Psilocybin administration leads to a recurrent high integrated and low segregated brain pattern

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Introduction. Psychedelic drugs have been used throughout history as a means to alter conscious experience and nowadays as therapeutic tools in clinical context (Carhart-Harris, 2019). Psilocybin is such a psychoactive substance, which induces profound distortions in subjective experience (Mason et al., 2020). Here we study whether and how the brain reconfigures in more functional states and what the inter-state dynamics look like under psilocybin.

Methods. In a double-blind, placebo-controlled, parallel group design, we utilized ultra-high field (7T) fMRI where participants were randomized to receive a single dose of psilocybin (0.17 mg/kg, n=22, age=23±2.9 y) or placebo (n=27, age=23.1±3.8 y).

Five dimensions of altered states of consciousness (5D-ASC) scale (*auditory alterations* (AA), *anxious ego dissolution* (AED), *oceanic boundlessness* (OB), *reduction of vigilance* (RV), *visual restructuralization* (VR); (Dittrich, 1998)) and the Ego Dissolution Inventory (EDI; (Nour et al., 2016)) were evaluated 360 minutes after drug administration. Further, 6 minutes of resting state fMRI were acquired from the participants with eyes open during peak subjective drug effect (102 minutes post treatment).

Schaefer atlas with 100 ROIs (Schaefer et al., 2018) were applied to the fMRI time series. Between-ROI Pearson correlation was calculated to estimate a static connectivity matrix for each participant. Further, phase-based coherence was used to calculate the time-varying connectivity profile of the brain at each time point and K-means clustering was used to summarize those matrices into 4 recurrent connectivity patterns (Demertzi et al., 2019). Intrinsic ignition was also calculated to investigate the capability of each region to propagate feed-forward and recurrent neuronal activity to other regions during rest.

A non-parametric Mann-Whitney U test was performed to compare the 5D-ASC and EDI scores between two groups. Independent t-test was performed to compare the static whole-brain, within-network, and between-network connectivity values as well as the occurrence rate of time varying connectivity patterns and global signal amplitude of placebo and psilocybin groups. Transition probabilities between dynamic states were estimated using a Markov model and significantly altered transitions between groups were identified using a Wilcoxon rank sum test. In all tests, FDR correction was applied to adjust p-values in case of multiple comparisons.

Results. Administration of psilocybin was associated with increased ratings on all behavioral dimensions of the 5D-ASC (**AA**: U=529.5, p≤0.001; **AED**: U=555.5, p<0.001, **OB**: U=583, p<0.001; **RV**: U=452, p=0.002; **VR**: U=589, p<0.001; **EDI**: U=487, p<0.001; Fig. 1).

Connectivity analysis revealed that, compared to placebo, there was an overall increase in the whole-brain connectivity after usage of psilocybin (t=3.087, p=0.003; Fig. 4A). This increase was due to an increased connectivity between the regions of the dorsal attentional network (DAN; t=2.620, p=0.042; Fig. 4B) and between DAN regions and all the other networks (Fig. 4C).

Time varying connectivity analysis further showed that a state of global positive connectivity recurred more frequently in the psychedelic state (t=3.731, p=0.001; Fig. 4D-E) along with a

decrease in the global signal amplitude (p=0.003). Transition to this pattern was also more probable in the psilocybin group (Fig. 4F). This was further proved by observing the significantly higher ignition power of cortical regions in psychedelic state which showed their higher tendency to make functional connections with each other. Additionally, OB was associated with transition from the complex to the global positive connectivity pattern (multiple linear regression, t=3.160, p=0.003).

Conclusions. These results indicate that in a psychedelic state our brain recurrently supports a high integrated and low segregated configuration, leading to such profound alerted experiential state.

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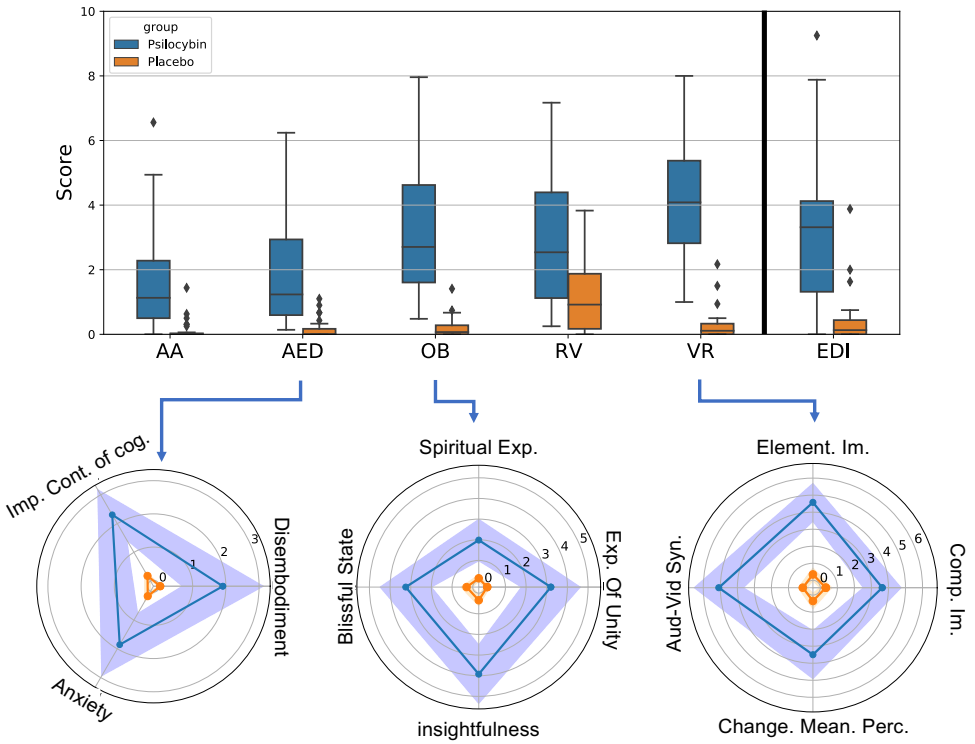

Fig. 1 Administration of psilocybin was associated with significantly increased ratings on all dimensions of the 5D-ASC.

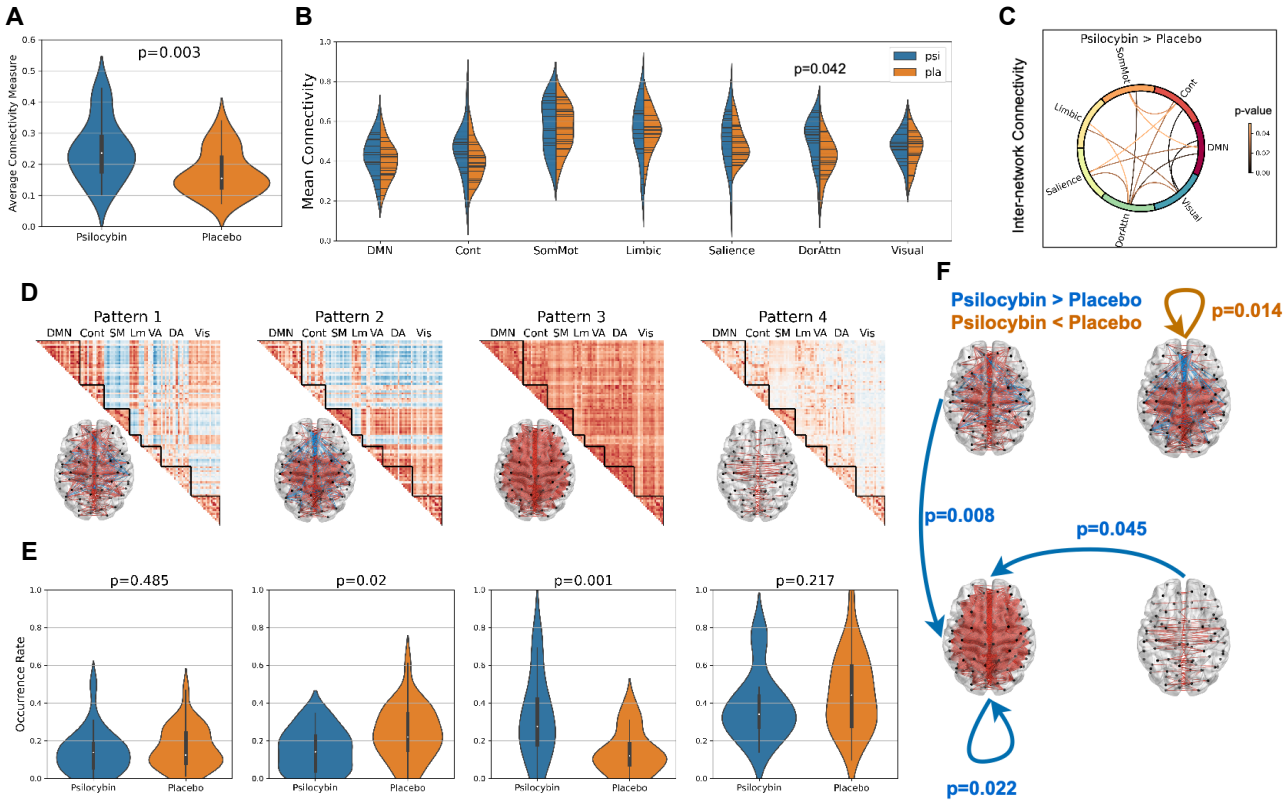

Fig 2. Administration of psilocybin was associated with A) higher whole-brain connectivity, B) higher within network connectivity in the dorsal attentional network, C) higher connectivity between dorsal attentional network and the other networks, D, E) higher occurrence rate of a globally positive connectivity pattern and F) higher transition probability to the state with globally positive connectivity pattern.