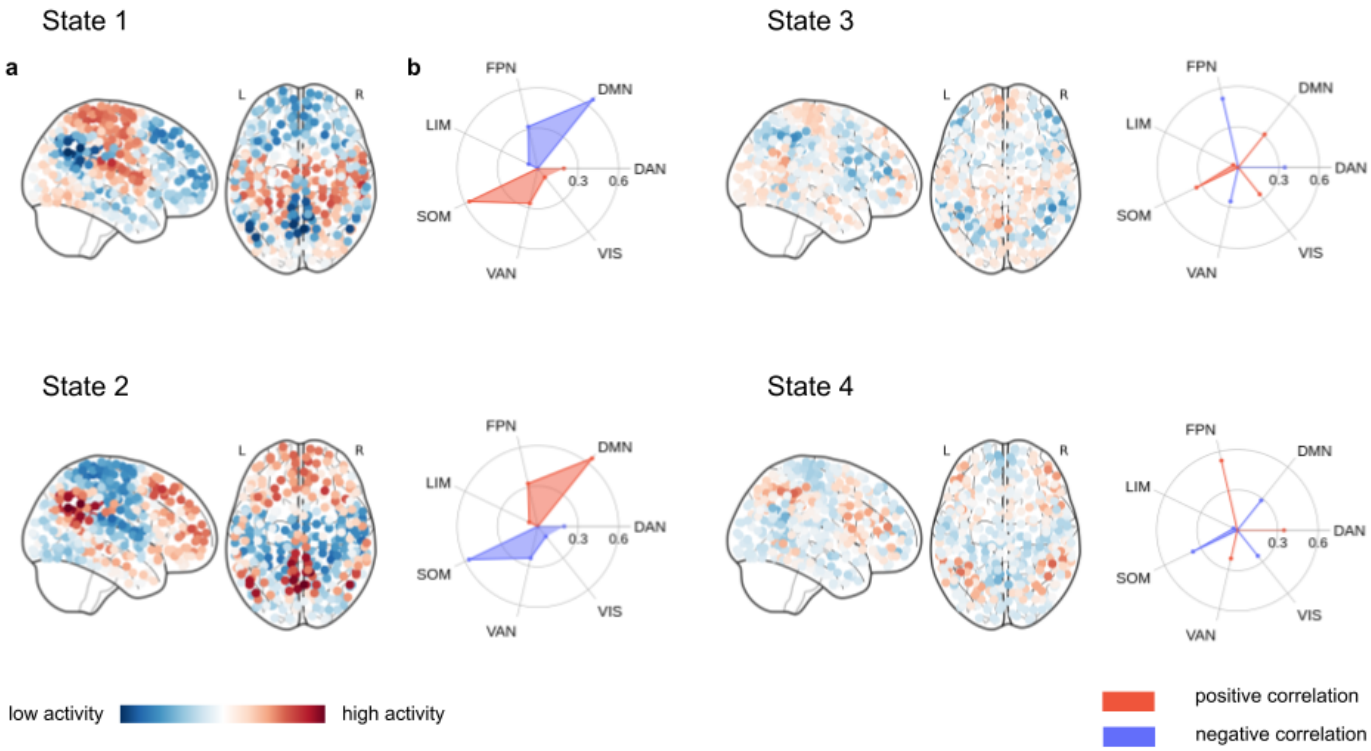

Fig. 2 Brain states' correlation with large-scale brain networks. **a** Each state is defined as a characteristic pattern of brain activity, which fluctuates from high to low. **b** Correlation with 7 large-scale brain networks obtained from Schaefer 2018 parcellation (FPN - frontoparietal network, DMN - default mode network, DAN - dorsal attention network, VIS - visual network, VAN - ventral attention network, SOM - somatomotor network, LIM - limbic network).

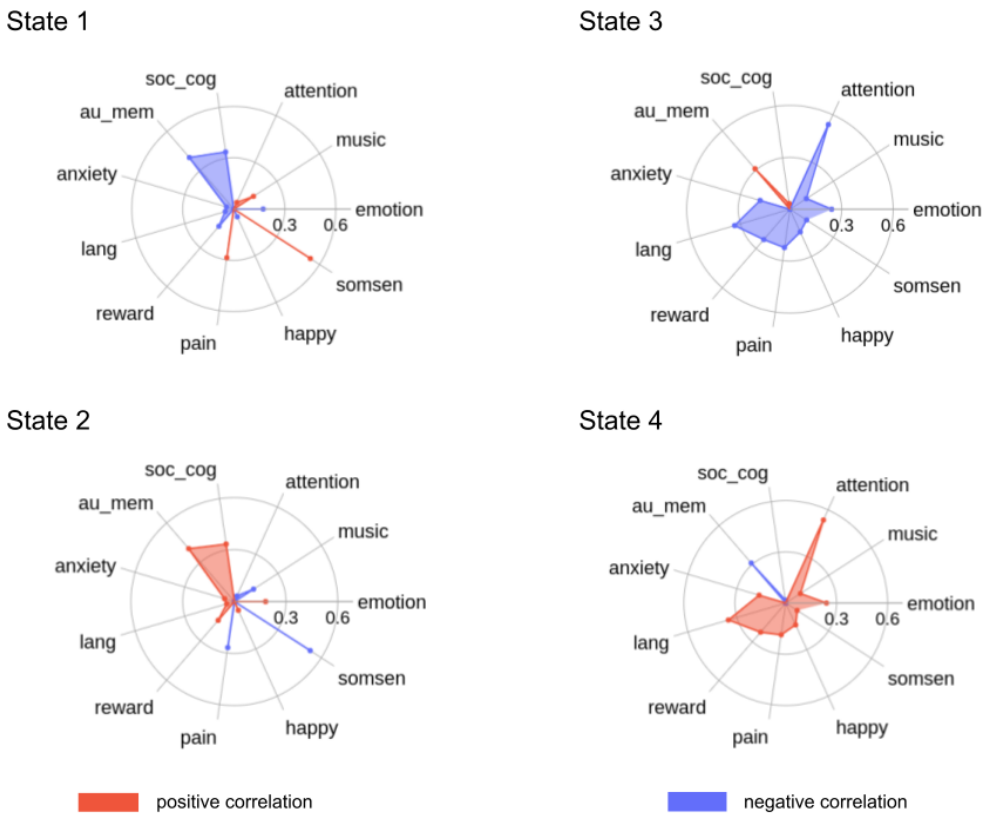

Fig. 3 Brain states' functional profiles. Uniformity test maps obtained from the Neurosynth database can potentially describe each brain state in the terms of potentially associated mental states, which can occur during psychedelic experience (soc_cog - social cognition, emotion - emotional, somsen - somatosensory, lang - language, au_mem - autobiographical memory).

Analysis of the time-varying brain activity

Next, we calculated three measures that allow us to investigate and analyze dynamics of the brain states: fractional occupancy, dwell time, and transition probability. Fractional occupancy is defined as the number of scans classified as the particular state, divided by the total number of scans. We can interpret the fractional occupancy measure as a time spent in a particular brain state relative to the total time spent during a run. Dwell time is calculated as the number of all time points classified as a particular state divided by the number of their consecutive appearances (eg. 11122112221, dwell time for state 1 equals 2); it represents the mean length of a duration of each state. Transition probability is defined as the probability of transitioning from state i to state j. The measure allows us to infer what was the common transition pattern between all brain states. Each measure was calculated on a subject level.

Statistical analysis and reproducibility

The main goal of our analyses was to investigate the effect of music on brain state activity after LSD intake. To approach this goal, we performed two major statistical comparisons. First, between resting-state prior to music listening (1st run) and music listening (2nd run), and second between both resting-state sessions (pre- and post-music experience; 1st and 3rd run) (Fig. 1). To check whether the analyzed variables (fractional occupancy, dwell time and transition probability) are normally distributed we performed a series of Kolmogorov-Smirnov tests. Statistical analyses for fractional occupancy and dwell time for both (LSD and

placebo) conditions were calculated using the paired t-test for related samples. Since the transition probability measures did not meet the criteria of normal distribution, we used the permutation non-parametric test to perform statistical analyses for both LSD and placebo sessions. In the permutation test we used the mean difference between two conditions, with 10000 permutation samples and random seed = 0. We set up the level of alpha to 0.05 in all analyses. Due to the small group sample (15 participants in resting state run, 12 in music listening run), thus a low power of the study, t-test results were not corrected for multiple comparisons. To ensure reproducibility, Python code for all analyses is publicly available (see section "Code availability"). Note that these analyses were performed on a small sample, therefore the results should be interpreted with caution and considered as preliminary.

Code availability

All code scripts used for analyses can be found at: github.com/igaadamska/LSD-music-brainstates

Results

Brain states characteristics

To investigate changes in the brain signal dynamics and analyze them under the influence of music listening and psychedelic experience, we identified repeated patterns of brain activity — *brain states*. To cluster fMRI timeseries into brain states, we used the K-Means clustering algorithm, which assigns each data point to the nearest of the a priori defined centroids (Le Cam and Neyman 1967; Hartigan and Wong 1979; Lloyd 1982). After calculating K-Means' measures (within- and between-cluster sum of squares, silhouette score, variance explained, gain in variance explained; Supplementary Fig. 1, 2), we chose $k = 4$ as the most optimal number of centroids (see "Methods").

The clustering analysis revealed four brain states, each of which can be characterized by a specific pattern of cortical activity of 7 a-priori defined networks (see "Methods"). State 1 is described by the high activity of the somatomotor (SOM) network and low activity of the default mode (DMN) and frontoparietal (FPN) networks (Fig. 2). Its activity pattern highly corresponds to the activation of the primary brain regions in response to basic visual, motor or tactile stimuli. Additionally, correlation with Neurosynth topic maps revealed that this state can manifest during music listening or pain perception (Fig. 3). State 2 presents the opposite activation pattern to state 1, which is characterized by a high activity of the DMN and the FPN, along with a low activity of the SOM network (Fig. 2). High DMN activity suggests that this state might be related to self-referential processing or mind-wandering, that are often altered after psychedelics intake (Carhart-Harris et al. 2012b, a; Kometer et al. 2015; Johnson et al. 2019). In line with that, Neurosynth correlation analysis showed a strong similarity of this state activity to activity patterns occurring during social cognition and autobiographical memory (Fig. 3). Moreover, simultaneous activity of the DMN and the FPN could be also relevant to working memory performance (Cocchi et al. 2013). State 3 is associated with the combined medium activity of DMN, SOM and VIS networks and low activity of task-positive networks (Fig. 2). This pattern of activation could be associated with self-referential and simple sensory stimuli processing; VIS networks activity may reflect the processing of visual stimuli, which is important in the context of the psychedelic experience for processing hallucinations (Kometer et al. 2013b; Johnson et al. 2019; Aday et al. 2021). Interestingly, based on the Neurosynth topic maps analysis, combined activity of these three networks could be crucial for autobiographical memory processing,

similarly to state 2 (Fig. 3). In contrast, state 4 is described by the high activity of task-positive networks, that is, FPN, DAN and VAN (Fig. 2). Such brain activity is characteristic for facilitating cognitively demanding tasks (cognitive control), executive functions and attention, together with integration of sensory, emotional, and cognitive information (Downar et al. 2000; Vossel et al. 2014). Here, this state could be responsible for integrating different aspects of the psychedelic experience. Results revealed by Neurosynth correlation analysis showed strong correlation with activity pattern occurring during attention-demanding tasks, what is consistent with the state's characteristics (Fig. 3).

Effect of LSD on brain states during music experience

The identification of brain states with the use of the K-Means clustering along with network and Neurosynth topic maps correlation analysis (see "Methods") allowed us to characterize the dynamics of time-varying brain activity during different runs of placebo and LSD sessions. To investigate the difference between resting-state and music experience we performed a series of comparisons involving both sessions (placebo and LSD) and 1st (resting-state) and 2nd (listening to music) runs (Fig.1). We hypothesized that brain states associated with emotion (limbic network), autobiographical memory (default mode network), and music processing (sensory networks) will be more frequent during music listening in comparison to resting-state. We did not include data from the 3rd run (resting-state), as we expected that it may be affected by the 2nd run (music listening). For the analyses, we used data from 12 subjects instead of 15, since 3 had technical problems in music listening conditions (see "Methods").

For each state we calculated measures which describe its dynamics: dwell time, fractional occupancy and transition probability (see "Methods"). All of the measures were included in these analyses. Firstly, using paired t-tests we assessed whether the observed fractional occupancy and dwell time for music listening (2nd run) differ from resting state (1st run) (Fig. 4a, b). We performed this analysis for each session, yet the results were not statistically significant. Even though, in the direct comparison of 1st and 2nd runs we did not observe any significant effect, there is a possibility that the difference between 2nd and 1st run could be significant. Therefore, we performed a similar analysis using paired t-test and differences between both runs (2nd run - 1st run), and compared them between LSD and placebo conditions for each state. Similarly, the results were not significant for both fractional occupancy and dwell time (Fig 4a, b). Since we were mostly interested in the effect of psychedelics during music experience, in the next step we compared the 2nd run involving music listening between placebo and LSD sessions. The results showed that for the music listening subjects' dwell time for state 4 was higher in the placebo compared to LSD session (paired t-test, $t = 2.24$, $p = 0.04$). These findings suggest music listening on LSD resulted in lower duration in state 4, associated with high activity of task-positive networks.

After finding that placebo and LSD conditions do not show significant differences in terms of state's fractional occupancy or dwell time, we were interested in how psychedelic experience combined with music can influence frequency of switches between brain states. To characterize the brain states' dynamics, we computed transition probability matrices for each session and run (see 'Methods'). The transition probability measures did not meet the normal distribution criteria, therefore for the statistical analyses we used a nonparametric permutation test (see "Statistical analysis and reproducibility"). To assess the difference in states' transitions between music listening and resting state for each session, we performed two comparisons. In the first step, we compared transition probability between the 2nd and 1st run for the placebo session (Supplementary Fig. 4a). Secondly, we performed the same analysis for the LSD session (Supplementary Fig. 4b). For both analyses none of the results was statistically significant. Next, we wanted

to track changes in transition probability that can occur during music listening between LSD and placebo (Supplementary Fig. 4c). Also here none of the results met the statistical significance criteria. Finally, we assessed whether the difference between both runs (2nd run - 1st run) could be significant (Supplementary Fig. 4d), however, the statistical analysis revealed that there is no effect.

Taken together, these results suggest that during psychedelic experience the difference between resting state and music listening is not observable, and the both conditions may be associated with a similar pattern of brain states' dynamics. Interestingly, music listening during placebo was associated with higher mean length of the duration of state 4, which could possibly reflect enhanced attention towards the stimuli (Fig. 3). However, due to small sample size and lack of correction for multiple comparisons, these results should be interpreted with caution.

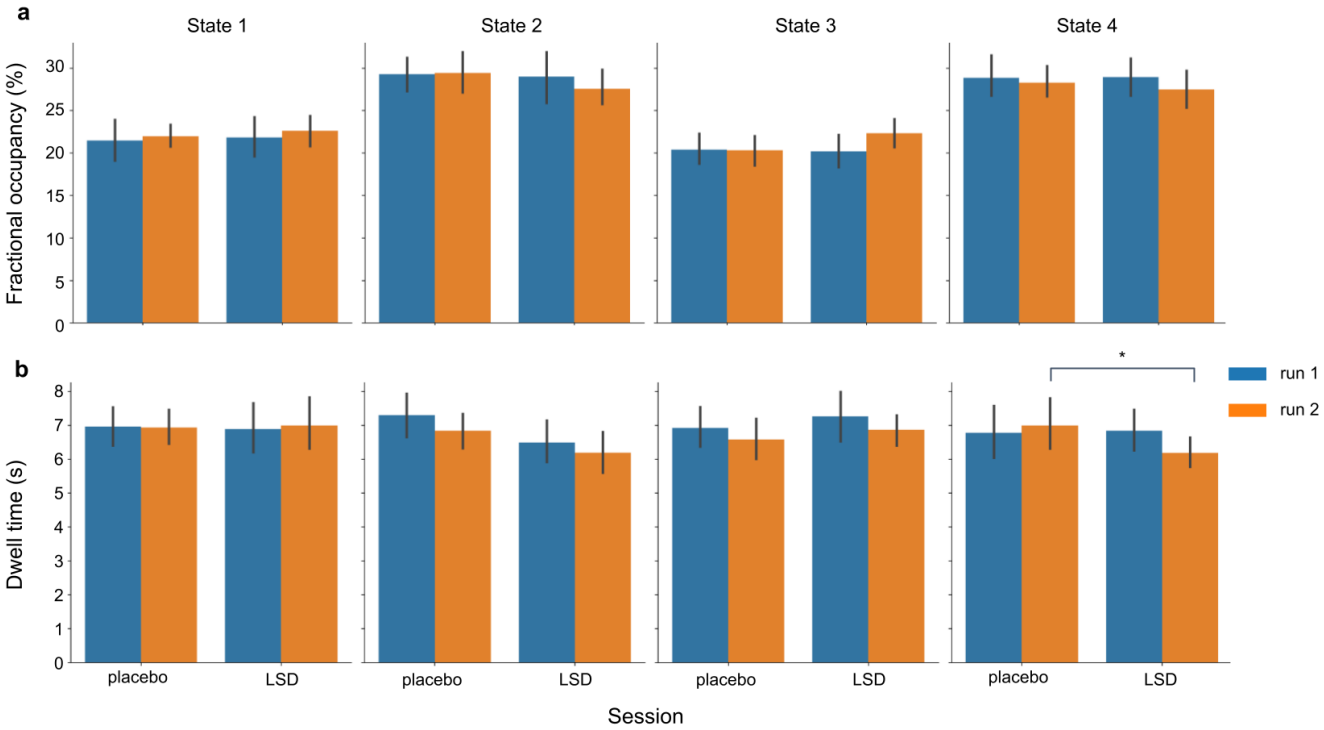

Fig. 4 Comparison of the resting state and music experience. **a** Fractional occupancy for 1st (resting-state) and 2nd (music listening) runs for both LSD and placebo conditions. For every state, we found no significant difference between- and within- both sessions. **b** Dwell time for 1st (resting-state) and 2nd (music listening) runs for both LSD and placebo conditions. During music listening, the state 4 throughout the placebo session showed higher dwell time in comparison to the LSD session (paired t-test, $t = 2.24$, $p = 0.04$).

Effect of LSD and music listening on brain states during resting state

Psychedelic sessions involving music listening facilitate emotion processing and mental imagery (Kaelen et al. 2015, 2016a, 2018; Carbonaro et al. 2018), what can possibly be associated with the local brain activity changes throughout the psychedelic experience. Therefore, we could hypothesize that psychedelic intake combined with music can induce changes in brain activity which could be observable on a longer timescale, thus altering the brain states' dynamics after music listening condition (3rd run — resting-state). Is brain states' dynamics during resting state *after* the music experience similar to the one before music listening?

To answer this question we analyzed and compared states' dynamics of resting-state during psychedelic experience and placebo before and after music listening. We included data from 15 participants

from both placebo and LSD sessions involving 1st run (resting state *before* music listening) and 3rd run (resting state *after* music listening) (Fig. 1). Next, to investigate changes in brain states' dynamics, we calculated dwell time, fractional occupancy and transition probability on an individual level (see "Methods").

To investigate possible changes between resting-state periods throughout placebo and LSD conditions, we started with a series of paired t-tests between 3rd run (resting-state *after* music listening) and 1st run (resting-state *before* music listening) for both fractional occupancy and dwell time measures (Fig. 5a, b). None of the results were statistically significant, however, for state 4 in the LSD session we observed a possible trend of higher dwell time during the 1st run compared to the 3rd run (paired t-test, $t = -2.02$, $p = 0.07$) (Fig. 5b). Furthermore, we assessed whether the difference between both runs (3rd run - 1st run) for each state is significantly different between the placebo and LSD sessions. The results for all states were not statistically significant. Ultimately, we did a direct comparison of each states' fractional occupancies and dwell times between LSD and placebo sessions only for the 3rd run. This analyses allowed us to examine whether resting-state after listening to music manifests different states' fluctuations on LSD compared to placebo. We found out that dwell time for state 4 was significantly higher during the placebo session in comparison with LSD (paired t-test, $t = 2.23$, $p = 0.04$) (Fig. 5b). The results from the rest of comparisons did not show any other statistically significant differences.

Our next step was to explore changes in brain states' dynamics with focus on their transitions. For this reason, for each participant and all possible transitions between the states we calculated transition probability (see "Methods"). The distribution of transition probability values was not normal, therefore for calculating the differences between conditions we used a nonparametric permutation test (see "Statistical analysis and reproducibility"). Firstly, we compared transition probabilities of each state between 3rd run and 1st run within each session (placebo and LSD) (Fig. 5c, d). The results revealed that during LSD condition participants had higher probability of transitioning from state 3 to state 4 during the resting-state after music listening (permutation test, mean difference = 0.04, $p = 0.02$) (Fig. 5d). Additionally, we wanted to examine whether post-music listening resting-state was different on LSD in comparison to placebo. However, the mean difference was not statistically significant for any of the possible transitions. Ultimately, we performed a permutation test between differences in both runs (3rd run - 1st run) between the LSD and placebo. We found that the difference between both runs was significantly higher in the LSD session in comparison with placebo for the transition from state 3 to state 4 (permutation test, mean difference = 0.06, $p = 0.03$) (Fig. 5f).

Taken together, these results support our hypothesis that both resting state runs, separated by music listening, manifest different brain states' dynamics. Specifically, resting state during psychedelic session after listening to music is associated with higher transition rate from state 3 to state 4. In contrast, it is the placebo session that is more associated with a higher appearance rate of state 4 (Fig. 5b). Such activity patterns may suggest that LSD combined with music promotes transitions between states, while states' fluctuations during placebo are more static and organized. Here again, due to small sample size and lack of correction for multiple comparisons, these results should be interpreted with caution.

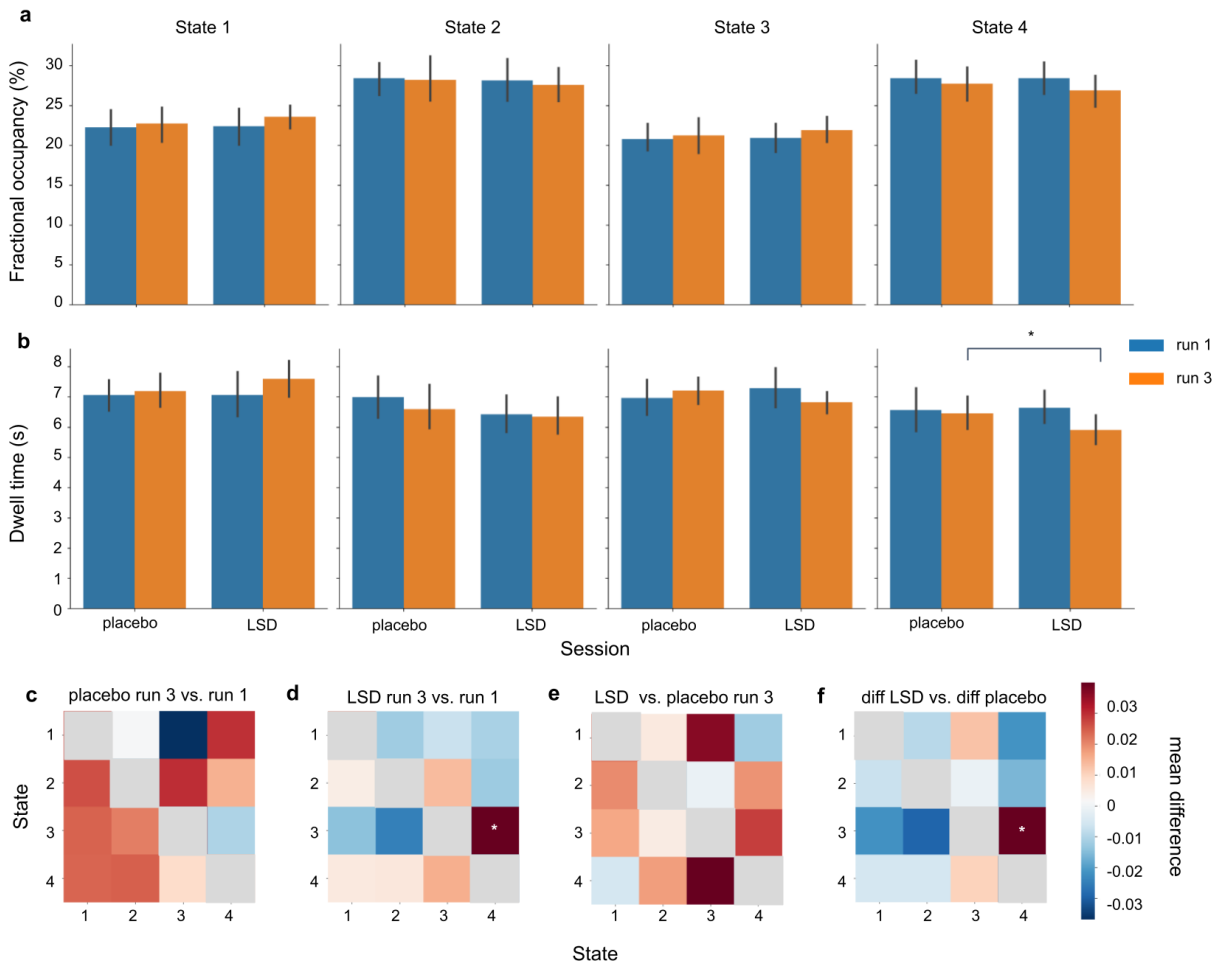

Fig. 5 Comparison of the pre- and post-music listening resting-state. **a** Fractional occupancy for 1st (resting-state) and 3rd (resting-state) runs for both LSD and placebo conditions. For every state, we found no significant difference between- and within-both sessions. **b** Dwell time for 1st (resting-state) and 3rd (resting-state) runs for both LSD and placebo conditions. For the resting-state *after* listening to music, the state 4 during the placebo session showed higher dwell time in comparison to the LSD session (paired t-test, $t = 2.23$, $p = 0.04$). **c** Transition matrix for the placebo session, 3rd run vs. 1st run; we found no significant differences. **d** During LSD session, resting-state after music listening was associated with higher probability of transitioning from state 3 to state 4 (permutation test, mean difference = 0.04, $p = 0.02$). **e** Transition matrix for the 3rd run (resting-state after music listening), LSD vs placebo session; we found no significant differences. **f** Transition matrix for the differences (3rd run - 1st run) between both sessions (LSD and placebo). We found that for transition from state 3 to 4 the difference between both resting-states was greater after the LSD intake (permutation test, mean difference = 0.06, $p = 0.03$).

Discussion

In this study, we aimed to investigate the effect of LSD and music on the dynamics of time-varying brain activity. Our analysis revealed that for both sessions (LSD and placebo) and conditions (resting-state and music) the brain activity can be reduced to four repetitive patterns, so-called *brain states*. We found that each state is characterized by a unique activity pattern of 7 a-priori defined brain networks and manifests different degrees of similarity to the mental states associated with psychedelic experience (see Fig. 2, 3). We observed that the brain states' dynamics during resting state and listening to music on both LSD and placebo does not differ significantly. Additionally, we found that the music itself could potentially have a long-term influence on the resting-state, in particular on states involving task-positive networks. Collectively, these findings

suggest that the whole-brain states' dynamics during psychedelic experience and placebo is relatively stable, however, music, as a crucial element of setting, can potentially have an influence on the subject's resting-state.

Based on previous findings on the music processing (Blood and Zatorre 2001; Koelsch 2011; Chan and Han 2022) and its role during the psychedelic experience (Bonny and Pahnke 1972; Barrett et al. 2018b), we hypothesized that music listening on the LSD will be associated with greater manifestation of brain states characterized by the high DMN, SOM, and LIM networks activity. Previous studies revealed that such network activity may be crucial for processing sensory and self-related stimuli that are often enhanced after psychedelics intake (Griffiths et al. 2006; Kometer et al. 2013a, 2015; Lebedev et al. 2015; Tagliazucchi et al. 2016; Liechti et al. 2017). We found that brain states' dynamics during resting-state does not differ notably from the resting-state involving music listening for both LSD and placebo. We observed that music listening on LSD resulted in lower duration in state 4, which is represented by the high activity of task-positive networks. These findings may suggest that LSD weakened the attention towards the musical stimuli. Interestingly, we did not observe any significant changes in brain states' dynamics involving the activity of DMN, SOM and LIM networks; thus, taken together the results do not support our hypothesis. Inconsistency of our results with the previous studies may be explained by the specificity of the analysis method we used. GLM-based methods represent differences between conditions as contrasts in whole-brain activity, whereas network neuroscience tools allow to investigate changes in structural and functional brain networks. The usage of both of these approaches in the context of psychedelic experience revealed change sin the BOLD signal and whole-brain network reorganization (Tagliazucchi et al. 2014; Petri et al. 2014; Lebedev et al. 2015; Preller et al. 2019, 2020; Lord et al. 2019; Varley et al. 2020; Luppi et al. 2021), especially regarding the DMN and the visual regions (Carhart-Harris et al. 2012a, 2016b; Palhano-Fontes et al. 2015). However, none of these approaches takes full advantage of the temporal resolution provided by the neuroimaging methods. Here, we applied the KMeans algorithm to cluster timeseries into brain states; thus, we focused more on the temporal rather than spatial resolution of the data. Our results show that changes in brain states' dynamics occurring between the LSD and placebo during the resting-state or music listening are so subtle that they are unobservable or there are no changes at all. Under no drug influence, Kay et al. (2012) reported similar patterns of DMN connectivity in subjects who were listening to music compared with those who were not. These results are similar to our observations of brain states' dynamics that does not differ between resting-state and music, except that we also found the lack of significant effect after the LSD intake.

The majority of psychedelics-based studies focus on their effect on the brain activity in comparison to the control groups, what allows one to get a deep insight into the biological and psychological effects of these drugs. Here, we also performed a similar comparison between the LSD and placebo sessions for the music listening. We observed lower manifestation of state 4, associated with high activity of task-positive networks in the LSD compared to placebo. Task-positive networks, such as frontoparietal, dorsal- and ventral-attention networks are responsible for cognitive control along with integration of sensory and cognitive information (Downar et al. 2000; Cocchi et al. 2013; Vossel et al. 2014). In line with that, these results can be explained in the psychological context of the psychedelic experience: under the psychedelics influence the subject's consciousness is more altered than during placebo, therefore it is harder to pay attention to the musical stimuli.

It is important to note that previous studies revealed that psychedelic experience combined with musical stimuli has a profound influence on the subject's mental condition, especially emotion processing (Kaelen et al. 2015, 2016b; Carbonaro et al. 2018) and meaning-making (Preller et al. 2017). Here, we

hypothesized that such a strong impact on the psychological state should also be accompanied by the changes in the dynamics of the time-varying brain activity. Specifically, we expected to observe different patterns of brain states' dynamics for the resting-state *before* and *after* listening to music. We found that resting-state runs, separated by music listening, have similar brain states' dynamics regarding the duration of states and their frequency, for both LSD and placebo sessions. Contrarily, we observed the difference between the two resting-states in terms of the states' transitions. We found that on LSD, resting-state after music listening showed higher probability of transition from state associated with high DMN, SOM and VIS networks activity to state characterized by high FPN, DAN and VAN activity, in comparison to resting-state prior to musical stimuli. Such pattern of transitions may reflect switching from common brain activity after psychedelics intake, involving self-referential and sensory networks, to activity crucial for cognitive control and integration of multiple stimuli; thus we may conclude that it could be crucial for processing the whole psychedelic experience.

The direct comparison of resting-state after the musical stimuli between LSD and placebo showed that psychedelic experience was associated with lower manifestation of state associated with task-positive networks. Interestingly, this effect was also observed during music listening. These results may suggest that the dynamics of states that occurred under the influence of music and LSD continued also during the resting-state after. Previous studies showed that the joint effect of psychedelics and music affects brain activity and network architecture (Kaelen et al. 2016a, b; Preller et al. 2017; Barrett et al. 2018a). In particular, Kaelen et al. (2016a) reported increased functional connectivity between the parahippocampus and visual cortex, while Preller et al. (2017) showed greater BOLD activity in the SMA, putamen, insula, and the PCC. Together, our observations expand upon the previous studies by demonstrating that music combined with psychedelics may have a long-term effect on the resting-state that can be observed in the dynamics of the time-varying brain activity.

Limitations

The main limitation of this study is the small sample size, which is a common problem for the studies involving psychedelics intake. The consequence of the small sample size is a low statistical power of the study, thus a high probability of the occurrence of false positives and false negatives. It is important to emphasize that these results should be considered as preliminary and further studies need to replicate the analysis and test our findings on larger samples. Finally, for the brain states identification we used the K-Means algorithm, which is the most frequently used in terms of clustering fMRI timeseries. However, brain states can be also identified using other clustering methods, such as hierarchical clustering (Ward 1963) or Hidden Markov-Model (Li and Biswas 1999; Ghassempour et al. 2014). Performing the analysis of brain states' dynamics using a different approach could test whether the effect of LSD and music is also present and consistent while applying other methodologies.

Conclusions

Here, we investigated the effect of psychedelics and music on the time-varying brain activity. We applied an unsupervised machine learning method KMeans to identify brain states and characterized their dynamics by calculating appropriate measures. Our study is the first to investigate an interaction between psychedelics and music on the brain states' dynamics in the long-term. We show that musical stimuli, as a part of setting, can have an influence on the subject's brain activity, and in consequence support the psychological outcomes

of the psychedelics experience, however, further studies are needed to confirm these effects on the larger sample size.

Competing Interest Statement

The authors have declared no competing interest.

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References

Aday JS, Wood JR, Bloesch EK, Davoli CC (2021) Psychedelic drugs and perception: a narrative review of the first era of research. Reviews in the Neurosciences 32:559–571

Allen EA, Damaraju E, Plis SM, et al (2014) Tracking whole-brain connectivity dynamics in the resting state. Cereb Cortex 24:663–676. https://doi.org/10.1093/cercor/bhs352

Barrett FS, Griffiths RR (2017) Classic Hallucinogens and Mystical Experiences: Phenomenology and Neural Correlates. Behavioral Neurobiology of Psychedelic Drugs 393–430

Barrett FS, Preller KH, Herdener M, et al (2018a) Serotonin 2A Receptor Signaling Underlies LSD-induced Alteration of the Neural Response to Dynamic Changes in Music. Cerebral Cortex 28:3939–3950

Barrett FS, Preller KH, Kaelen M (2018b) Psychedelics and music: neuroscience and therapeutic implications. International Review of Psychiatry 30:350–362

Barrett FS, Robbins H, Smooke D, et al (2017) Qualitative and Quantitative Features of Music Reported to Support Peak Mystical Experiences during Psychedelic Therapy Sessions. Frontiers in Psychology 8

Blood AJ, Zatorre RJ (2001) Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. Proceedings of the National Academy of Sciences 98:11818–11823

Bogenschutz MP, Forcehimes AA, Pommy JA, et al (2015) Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol 29:289–299. https://doi.org/10.1177/0269881114565144

Bogenschutz MP, Johnson MW (2016) Classic hallucinogens in the treatment of addictions. Progress in Neuro-Psychopharmacology and Biological Psychiatry 64:250–258

Bonny HL, Pahnke WN (1972) The Use of Music in Psychedelic (LSD) Psychotherapy. Journal of Music Therapy 9:64–87

Carbonaro TM, Johnson MW, Hurwitz E, Griffiths RR (2018) Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: similarities and differences in subjective experiences. Psychopharmacology 235:521–534

Carhart-Harris RL, Bolstridge M, Rucker J, et al (2016a) Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 3:619–627. https://doi.org/10.1016/S2215-0366(16)30065-7

Carhart-Harris RL, Erritzoe D, Williams T, et al (2012a) Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. Proc Natl Acad Sci U S A 109:2138–2143. https://doi.org/10.1073/pnas.1119598109

Carhart-Harris RL, Leech R, Williams TM, et al (2012b) Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with psilocybin. British Journal of Psychiatry 200:238–244

Carhart-Harris RL, Muthukumaraswamy S, Roseman L, et al (2016b) Neural correlates of the LSD experience revealed by multimodal neuroimaging. Proceedings of the National Academy of Sciences 113:4853–4858

Carhart-Harris RL, Roseman L, Haijen E, et al (2018) Psychedelics and the essential importance of context. J Psychopharmacol 32:725–731. https://doi.org/10.1177/0269881118754710

Carhart-Harris RL, et al (2020) Neural correlates of the LSD experience revealed by multimodal neuroimaging. OpenNeuro. [Dataset] doi: 10.18112/openneuro.ds003059.v1.0.0

Chan MMY, Han YMY (2022) The functional brain networks activated by music listening: A neuroimaging meta-analysis and implications for treatment. Neuropsychology 36:4–22

Cocchi L, Zalesky A, Fornito A, Mattingley JB (2013) Dynamic cooperation and competition between brain systems during cognitive control. Trends in Cognitive Sciences 17:493–501

Cornblath EJ, Ashourvan A, Kim JZ, et al (2020) Temporal sequences of brain activity at rest are constrained by white matter structure and modulated by cognitive demands. Commun Biol 3:261. https://doi.org/10.1038/s42003-020-0961-x

Császár-Nagy N, Kapócs G, Bókkon I (2019) Classic psychedelics: the special role of the visual system. Reviews in the Neurosciences 30:651–669

Davis AK, Barrett FS, May DG, et al (2021) Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry 78:481–489. https://doi.org/10.1001/jamapsychiatry.2020.3285

Downar J, Crawley AP, Mikulis DJ, Davis KD (2000) A multimodal cortical network for the detection of changes in the sensory environment. Nature Neuroscience 3:277–283

Eisner B (1997) Set, Setting, and Matrix. Journal of Psychoactive Drugs 29:213–216

Forstmann M, Yudkin DA, Prosser AMB, et al (2020) Transformative experience and social connectedness mediate the mood-enhancing effects of psychedelic use in naturalistic settings. Proc Natl Acad Sci U S A 117:2338–2346. https://doi.org/10.1073/pnas.1918477117

Friston KJ, Holmes AP, Worsley KJ, et al (1994) Statistical parametric maps in functional imaging: A general linear approach. Human Brain Mapping 2:189–210

Gasser P, Kirchner K, Passie T (2015) LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. J Psychopharmacol 29:57–68. https://doi.org/10.1177/0269881114555249

Ghassempour S, Girosi F, Maeder A (2014) Clustering Multivariate Time Series Using Hidden Markov Models. International Journal of Environmental Research and Public Health 11:2741–2763

Goutte C, Toft P, Rostrup E, et al (1999) On Clustering fMRI Time Series. NeuroImage 9:298–310

Griffiths RR, Johnson MW, Carducci MA, et al (2016) Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol 30:1181–1197. https://doi.org/10.1177/0269881116675513

Griffiths RR, Johnson MW, Richards WA, et al (2018) Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. J Psychopharmacol 32:49–69. https://doi.org/10.1177/0269881117731279

Griffiths RR, Johnson MW, Richards WA, et al (2011) Psilocybin occasioned mystical-type experiences: immediate and

persisting dose-related effects. Psychopharmacology 218:649–665. https://doi.org/10.1007/s00213-011-2358-5

Griffiths RR, Richards WA, McCann U, Jesse R (2006) Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology 187:268–83; discussion 284–92. https://doi.org/10.1007/s00213-006-0457-5

Grimm O, Kraehenmann R, Preller KH, et al (2018) Psilocybin modulates functional connectivity of the amygdala during emotional face discrimination. Eur Neuropsychopharmacol 28:691–700. https://doi.org/10.1016/j.euroneuro.2018.03.016

Grob CS, Danforth AL, Chopra GS, et al (2011) Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry 68:71–78. https://doi.org/10.1001/archgenpsychiatry.2010.116

Guerra-Doce E (2015) Psychoactive Substances in Prehistoric Times: Examining the Archaeological Evidence. Time and Mind 8:91–112

Hartigan JA, Wong MA (1979) Algorithm AS 136: A K-Means Clustering Algorithm. Applied Statistics 28:100

Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR (2014) Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol 28:983–992. https://doi.org/10.1177/0269881114548296

Johnson MW, Hendricks PS, Barrett FS, Griffiths RR (2019) Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function. Pharmacology & Therapeutics 197:83–102

Kaelen M, Barrett FS, Roseman L, et al (2015) LSD enhances the emotional response to music. Psychopharmacology 232:3607–3614

Kaelen M, Giribaldi B, Raine J, et al (2018) The hidden therapist: evidence for a central role of music in psychedelic therapy. Psychopharmacology 235:505–519

Kaelen M, Roseman L, Kahan J, et al (2016a) LSD modulates music-induced imagery via changes in parahippocampal connectivity. European Neuropsychopharmacology 26:1099–1109

Kaelen M, Roseman L, Lorenz R, et al (2016b) Effects of LSD and music on brain activity. European Neuropsychopharmacology 26:S130

Kay BP, Meng X, DiFrancesco MW, et al (2012) Moderating effects of music on resting state networks. Brain Res 1447:53–64. https://doi.org/10.1016/j.brainres.2012.01.064

Koelsch S (2011) Toward a Neural Basis of Music Perception – A Review and Updated Model. Frontier in Psychology 2

Kometer M, Pokorny T, Seifritz E, Volleinweider FX (2015) Psilocybin-induced spiritual experiences and insightfulness are associated with synchronization of neuronal oscillations. Psychopharmacology 232:3663–3676. https://doi.org/10.1007/s00213-015-4026-7

Kometer M, Schmidt A, Bachmann R, et al (2012) Psilocybin Biases Facial Recognition, Goal-Directed Behavior, and Mood State Toward Positive Relative to Negative Emotions Through Different Serotonergic Subreceptors. Biol Psychiatry 72:898–906. https://doi.org/10.1016/j.biopsych.2012.04.005

Kometer M, Schmidt A, Jäncke L, Vollenweider FX (2013a) Activation of serotonin 2A receptors underlies the psilocybin-induced effects on α oscillations, N170 visual-evoked potentials, and visual hallucinations. J Neurosci 33:10544–10551. https://doi.org/10.1523/JNEUROSCI.3007-12.2013

Kometer M, Schmidt A, Jancke L, Vollenweider FX (2013b) Activation of Serotonin 2A Receptors Underlies the Psilocybin-Induced Effects on Oscillations, N170 Visual-Evoked Potentials, and Visual Hallucinations. Journal of Neuroscience 33:10544–10551

Kraehenmann R, Pokorny D, Vollenweider L, et al (2017) Dreamlike effects of LSD on waking imagery in humans depend on serotonin 2A receptor activation. Psychopharmacology 234:2031–2046. https://doi.org/10.1007/s00213-017-4610-0

Kraehenmann R, Preller KH, Scheidegger M, et al (2015) Psilocybin-Induced Decrease in Amygdala Reactivity Correlates with Enhanced Positive Mood in Healthy Volunteers. Biol Psychiatry 78:572–581. https://doi.org/10.1016/j.biopsych.2014.04.010

Lebedev AV, Kaelen M, Lövdén M, et al (2016) LSD-induced entropic brain activity predicts subsequent personality change. Hum Brain Mapp 37:3203–3213

Lebedev AV, Lövdén M, Rosenthal G, et al (2015) Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin. Hum Brain Mapp 36:3137–3153. https://doi.org/10.1002/hbm.22833

Le Cam LM, Neyman J (1967) Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability: Held at the Statistical Laboratory, University of California, June 21-July 18, 1965 and December 27, 1965-January 7, 1966. University of California Press

Li C, Biswas G (1999) Clustering sequence data using hidden Markov model representation. Data Mining and Knowledge Discovery: Theory, Tools, and Technology

Liechti ME, Dolder PC, Schmid Y (2017) Alterations of consciousness and mystical-type experiences after acute LSD in humans. Psychopharmacology 234:1499–1510. https://doi.org/10.1007/s00213-016-4453-0

Lloyd S (1982) Least squares quantization in PCM. IEEE Transactions on Information Theory 28:129–137

Lord L-D, Expert P, Atasoy S, et al (2019) Dynamical exploration of the repertoire of brain networks at rest is modulated by psilocybin. Neuroimage 199:127–142. https://doi.org/10.1016/j.neuroimage.2019.05.060

Luppi AI, Carhart-Harris RL, Roseman L, et al (2021) LSD alters dynamic integration and segregation in the human brain. Neuroimage 227:117653. https://doi.org/10.1016/j.neuroimage.2020.117653

MacLean KA, Johnson MW, Griffiths RR (2011) Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. J Psychopharmacol 25:1453–1461. https://doi.org/10.1177/0269881111420188

Mason NL, Kuypers KPC, Müller F, et al (2020) Me, myself, bye: regional alterations in glutamate and the experience of ego dissolution with psilocybin. Neuropsychopharmacology 45:2003–2011. https://doi.org/10.1038/s41386-020-0718-8

Mason NL, Mischler E, Uthaug MV, Kuypers KPC (2019) Sub-Acute Effects of Psilocybin on Empathy, Creative Thinking, and Subjective Well-Being. J Psychoactive Drugs 51:123–134. https://doi.org/10.1080/02791072.2019.1580804

Meer JN van der, van der Meer JN, Breakspear M, et al (2020) Movie viewing elicits rich and reliable brain state dynamics. Nature Communications 11

Mithoefer MC, Feduccia AA, Jerome L, et al (2019) MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. Psychopharmacology 236:2735–2745. https://doi.org/10.1007/s00213-019-05249-5

O'Callaghan C, Hubik DJ, Dwyer J, et al (2020) Experience of Music Used With Psychedelic Therapy: A Rapid Review and Implications. Journal of Music Therapy 57:282–314

Ot'alora G M, Grigsby J, Poulter B, et al (2018) 3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial. J Psychopharmacol 32:1295–1307. https://doi.org/10.1177/0269881118806297

Palhano-Fontes F, Andrade KC, Tofoli LF, et al (2015) The psychedelic state induced by ayahuasca modulates the

activity and connectivity of the default mode network. PLoS One 10:e0118143. https://doi.org/10.1371/journal.pone.0118143

Parker Singleton S, Luppi AI, Carhart-Harris RL, et al (2021) Psychedelics Flatten the brain's energy landscape: evidence from receptor-informed network control theory. bioRxiv 2021.05.14.444193

Petri G, Expert P, Turkheimer F, et al (2014) Homological scaffolds of brain functional networks. J R Soc Interface 11:20140873. https://doi.org/10.1098/rsif.2014.0873

Pokorny T, Preller KH, Kometer M, et al (2017) Effect of Psilocybin on Empathy and Moral Decision-Making. Int J Neuropsychopharmacol 20:747–757. https://doi.org/10.1093/ijnp/pyx047

Preller KH, Duerler P, Burt JB, et al (2020) Psilocybin Induces Time-Dependent Changes in Global Functional Connectivity. Biol Psychiatry 88:197–207. https://doi.org/10.1016/j.biopsych.2019.12.027

Preller KH, Herdener M, Pokorny T, et al (2017) The Fabric of Meaning and Subjective Effects in LSD-Induced States Depend on Serotonin 2A Receptor Activation. Current Biology 27:451–457

Preller KH, Razi A, Zeidman P, et al (2019) Effective connectivity changes in LSD-induced altered states of consciousness in humans. Proc Natl Acad Sci U S A 116:2743–2748. https://doi.org/10.1073/pnas.1815129116

Ross S, Bossis A, Guss J, et al (2016) Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol 30:1165–1180. https://doi.org/10.1177/0269881116675512

Schaefer A, Kong R, Gordon EM, et al (2018) Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. Cereb Cortex 28:3095–3114. https://doi.org/10.1093/cercor/bhx179

Schmid Y, Liechti ME (2018) Long-lasting subjective effects of LSD in normal subjects. Psychopharmacology 235:535–545. https://doi.org/10.1007/s00213-017-4733-3

Smigielski L, Kometer M, Scheidegger M, et al (2020) P300 -mediated modulations in self–other processing under psychedelic psilocybin are related to connectedness and changed meaning: A window into the self–other overlap. Human Brain Mapping 41:4982–4996

Smigielski L, Scheidegger M, Kometer M, Vollenweider FX (2019) Psilocybin-assisted mindfulness training modulates self-consciousness and brain default mode network connectivity with lasting effects. Neuroimage 196:207–215. https://doi.org/10.1016/j.neuroimage.2019.04.009

Tagliazucchi E, Carhart-Harris R, Leech R, et al (2014) Enhanced repertoire of brain dynamical states during the psychedelic experience. Hum Brain Mapp 35:5442–5456. https://doi.org/10.1002/hbm.22562

Tagliazucchi E, Roseman L, Kaelen M, et al (2016) Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution. Curr Biol 26:1043–1050. https://doi.org/10.1016/j.cub.2016.02.010

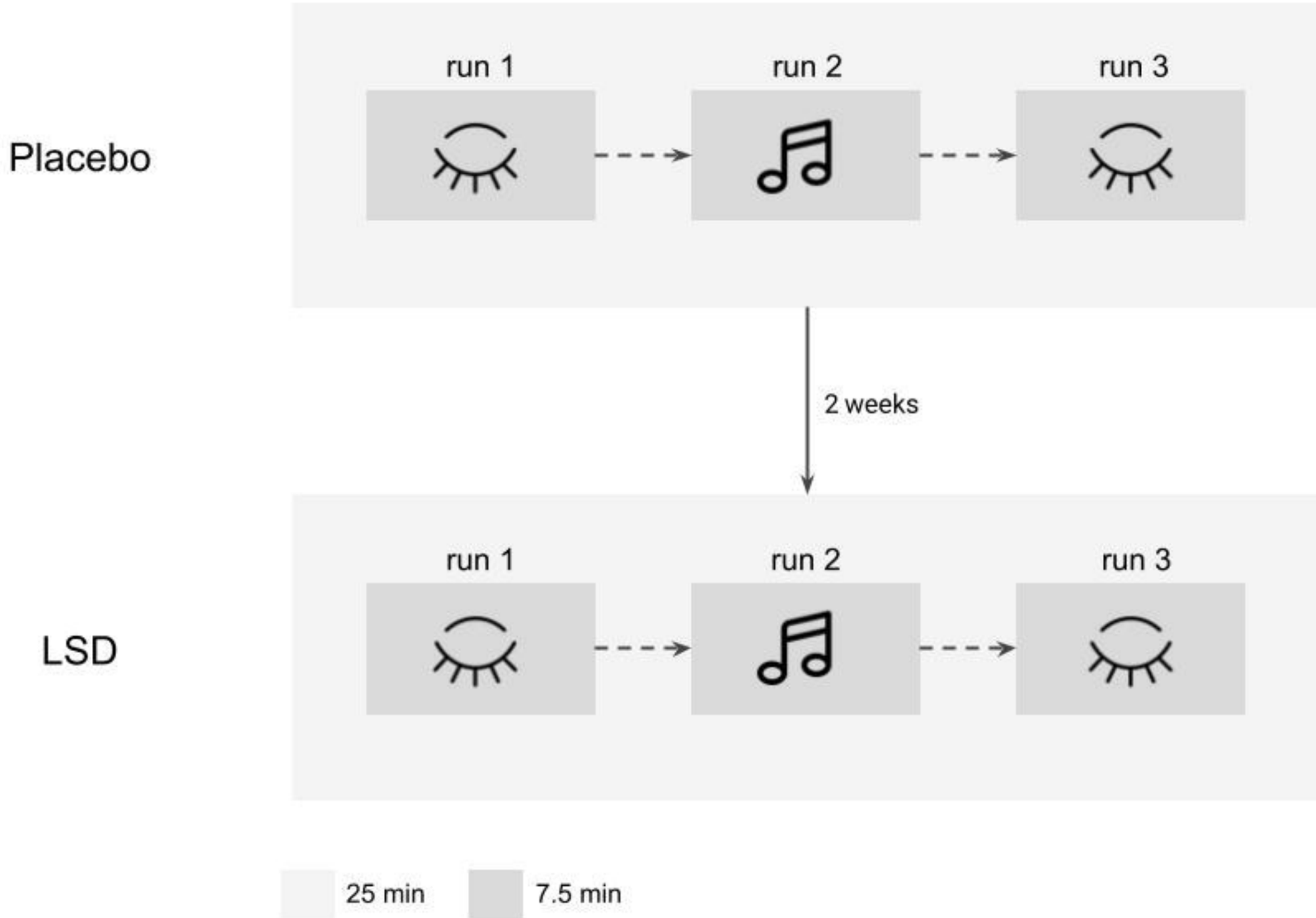
Varker T, Watson L, Gibson K, et al (2021) Efficacy of Psychoactive Drugs for the Treatment of Posttraumatic Stress Disorder: A Systematic Review of MDMA, Ketamine, LSD and Psilocybin. J Psychoactive Drugs 53:85–95. https://doi.org/10.1080/02791072.2020.1817639

Varley TF, Carhart-Harris R, Roseman L, et al (2020) Serotonergic psychedelics LSD & psilocybin increase the fractal dimension of cortical brain activity in spatial and temporal domains. Neuroimage 220:117049. https://doi.org/10.1016/j.neuroimage.2020.117049

Vossel S, Geng JJ, Fink GR (2014) Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. Neuroscientist 20:150–159. https://doi.org/10.1177/1073858413494269

Vuilleumier P, Trost W (2015) Music and emotions: from enchantment to entrainment. Annals of the New York Academy of Sciences 1337:212–222

Ward JH (1963) Hierarchical Grouping to Optimize an Objective Function. Journal of the American Statistical Association 58:236–244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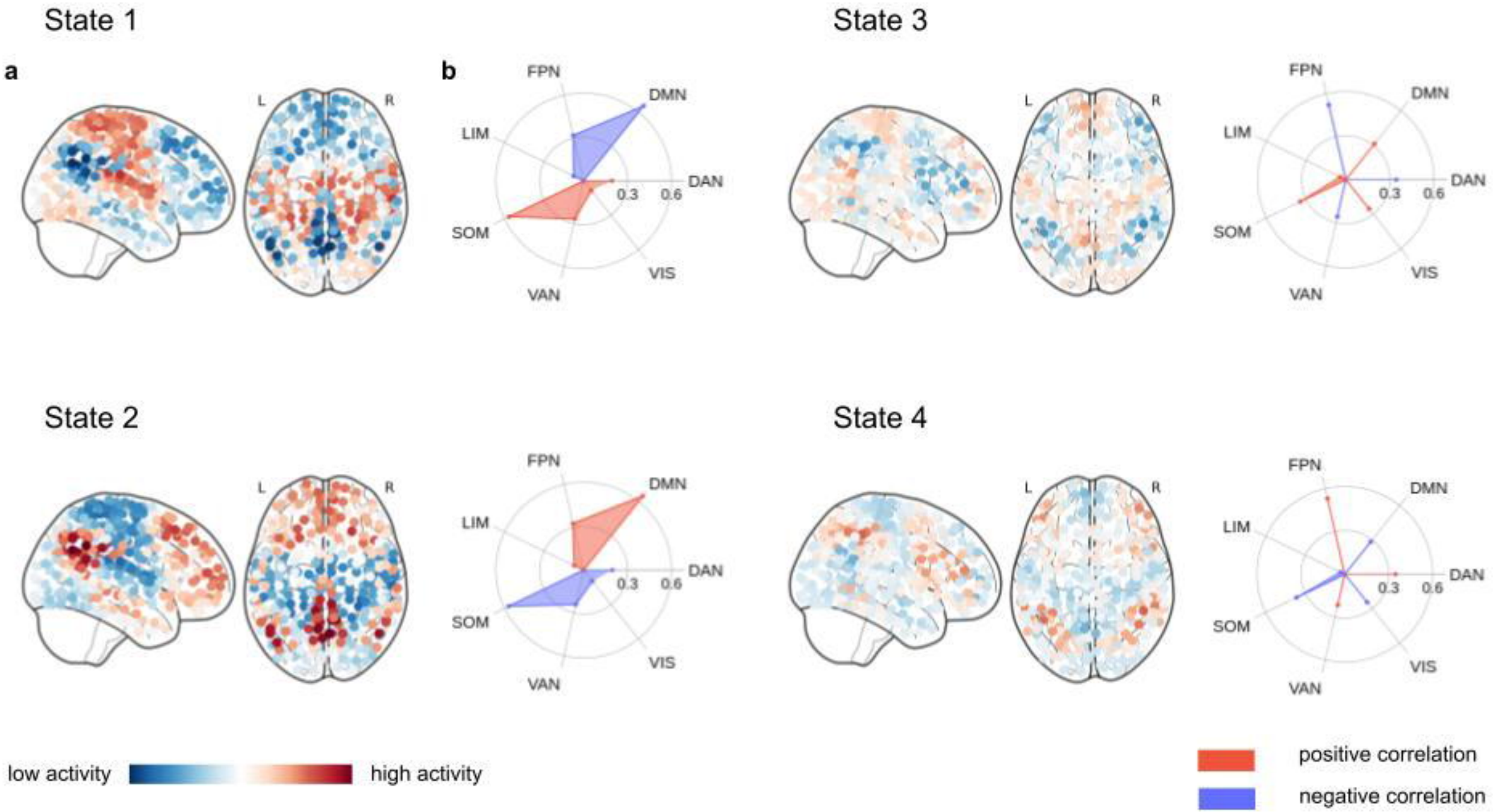
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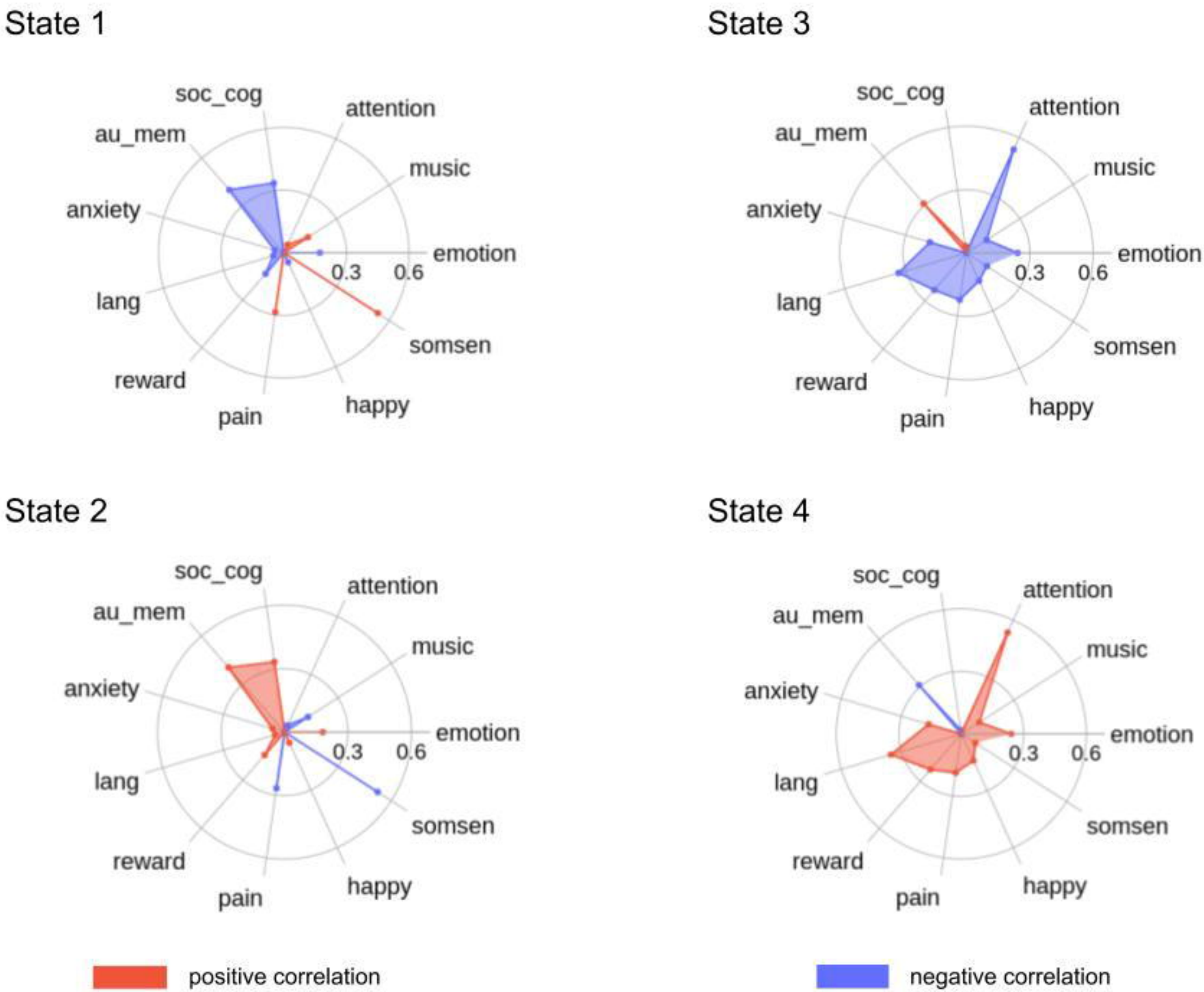
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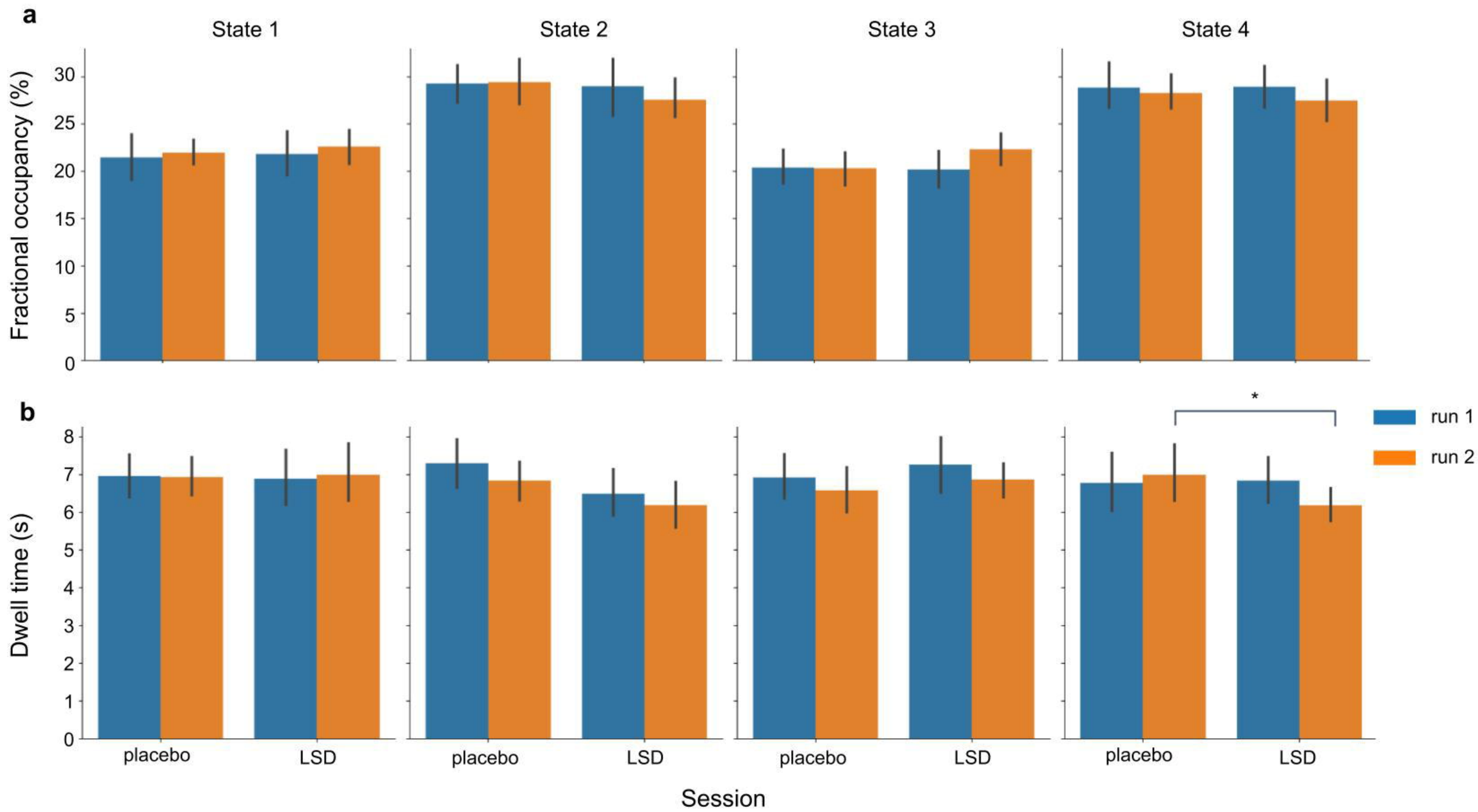
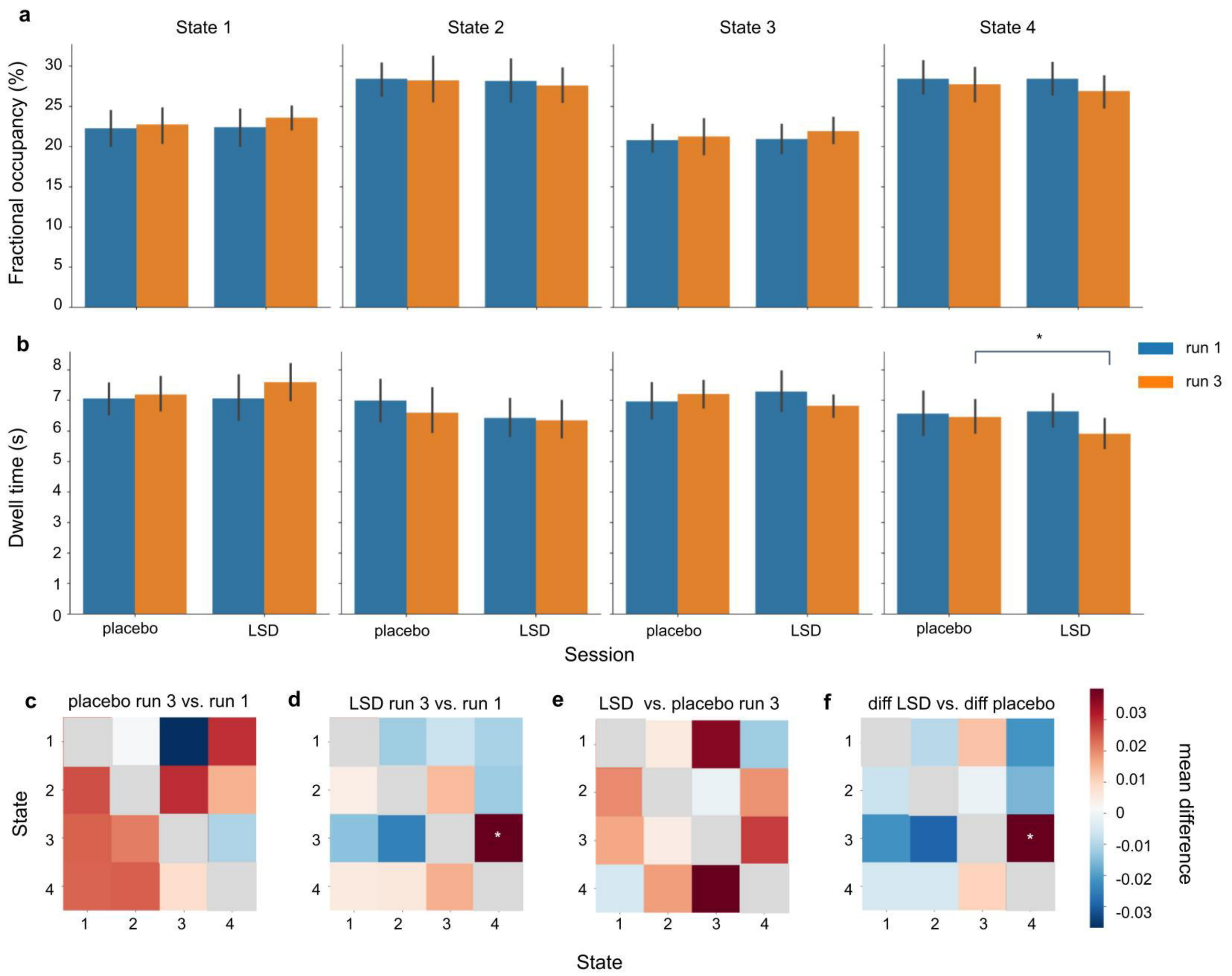
happy
pain
State 3
soc_cog
attention
au_mem
music
anxiety
emotion
0.3
0.6
lang
somsen
reward
happy
pain
State 2
soc_cog
attention
au_mem
music
anxiety
emotion
0.3
0.6
lang
somsen
reward
happy
pain
State 4
soc_cog
attention
au_mem
music
anxiety
emotion
0.3
0.6
lang
somsen
reward
happy
pain
positive correlation
negative correlation


a
State 1
State 2
State 3
State 4
Fractional occupancy (%)
0
5
10
15
20
25
30
b
Dwell time (s)
0
1
2
3
4
5
6
7
8
*
run 1
run 2
placebo
LSD
placebo
LSD
placebo
LSD
placebo
LSD
Session


a
State 1
State 2
State 3
State 4
Fractional occupancy (%)
0
5
10
15
20
25
30
b
Dwell time (s)
0
1
2
3
4
5
6
7
8
*
run 1
run 3
placebo
LSD
placebo
LSD
placebo
LSD
placebo
LSD
Session
c
placebo run 3 vs. run 1
d
LSD run 3 vs. run 1
e
LSD vs. placebo run 3
f
diff LSD vs. diff placebo
State
1
2
3
4
*
0.03
0.02
0.01
0
-0.01
-0.02
-0.03
mean difference
State