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Scientific Final Report - BIAL Foundation - Grant Nr. 333/20

Mindfulness and Psychedelics: A neurophenomenological approach to the characterization of acute and sustained response to DMT in experienced meditators

Dear Sir or Madam,

We appreciate the financial support from the BIAL Foundation to carry out the above-mentioned research project. We hereby provide the *scientific final report*.

Aims
The central aim is to investigate changes in experiential markers and brain activity following intake of the psychedelic drug DMT during meditation. Accordingly, the experiential features and brain activity patterns characteristic to the mindfulness-related effects of DMT were elucidated.

Method
We conducted an innovative double-blind, randomized, placebo-controlled, between-subjects study design that included fMRI recordings, phenomenological interviews, and psychometric self-reports from 40 experienced male and female meditators before and after the administration of DMT (120 mg per session) with MAO-inhibitor harmine (120 mg per session) or placebo during a mindfulness group retreat.

Participants. 40 experienced meditators (18 female, 22 male), participated in one of two 3-day meditation retreats, receiving in a double-blind manner either placebo or DMT combined with harmine. Participants had a mean age of 43.73 years (27–60, SD: 10.30) and 82.5% had post-graduate degrees. 95% of the participants were Caucasian. Participants reported an average of 2422.5 hours of meditation (800–10,000), coming from various traditions, including Zen, Vipassana, and Tibetan Buddhism.
The study was approved by the Cantonal Ethics Committee of Zurich, Switzerland, and received an exemption from the Federal Office of Public Health (FOPH) for the administration of the controlled substance DMT.

Written informed consent was obtained from all participants. The study was performed according to the Declaration of Helsinki (ClinicalTrials.gov identifier: NCT05780216).

Instruments/measures. The outcome measures can be distinguished along the two aims of the research project: psychometric experiential markers and neurodynamic activity patterns.

The psychometric experiential part outcome measures of this study can be distinguished into four clusters: (1) mindfulness, (2) compassion, (3) insight, and (4) transcendence. Additional outcome measures included items on the perceived meaningfulness and spiritual significance of the study experience and items assessing the blinding efficacy of the double-blind study design. The following psychometric instruments were central: Toronto Mindfulness Scale- State Version (TMS-13), Freiburg Mindfulness Inventory-13 (FMI-13), Sussex-Oxford Compassion Scales for Self and Other (SOCS-O & SOCS-S), Psychological Insight Scale (PIS-6), Emotional Breakthrough Inventory (EBI), Mystical Experience Questionnaire (MEQ30), Nondual Awareness Dimensional Assessment – State (NADA-S).

Resting-state fMRI scans (7.5 minutes, closed eyes) were acquired one day before and one day after the retreat, i.e., 2 days pre- and two days post-drug administration. Functional data were preprocessed using the nipype-based fMRIprep pipeline (v23.0.2) and analyzed with the Conn Toolbox (v22.a) in Matlab. Denoising involved 24 head motion parameters, component-based noise reduction (aCompCor), and scrubbing (FD<0.5 mm). Analyses included seed-to-voxel analyses of seven resting-state networks (RSN), as defined by Yeo and colleagues, between- and within-network changes, and global connectivity. For between- and within-network changes, mean timeseries of each network were extracted and correlated with each voxel of the brain (between-network approach) or with each voxel of the network (within-network approach). The full GLM design matrix included both conditions (verum-placebo) and both timepoints (post-pre). We also analyzed pre to post changes in the placebo and verum group independently, as well as changes between the two groups in the post-intervention scans. Global correlation maps were used to calculate network centrality at each voxel and analyzed with a GLM at the second level using the approach from above. All voxel-thresholds were set to $p < 0.001$, cluster-thresholds were set to $p < 0.05$, FDR-corrected.

Procedure. The study followed a double-blind, placebo-controlled, between-subject design and investigated the effects of DMT-harmine on multiple attitudinal and experiential outcome measures.

Each of the 40 participants was randomly assigned to one of two groups (placebo, DMT-harmine) which were matched for gender, age, and lifetime meditation hours.

Participants completed one of two subsequent 3-day meditation retreats, with 19 participants (9 DMT-harmine, 10 placebo) in the first retreat and 21 participants (11 DMT-harmine, 10 placebo) in the second retreat.

The 3-day retreats took place in a meditation center where participants practiced mindfulness and compassion meditation in structured daily group sessions. Each day of the retreat, sitting meditation in the zendo, i.e. a traditional Zen meditation hall, was interleaved with walking meditation, mindful physical work, short breaks, and meals.

On the second day of the retreat, participants continued their meditation practice while receiving incremental doses of DMT-harmine or placebo, administered in a double-blind manner. The dose administrations started at 10:30 in the morning followed by periods of (1) sitting meditation (20 min), (2) vital sign measurements and acute psychometry (5 min), and (3) walking meditation (5 min). Placebo or DMT-harmine was administered after the walking meditation and before the next sitting meditation period. Moreover, the adapted retreat schedule contained additional musical elements and relaxation periods after the last dose administration. Participants were encouraged to engage in a formal meditation posture only to the extent to which it

remained comfortable to them and to take a gentle approach to meditation with an effortless rather than forceful attitude.
Accordingly, the retreat consisted of three phases: preparation (day 1), placebo or DMT-harmine administration (day 2), and integration (day 3). During the retreat, questionnaires were filled out at the end of day 1 (18:30), day 2 (14:30 and 16:30), and day 3 (18:30). On day 2 acute psychometric questions were filled out at baseline as well as 30, 60, 90, 120, 180, 240, and 360 minutes after the first drug/placebo intake. Moreover, participants filled out questionnaires one day before and one day after the retreat, as well as at 1-week follow-up and 1-month follow-up.

Results Summary

Compared to meditation with a placebo, meditators who received DMT and harmine self-attributed greater levels of mystical-type experiences, non-dual awareness, and emotional breakthrough during the acute substance effects and, if corrected for baseline differences, greater psychological insight one day later. Mindfulness and compassion were not significantly different in the DMT-harmine group compared to placebo. At 1-month follow-up, the meditators who received DMT and harmine rated their experience as substantially more personally meaningful, spiritually significant, and well-being-enhancing than the meditators who received placebo. This study contributes novel evidence highlighting the potential meditation-enhancing effects of the psychedelic compound DMT combined with harmine.
The comparison of post-pre scans for the placebo condition revealed significantly reduced connectivity changes between 6 out 7 (except the sensory-motor network) RSNs and other clusters in the brain. Within-network analyses did not yield significance. Global correlation analysis revealed three clusters with decreased connectivity for the post-pre contrast of placebo scans in the precentral gyrus, the inferior frontal gyrus and the precuneus. Post-pre comparisons of the verum group revealed significantly increased connectivity from the visual, dorsal attention and salience network to the left occipital pole. Within-network and global correlation analyses did not yield significance. No differences were found between the two groups' pre-intervention scans for any measure. Regarding the verum-placebo post-pre contrast, we observed significantly increased salience network connectivity to bilateral occipital poles, bilateral cuneal cortex and lateral occipital cortex, while the visual network showed increased functional connectivity to left and right insula.

Discussion & Conclusions

Contributing to a rapidly growing body of research targeting potential synergistic effects between meditation and psychedelics, this present study brings nuance into how psychedelics may support meditation practice and well-being. The results of the present study indicate that the psychedelic substance DMT combined with the MAO inhibitor harmine may support meditative processes, in particular through occasioning deeply meaningful mystical-type experiences with increased non-dual awareness and emotional breakthroughs that may facilitate subsequent meditative psychological insights. These results suggest that DMT-harmine may promote meditation-related well-being through eliciting experiences of insight, transcendence, and meaning rather than through mindfulness or compassion.
Regarding brain activity, our findings suggest that subacute effects of combining DMT and harmine in a meditation retreat setting enhance connectivity between various brain networks, contrasting with the opposing effects observed without pharmacological intervention. Furthermore, subacute effects of the psychedelic did not alter within-network or global connectivity. This underscores distinctions in neurodynamics between altered states induced by the psychedelic ayahuasca-derived formulation and contemplative practice alone.

Outputs and Outcomes

In the first phase of the project (October 2021 - March 2022), the following milestones were achieved:

1) We have contracted the German manufacturer Central Glass GmbH to synthesize a batch of N,N-Dimethyltryptamine (DMT) for human clinical trials. The costs for the production are covered by Reconnect Labs AG, a spin-off at the University of Zurich, with the advantage that the study medication will be provided free of charge for this research project.
2) More than 200 experienced meditators were pre-screened by telephone interviews and 43 participants were selected for medical/psychological screenings on-site.
3) A project database (eCRF) was implemented in collaboration with Webspirit Systems GmbH.
4) The fMRI sequences were implemented and tested in pilot subjects (including an additional behavioral fMRI task focusing on compassion and Theory of Mind processing).
5) The trial master file (TMF), data management system, and monitoring plan were finalized in Q1 2022 (including the initial site initiation visit and training of study personnel).
6) In terms of scientific output, our team has produced two peer-reviewed articles, duly acknowledging the BIAL Foundation's support: A conceptual paper on meditation research has already been accepted in Frontiers in Psychology and an empirical paper about meditation and psychedelics is ready for submission to Nature Scientific Reports.
7) Additional funding (17k EUR) for this project has been granted by Mind and Life (European Varela Award), to cover complementary research expenses and to bridge salary expenses resulting from study-specific delays.

In the second phase of the project (April 2022 – September 2023), the following milestones were achieved:
Expected and achieved output:

1) More than 200 experienced meditators were pre-screened by telephone interviews and 45 participants were selected for medical/psychological screenings on-site. The participant recruitment has been successfully completed: 20 participants were enrolled for the first study retreat (May 22nd-28th 2023; 1 participant dropped out due to health reasons); 21 participants were enrolled for the second study retreat (July 31st – August 5th 2023), leading to a total of 40 participants.
2) Both study retreats (May 2023 and August 2023) were successfully conducted, including the pharmacological intervention and the meditation intervention.
3) Most of the data were successfully collected: The fMRI data were collected, including resting state functional connectivity and neural responding to the EmpaToM task, a validated fMRI paradigm to manipulate empathy and Theory of Mind. Also, psychometric data were successfully collected, including the 1-week and 1-month follow-up of the first study cohort (May retreat cohort). The 1-week and 1-month follow-up psychometric data of the second study cohort (August retreat cohort) were collected in mid-August and early September 2023. Micro-phenomenological interviews with the participants were conducted, targeting the phenomenological structure of their experiences. Blood samples before and after the retreats have been collected as well.
4) In summary, all the relevant data acquisition was completed in early September 2023 including collection of the last psychometric measurements at 1-month follow-up.

In the final phase of the project (September 2023 – March 2024), the following milestones were achieved:

1) Data analysis for the main publication is completed.
2) Manuscript preparation of the main publication is completed.
3) The main manuscript is submitted to a peer-reviewed journal.
4) Two abstracts were submitted to the 13th Symposium of BIAL Foundation

Expected and achieved output:

Expected Output	Achieved Output
32 participants	40 participants
Meditation retreats: March 1st to March 6th, 2022 (Group A) and from May 9th to 14th, 2022 (Group B)	Meditation retreats: May 22nd - 28th 2023 (Group A) and July 31st – August 5th 2023 (Group B)
Completion of Data acquisition (including 1-month follow-up) was expected for June 2022	Data acquisition (including 1-month follow-up) was completed September 2023
Methods: multimodal EEG/fMRI	Methods: fMRI (we encountered technical problems with simultaneous EEG/fMRI recordings (artifacts) at our study site, which would significantly impair the quality and interpretation of the EEG signals. After consulting with several experts, we were advised to rather conduct only one imaging modality (fMRI). To use the scanning time efficiently and to assess additional modulatory effects of the DMT-assisted meditation retreat on brain activity, we propose to include a well-established and validated compassion task (EmpaToM) provided by Prof. Tania Singer (Social Neuroscience Lab, Max Planck Society).
DMT production by Central Glass GmbH	DMT production through extraction (due to repeated delays communicated to us by Central Glass GmbH)

List of Publications that duly acknowledge the BIAL Foundation's support:

Meling, D., Egger, K., Aicher, H.D., Jareño Redondo, J., Mueller, J., Dornbierer, J., Temperli, E., Vasella, E.A., Caflisch, L., Pfeiffer, D.J., Schlomberg, J.T.T., Smallridge, J.W., Dornbierer, D.A., Scheidegger, M., under review. Meditating on psychedelics. A randomized placebo-controlled study of DMT and harmine in a mindfulness retreat. Journal of Psychopharmacology. https://www.dropbox.com/scl/fi/2g2d5lusk4kzkmpid1dga/draft_Proof_hi.pdf?rlkey=v0yzwje2wjdtjdy67ul3si2ep&dl=0

Singer, B., Meling, D., Hirsch-Hoffmann, M., Michels, L., Kometer, M., Smigielski, L., Dornbierer, D., Seifritz, E., Vollenweider, F.X., Scheidegger, M., accepted. Psilocybin enhances insightfulness in meditation: a perspective on the global topology of brain imaging during meditation. *Sci Rep* 14, 7211 (2024). https://doi.org/10.1038/s41598-024-55726-x

Aicher, H. D., Mueller, M. J., Dornbierer, D. A., Suay, D., Meling, D., Mueller, J., ... & Scheidegger, M. (2024). Potential therapeutic effects of an ayahuasca-inspired N, N-DMT and harmine formulation: a controlled trial in healthy subjects. Frontiers in Psychiatry, 14, 1302559. https://doi.org/10.3389/fpsyt.2023.1302559

Meling, D., Scheidegger, M., 2023. Not in the drug, not in the brain: Causality in psychedelic experiences from an enactive perspective. Frontiers in Psychology. 14, 1100058. https://doi.org/10.3389/fpsyg.2023.1100058

Meling, D., 2022. Knowing the Knowing. Non-dual Meditative Practice From an Enactive Perspective. Frontiers in Psychology. 13, 778817. https://doi.org/10.3389/fpsyg.2022.778817

With the completion of this project and the approval of the scientific and financial final report, we herewith kindly request the reimbursement of the grant's last installment.

Thank you for evaluating our final report and for supporting our research. If you have any further questions, please do not hesitate to contact me.

Yours sincerely,

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