Self-perception and Connectivity: How Perception of the Self Correlates with Connections between Different Brain Regions

Psychedelics such as psilocybin and LSD have gradually been demonstrated as effective drugs for treating psychiatric distress, which some research suggests may originate from the ego-dissolution effect of psychedelics. To better understand how LSD functions therapeutically, it is necessary to know the underlying neural mechanisms of self-perception and ego-dissolution (the term is used as the opposite of self-perception in this paper) and how psychedelics may influence perception. After examining research on connectivity between different brain areas and self-perception, we hypothesize that connectivity between the medial prefrontal cortex (mPFC), the medial temporal lobe, and the thalamus may be important to the conscious experience of the self. Utilizing the ego-dissolution influence of LSD, we design this fMRI experiment to evaluate the correlation and thus test the hypothesis.

**Introduction**

Despite being prohibited from medical treatment for several decades, psychedelics were once again accepted and functioned effectively in the treatment of psychiatric disorders originating from serious cancer and other terminal illnesses (Ross 2018). Ross (2018) suggests that “psychedelic-assisted treatment can produce rapid, robust, and sustained improvements in cancer-related psychological and existential distress”. Similarly, Griffiths et al. (2016) demonstrates that high-dose psilocybin produced large decreases in depressed mood and anxiety (Also see Yaden et al., 2021). The therapeutic effect persists in healthy participants as well (Griffiths et al., 2017). Some studies consider that this function arises from ego-dissolution experienced during the psychedelic experience (Kałużna et al., 2022). Based on previous research, we want to further explore how psychedelics, particularly Lysergic acid diethylamide (LSD), influence the perception of the self neurologically and infer how self-perception arises.

Some previous studies using LSD have demonstrated that connectivity between brain areas plays a role in self-perception. Recently, Stoliker et al. (2023) found that “change in inhibitory effective connectivity from the salience network (SN) to the default mode network (DMN) became excitatory, and inhibitory effective connectivity from DMN to the dorsal attention network (DAN) decreased under the peak effect of LSD… reflect diminution of the anticorrelation between resting state networks that may be a key neural mechanism of LSD-induced ego dissolution”. Lebedev et al. (2015) also concluded that there is an association between “the psilocybin-induced ego-dissolution and decreased functional connectivity between the medial temporal lobe and high-level cortical regions” as well as the “disintegration” of the salience network and interhemispheric communication. Tagliazucchi et al. (2016) further introduce the thalamus into the system, claiming that “[h]igh-level association cortices (partially overlapping with the default-mode, salience, and frontoparietal attention networks) and the thalamus showed increased global connectivity under the drug”, which is correlated with subjective reports of “ego dissolution”. Based on the result, the connectivity between a variety of areas of the brain is involved in the process, primarily including the medial prefrontal cortices (mPFC), medial and lateral temporal cortex, and thalamus[[1]](#footnote-2) (Raichle, 2015; Seeley, 2019; Szczepanski et al., 2013). However, these studies do not show whether there is a correlation between the connectivity between these three areas and ego-dissolution.

Another group of neuroscientists investigating the neural base of self-perception focus on Cortical midline structures (CMS), which primarily includes “the orbital and adjacent medial prefrontal cortex (OMPFC), the anterior cingulate (AC), the dorsomedial prefrontal cortex (DMPFC) and the posterior cingulate cortex (PC)” (Northoff & Bermpohl, 2004). Studies show that CMS is associated with the representation, monitoring, evaluation, and integration of self-referential stimuli (Northoff & Bermpohl, 2004), reflecting on the present self[[2]](#footnote-3) (D’Argembeau et al., 2008), and is critical for elaborating experiential feelings of self (Northoff et al., 2006).

Taken from the results, the significance of the medial prefrontal cortex (mPFC) is shared between the two groups, which aligns well with the amount of research that reveals the relationship between the mPFC and self-referential processing (Stendardi et al., 2021; Kelley et al., 2002; Gusnard et al., 2001; Wittmann et al., 2021). To better understand the mechanism behind self-perception, a focus on the mPFC would be inevitable.

**Experimental Design**

The results of Lebedev et al. (2015) and Tagliazucchi et al. (2016) show that ego-dissolution is correlated to decreased functional connectivity between the medial temporal lobe and high-level cortical regions, which partially overlap with the mPFC, as well as the increase in global connectivity between high-level [association cortices](https://www.sciencedirect.com/topics/neuroscience/association-cortex), which also involves the frontoparietal cortex[[3]](#footnote-4), and the thalamus. Based on the two theories, we would like to narrow down the high-level cortical areas involved and further investigate whether there are functional and structural connections between the mPFC, the medial temporal lobe, and the thalamus. Based on the spatial relationship between the mPFC and high-level cortical regions, we hypothesize that a stronger neural connection between the medial temporal lobe and the mPFC, and a weaker connection between the mPFC and the thalamus, may contribute to higher-level self-perception.

**Hypothesis**

When participants experience LSD-induced ego-dissolution, the functional connectivity between the medial temporal lobe and the mPFC would decrease, while that between the mPFC and the thalamus would increase.

**Experimental Procedures**

After participants are recruited and have provided informed consent, we conduct a placebo-controlled experiment. Through random assignment, participants are divided into two experimental (LSD) groups and one control (placebo) group. The experiment consists of two parts.

In the first part, participants in each group are provided with a blotter tab which is either infused with (for the first experimental group) , (for the second) of LSD, or water (placebo) and asked to hold the tab on or under the tongue for 15 minutes so that the drug can get into the bloodstream. The design of having two experimental groups taking different doses of LSD is to allow a comparison between different levels of ego-dissolution (For evidence of higher doses of LSD lead to higher levels of ego-dissolution, see Liechti et al., 2016) when participants are under the effect of LSD. The control group alone may not account for all the differences in brain connectivity occurring after taking LSD/the placebo[[4]](#footnote-5). The dose of is chosen to align with the one currently used in psychotherapy in Switzerland, and in imaging studies (Liechti et al., 2016). Besides, we choose water as the placebo because LSD is colorless, odorless, and tasteless (See [Drug Fact Sheet: LSD (dea.gov)](https://www.dea.gov/sites/default/files/2023-04/LSD%202022%20Drug%20Fact%20Sheet.pdf) for more detail).

After 30 minutes of waiting for LSD to fully take effect, the experiment enters the second part. In this part, participants take an fMRI scan to measure brain connectivity while taking the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale for ego-dissolution measurement. The results of the scan and the 5D-ASC scale are recorded. The scale has been widely used by previous research (Hasler et al., 2004; Hysek et al., 2011; Schmid et al., 2015; Studerus et al., 2010; Vollenweider & Kometer, 2010). Once the scan and the 5D-ASC scale are completed, participants are debriefed and dismissed.

**Result Analysis**

The independent variable in the study is the dose of LSD taken, and the dependent variable is the connectivity between the mPFC, the medial temporal lobe, and the thalamus. In the 5D-ASC scale, the field related to the study is the dimension “Dread of Ego Dissolution (AIA)”, which measures ego disintegration and loss of self-control phenomena, “oceanic Boundlessness (OSE)”, which measures derealization and depersonalization associated with positive emotional states (Dittrich, 1998), and ego dissolution item 71 (“the boundaries between myself and my surroundings seemed to blur”). Performing analysis on these fields can reveal the degree of ego-dissolution (and self-perception) in the mind of the participants.

To validate our hypothesis, we expect individuals who experience the highest degree of ego-dissolution, which should be in the experimental group, to show weaker connectivity between the mPFC and the medial temporal lobe, and greater one between the mPFC and the thalamus. This should also hold for the comparison between the experimental group and the control group, as well as between the experimental group and the control group.

**Discussion**

The experiment we proposed in this paper can help refine the conclusion of previous studies on connectivity between high-level cortices and other brain areas and examine whether the mPFC, which is part of the high-level cortices and is shown to play a significant role in self-perception, also show the same connectivity pattern. If the hypothesis is validated, there are some intriguing questions to be explored: why might a stronger connection between the medial temporal lobe and the mPFC, whereas a weaker connection between the mPFC and the thalamus, lead to higher-level self-perception? Can it be relevant to the functions of these brain areas? If so, which functions may cause this difference? To find the answers to these questions, future studies can focus on a functional and structural comparison between the two regions.

References

D’Argembeau, A., Feyers, D., Majerus, S., Collette, F., Van der Linden, M., Maquet, P., & Salmon, E. (2008). Self-reflection across time: cortical midline structures differentiate between present and past selves. *Social Cognitive and Affective Neuroscience*, *3*(3), 244–252. https://doi.org/10.1093/scan/nsn020

Dittrich, A. (1998). The Standardized Psychometric Assessment of Altered States of Consciousness (ASCs) in Humans. *Pharmacopsychiatry*, *31*(S 2), 80–84. https://doi.org/10.1055/s-2007-979351

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, *30*(12), 1181–1197. https://doi.org/10.1177/0269881116675513

Griffiths, R. R., Johnson, M. W., Richards, W. A., Richards, B. D., Jesse, R., MacLean, K. A., Barrett, F. S., Cosimano, M. P., & Klinedinst, M. A. (2017). 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. *Journal of Psychopharmacology*, *32*(1), 49–69. https://doi.org/10.1177/0269881117731279

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*(7), 4259–4264. https://doi.org/10.1073/pnas.071043098

Hasler, F., Grimberg, U., Benz, M. A., Huber, T., & Vollenweider, F. X. (2004). Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose–effect study. *Psychopharmacology*, *172*, 145–156. https://doi.org/10.1007/s00213-003-1640-6

Hysek, C. M., Simmler, L. D., Ineichen, M., Grouzmann, E., Hoener, M. C., Brenneisen, R., Huwyler, J., & Liechti, M. E. (2011). The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA (“ecstasy”) in humans. *Clinical Pharmacology and Therapeutics*, *90*(2), 246–255. https://doi.org/10.1038/clpt.2011.78

Kałużna, A., Schlosser, M., Gulliksen Craste, E., Stroud, J., & Cooke, J. (2022). Being no one, being One: The role of ego-dissolution and connectedness in the therapeutic effects of psychedelic experience. *Journal of Psychedelic Studies*, *6*(2), 111–136. https://doi.org/10.1556/2054.2022.00199

Kelley, W. M., Macrae, C. N., Wyland, C. L., Caglar, S., Inati, S., & Heatherton, T. F. (2002). Finding the Self? An Event-Related fMRI Study. *Journal of Cognitive Neuroscience*, *14*(5), 785–794. https://doi.org/10.1162/08989290260138672

Lebedev, A. V., Lövdén, M., Rosenthal, G., Feilding, A., Nutt, D. J., & Carhart-Harris, R. L. (2015). Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin. *Human Brain Mapping*, *36*(8), 3137–3153. https://doi.org/10.1002/hbm.22833

Liechti, M. E., Dolder, P. C., & Schmid, Y. (2016). Alterations of consciousness and mystical-type experiences after acute LSD in humans. *Psychopharmacology*, *234*(9-10), 1499–1510. https://doi.org/10.1007/s00213-016-4453-0

Northoff, G., & Bermpohl, F. (2004). Cortical midline structures and the self. *Trends in Cognitive Sciences*, *8*(3), 102–107. https://doi.org/10.1016/j.tics.2004.01.004

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain—A meta-analysis of imaging studies on the self. *NeuroImage*, *31*(1), 440–457. https://doi.org/10.1016/j.neuroimage.2005.12.002

Raichle, M. E. (2015). The Brain’s Default Mode Network. *Annual Review of Neuroscience*, *38*(1), 433–447. https://doi.org/10.1146/annurev-neuro-071013-014030

Ross, S. (2018). Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress. *International Review of Psychiatry*, *30*(4), 317–330. https://doi.org/10.1080/09540261.2018.1482261

Schmid, Y., Enzler, F., Gasser, P., Grouzmann, E., Preller, K. H., Vollenweider, F. X., Brenneisen, R., Müller, F., Borgwardt, S., & Liechti, M. E. (2015). Acute Effects of Lysergic Acid Diethylamide in Healthy Subjects. *Biological Psychiatry*, *78*(8), 544–553. https://doi.org/10.1016/j.biopsych.2014.11.015

Seeley, W. W. (2019). The Salience Network: A Neural System for Perceiving and Responding to Homeostatic Demands. *The Journal of Neuroscience*, *39*(50), 9878–9882. https://doi.org/10.1523/jneurosci.1138-17.2019

Stendardi, D., Biscotto, F., Bertossi, E., & Ciaramelli, E. (2021). Present and future self in memory: the role of vmPFC in the self-reference effect. *Social Cognitive and Affective Neuroscience*, *16*(12). https://doi.org/10.1093/scan/nsab071

Stoliker, D., Novelli, L., Vollenweider, F. X., Egan, G. F., Preller, K. H., & Razi, A. (2023). Effective Connectivity of Functionally Anticorrelated Networks Under Lysergic Acid Diethylamide. *Biological Psychiatry*, *93*(3), 224–232. https://doi.org/10.1016/j.biopsych.2022.07.013

Studerus, E., Gamma, A., & Vollenweider, F. X. (2010). Psychometric Evaluation of the Altered States of Consciousness Rating Scale (OAV). *PLoS ONE*, *5*(8), e12412. https://doi.org/10.1371/journal.pone.0012412

Szczepanski, S. M., Pinsk, M. A., Douglas, M. M., Kastner, S., & Saalmann, Y. B. (2013). Functional and structural architecture of the human dorsal frontoparietal attention network. *Proceedings of the National Academy of Sciences*, *110*(39), 15806–15811. https://doi.org/10.1073/pnas.1313903110

Tagliazucchi, E., Roseman, L., Kaelen, M., Orban, C., Muthukumaraswamy, Suresh D., Murphy, K., Laufs, H., Leech, R., McGonigle, J., Crossley, N., Bullmore, E., Williams, T., Bolstridge, M., Feilding, A., Nutt, David J., & Carhart-Harris, R. (2016). Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution. *Current Biology*, *26*(8), 1043–1050. https://doi.org/10.1016/j.cub.2016.02.010

Vollenweider, F. X., & Kometer, M. (2010). The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. *Nature Reviews Neuroscience*, *11*(9), 642–651. https://doi.org/10.1038/nrn2884

Wittmann, M. K., Trudel, N., Trier, H. A., Klein-Flügge, M. C., Sel, A., Verhagen, L., & Rushworth, M. F. S. (2021). Causal manipulation of self-other mergence in the dorsomedial prefrontal cortex. *Neuron*, *109*(14), 2353-2361.e11. https://doi.org/10.1016/j.neuron.2021.05.027

Yaden, D. B., Nayak, S. M., Gukasyan, N., Anderson, B. T., & Griffiths, R. R. (2021). The Potential of Psychedelics for End of Life and Palliative Care. *Current Topics in Behavioral Neurosciences*, *56*. https://doi.org/10.1007/7854\_2021\_278

1. For the Stoliker et al. (2023)’s study, the whole list of brain areas involved includes (for DMN) cortical areas in the medial and lateral parietal, medial prefrontal, and medial and lateral temporal cortices (Raichle, 2015); (for SN) anterior cingulate, ventral anterior insular (frontoinsular) cortices, and nodes in the thalamus, etc. (Seeley, 2019); and (for DAN) the frontal eye fields and the posterior parietal cortex (Szczepanski et al., 2013). [↑](#footnote-ref-2)
2. The study also shows that CMS is more recruited when reflecting on the present self than when reflecting on the past self or when reflecting on the other person, which demonstrates that it may play a role in present-past selves differentiation. [↑](#footnote-ref-3)
3. The whole list of brain areas that show a correlation to ego-dissolution and are mentioned in the study involves the frontoparietal cortex, the precuneus, temporo-parietal junctions, the bilateral insular cortex, and the bilateral thalamus (Tagliazucchi et al., 2016). [↑](#footnote-ref-4)
4. The limitation of the control group: it is not a double-blind experiment because without having an LSD-induced mystical-type experience, participants in the control group can figure out that they belong to the control group, which may impact the result. There may be some differences in patterns of brain activities that are not caused by LSD but by other thinking behaviors, such as random thoughts as a result of boredom during the fMRI. A different approach may need to be taken for future research. [↑](#footnote-ref-5)