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Psychedelics and Pain: Understanding the Roles of Psychedelics and Clinicians in Facilitating Brain Change

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Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

- Consultant, Cala Health, Inc.
- Consultant, Click Therapeutics, Inc.

Why Psychedelics for Chronic Pain?



- 30% prevalence in adult US population (Johannes, et al. 2010)
- Difficult to treat → system changes affecting *sensory, emotional, & cognitive* processes (Varrassi, et al. 2010)
- 70% of chronic neuropathic pain patients fail to respond to opioids or other conventional analgesics
- Mediators for pain overlap neuropsychiatric factors (catastrophizing, negative affect, etc.)

Fear-Avoidance Model of Chronic Pain

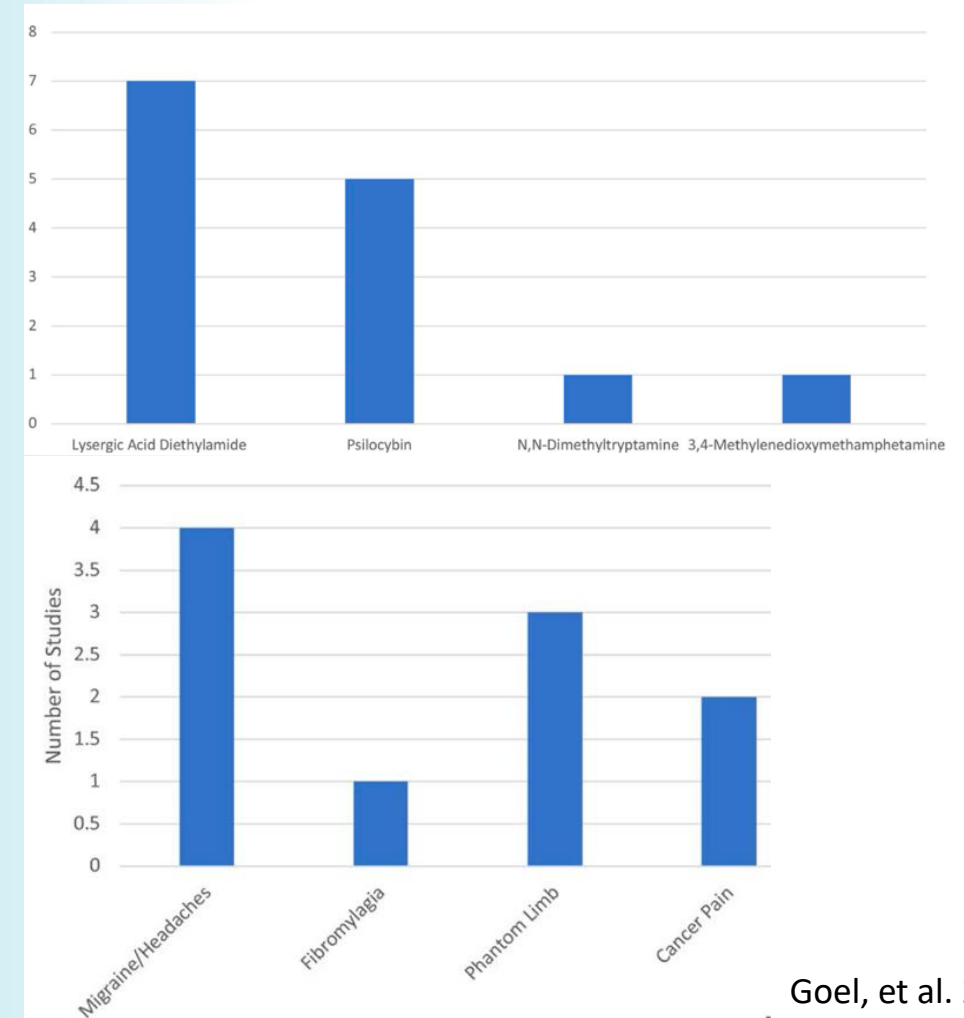


McCracken, et al. 1992. Waddell, et al. 1993. Vlaeyen, et al. 1995. Asmundson, et al. 1999.

Why Psychedelics for Chronic Pain?



- Limited literature on classic psychedelics and chronic pain → mainly reviews (e.g., Goel, et al. 2023)
- Psychedelics-induced analgesia
 - LSD for cancer pain (Kast & Collins, 1964)
 - LSD &/or psilocybin for phantom limb pain (Kuromaru, et al. 1967, Fanciullacci, et al. 1977, Ramachandran, et al. 2018)
 - LSD &/or psilocybin for cluster headaches (Sewell, et al. 2006, Karst, et al. 2010, Schindler, et al. 2015, Andersson, et al. 2017)



Goel, et al. 2023

Current trials for Chronic Pain



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Psilocybin in Adults With
Fibromyalgia

UMich, Ann Arbor

Psilocybin Therapy for
Chronic Low Back Pain

UCSF, San Francisco

Psilocybin-assisted Therapy
for **Phantom Limb Pain**

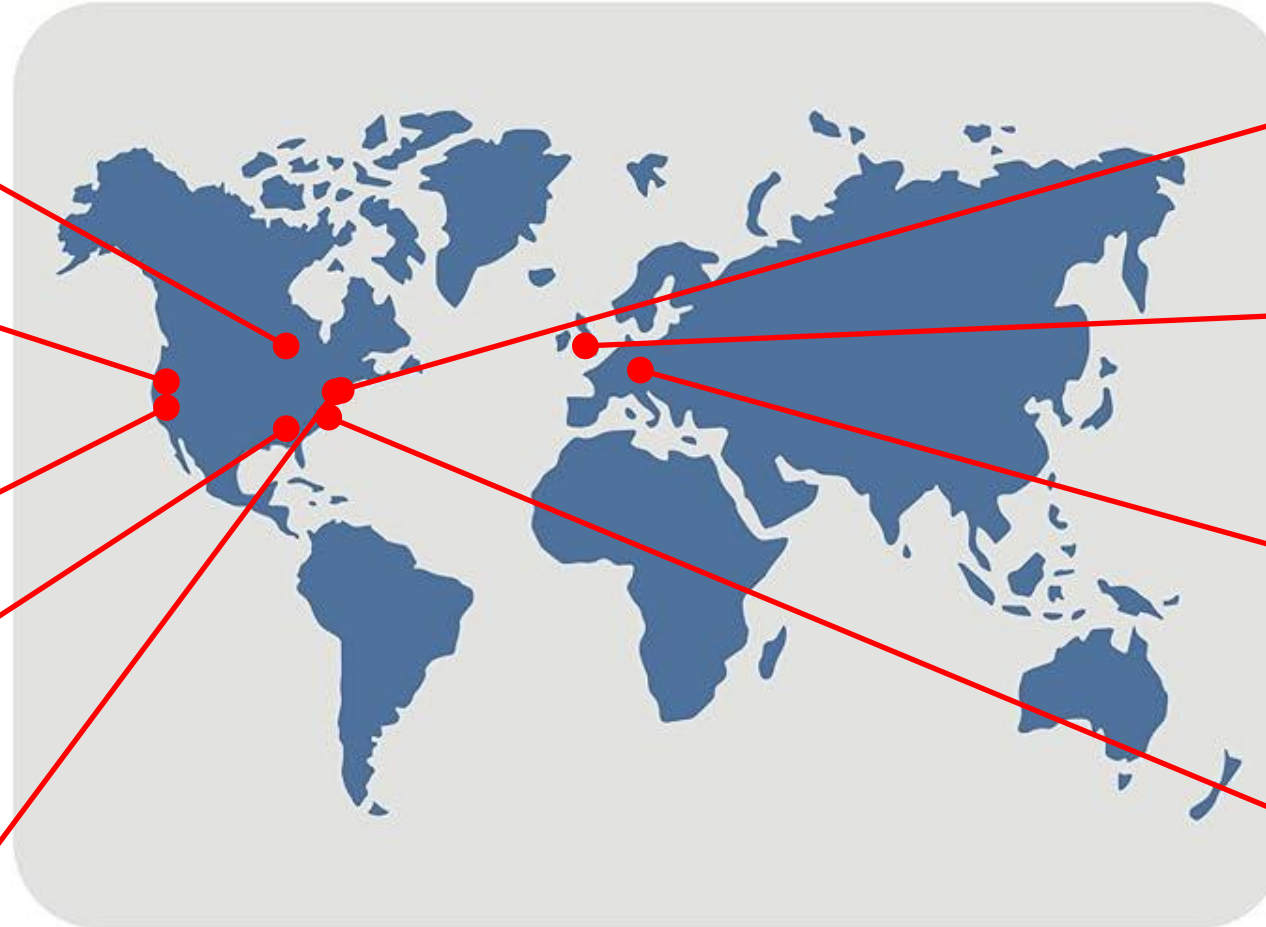
UCSD, San Diego

Psilocybin-facilitated
Treatment for **Chronic Pain**

UAB, Birmingham

MDMA-assisted Therapy
for **Fibromyalgia**

Spaulding Rehab, Boston



Psilocybin in
Cancer Pain Study

Dana-Farber, Boston

Psilocybin in **Fibromyalgia:**

EEG Brain Biomarkers

Imperial College, London

Lysergic Acid

Diethylamide (LSD) as

Treatment for **Cluster
Headache**

Basel, Switzerland

Psilocybin in **Cancer**

Survivors With Chronic **Pain**

Emory U, Atlanta

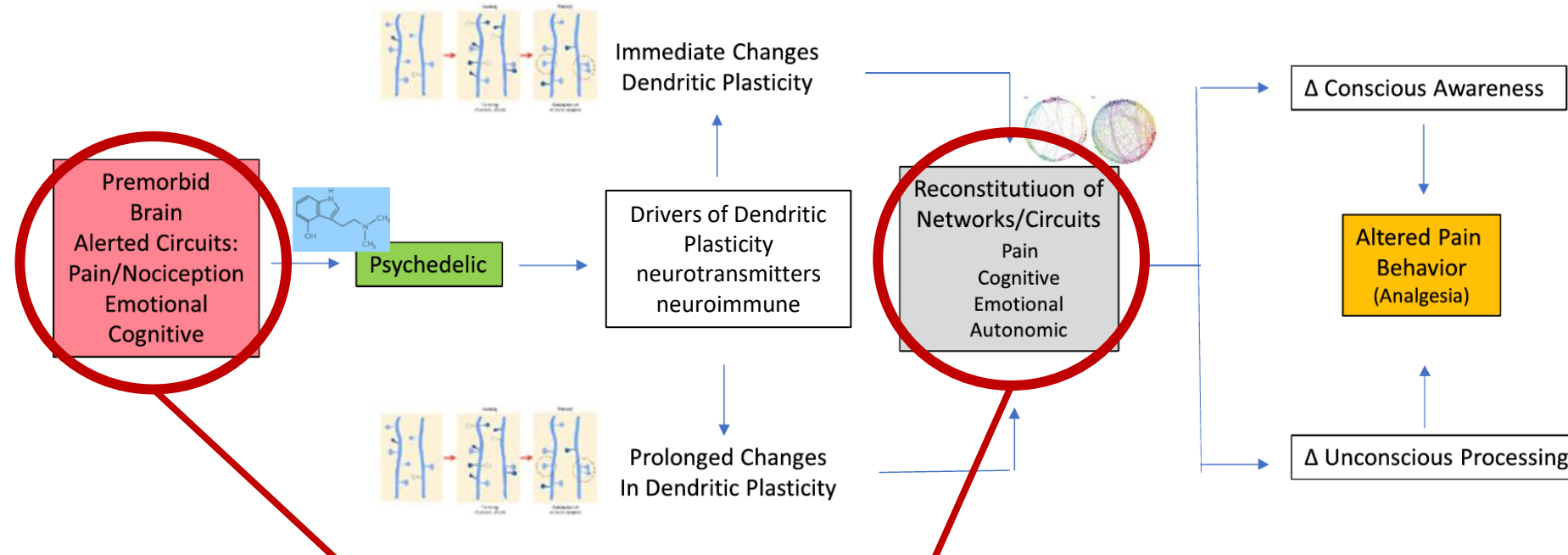
ClinicalTrials.gov

WWW.MGHCMCME.ORG

Model: Psychedelics Target Brain Network Plasticity?

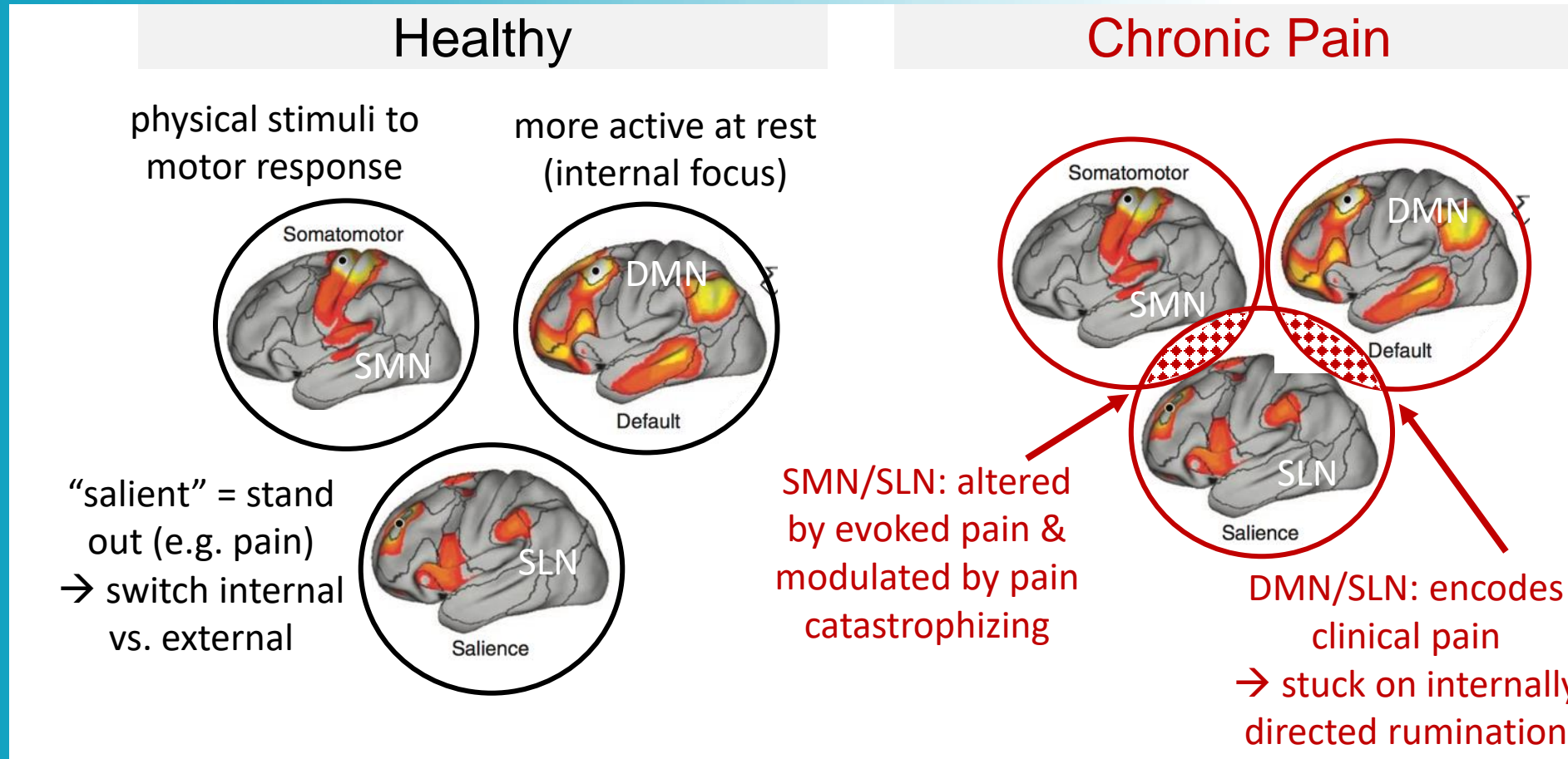


Model “How psychedelics may alter pain behavior”: effects on pain systems (Elman, et al. 2022)



Mechanistic studies needed to understand brain networks for chronic pain & psychedelics

Chronic Pain Characterized by Brain Network Enmeshment (maladaptive neuroplasticity?)



Kim, et al. *Pain* 2019

Chronic Pain Characterized by Brain Network Enmeshment



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- Psychedelics-assisted therapy to optimize pain management skills vs. analgesic effects (e.g. PTSD / depression approaches)
 - Psychedelic experience → heightened cognitive clarity and increased emotional receptivity
 - Potential cognitive reattribution processes that target dysfunctional thoughts towards pain (e.g., pain catastrophizing, negative affect)
 - Boosting therapeutic alliance i.e., a positive patient-clinician relationship → increased range of positive emotions, interpersonal trust, and heighten state of empathic rapport



Psychedelics generally not considered a therapy in itself but rather “a tool for patient and therapist” (MAPS guidelines, <https://maps.org>).

Therapeutic Alliance Important for Pain and Depression



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Ferreira, et al. 2013

- RCT of spinal manipulation, exercise for cLBP (N=182): patient-clinician “therapeutic alliance” was predictor and moderator of pain and other outcomes → authors suggest: boost efficacy of interventions by enhancing therapeutic alliance

Wampold, 2015

- psychotherapy for depression meta-analysis: effect size for contextual factors (empathy, alliance) > specific factors



Upregulating Neuroplasticity for Enhanced Therapy



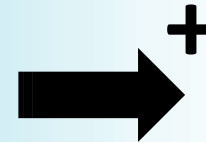
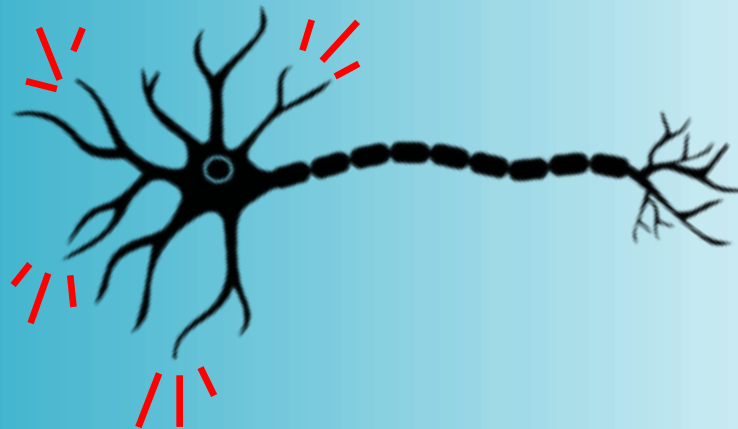
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psychedelics



neuroplasticity



Psychedelic-assisted therapy



How to investigate the neural mechanisms supporting psychedelic-assisted therapy and patient/clinician therapeutic alliance?

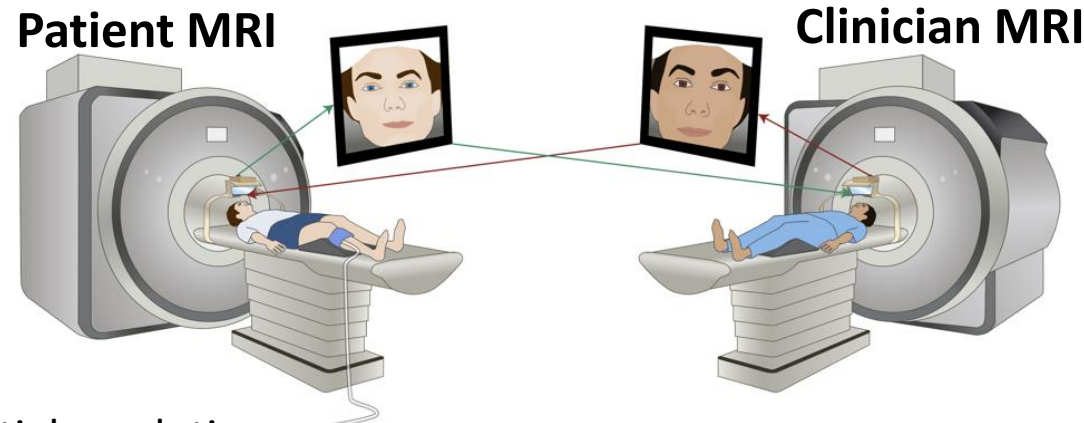


“Hyperscanning” Brain Mechanisms of Therapeutic Alliance



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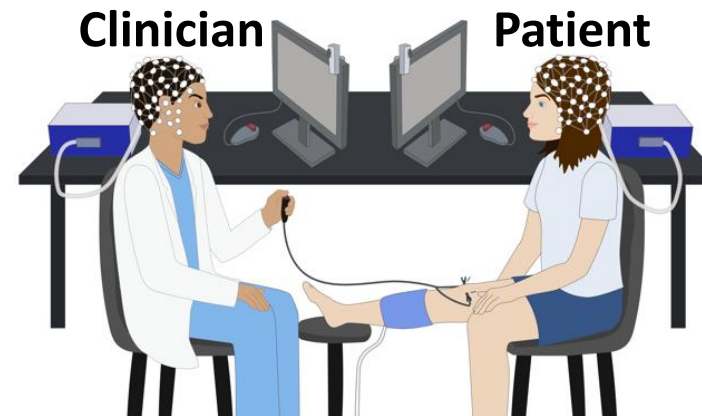
Arvina Grahl, PhD
(SRH/Harvard)

MRI: high spatial resolution

→ precise location of involved brain regions

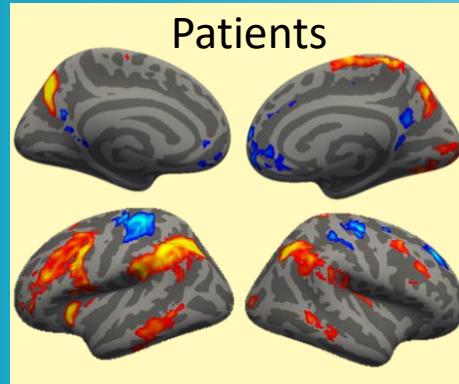
EEG: high temporal resolution

→ temporal dynamics of underlying processes

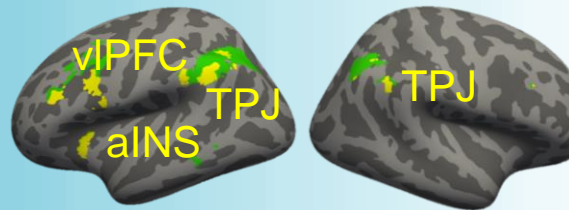
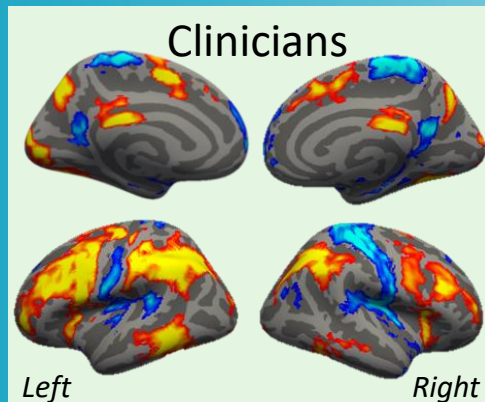


Alessandra Anzolin,
PhD (SRH/Harvard)

“*Hyperscanning*” Brain Mechanisms of Therapeutic Alliance



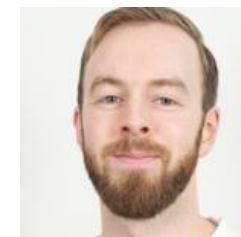
Brain responses during anticipation of pain/treatment



- Overlap (Patients \cap Clinicians)
- Overlap with *a priori* social mirroring circuitry

Temporoparietal Junction (TPJ) is known for brain processing of social mirroring & theory of mind (ToM)

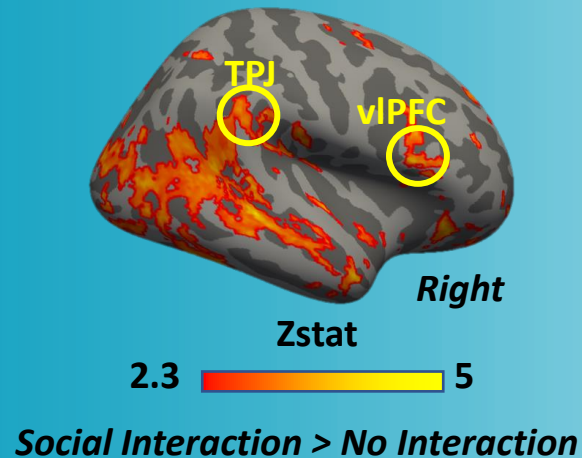
Ellingsen, et al. *Science Advances*. 2020



“Hyperscanning” Brain Mechanisms of Therapeutic Alliance

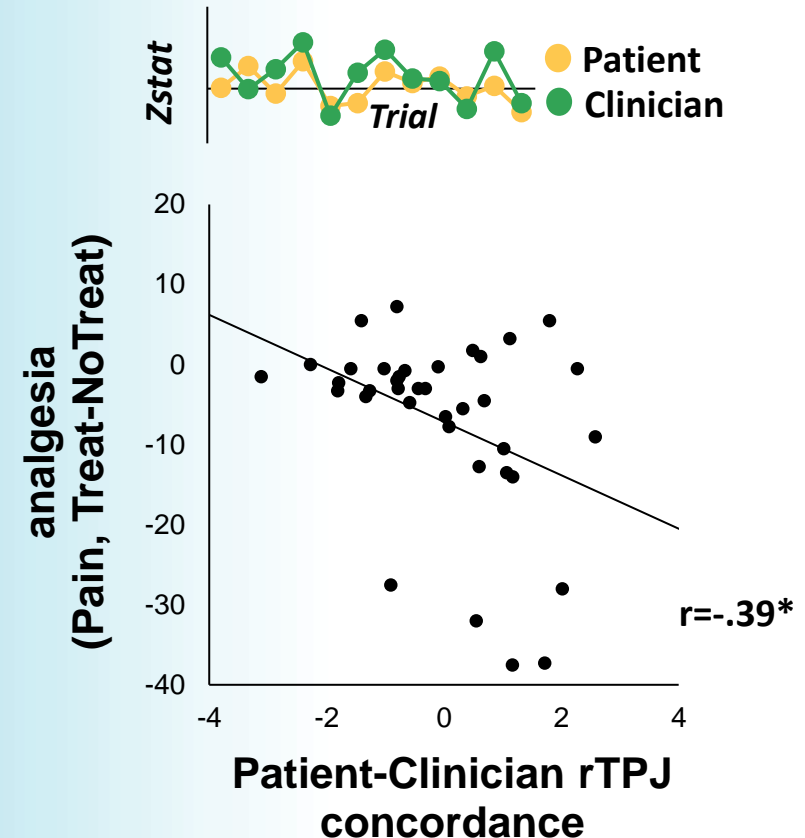


Clinicians’ dynamic concordance with patients’ rTPJ



Greater TPJ concordance and facial expression mirroring associated with greater analgesia → ToM processing via facial mirroring (i.e., non-verbal) supporting socially-mediated analgesia during clinical context

Patient-clinician concordance in right TPJ



Pilot study: Hyperscanning MDMA-Assisted Therapy for Pain



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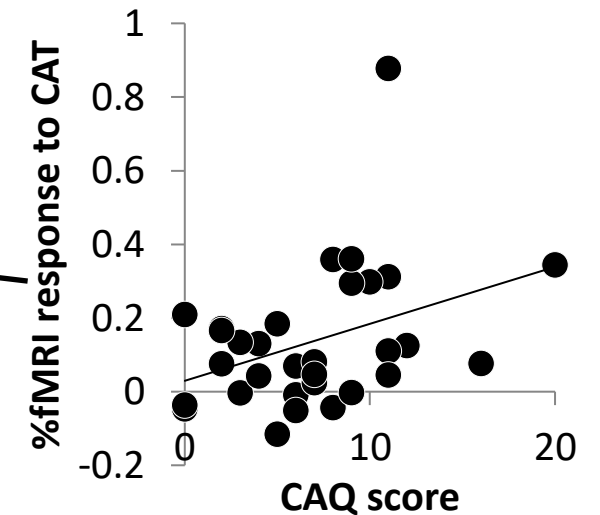
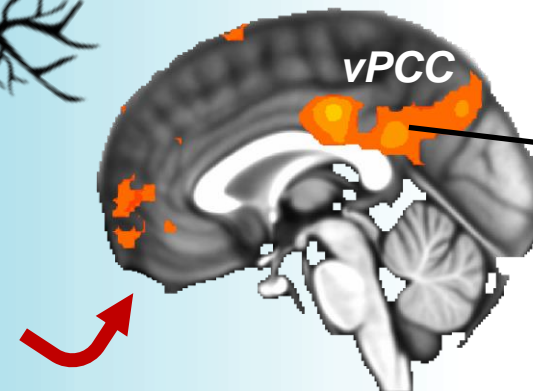
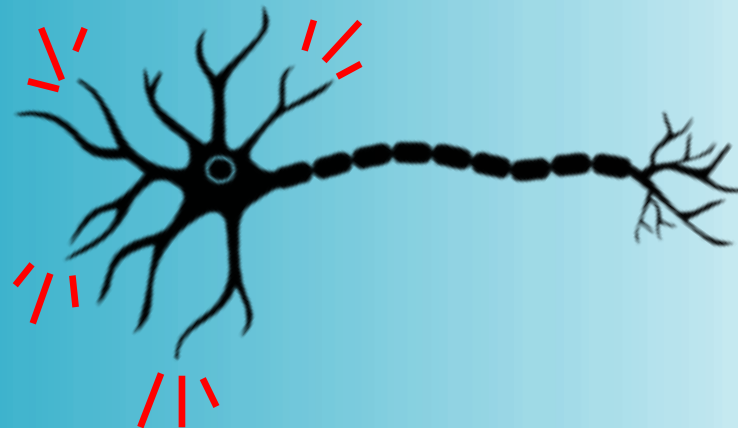
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MDMA-assisted therapy

pro-social
psychedelic
(MDMA)



neuroplasticity



Use task focused on pain rumination
(Lee, et al. *Arthritis & Rheumatology* 2018)

MDMA-Assisted Therapy for PTSD



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nature
medicine

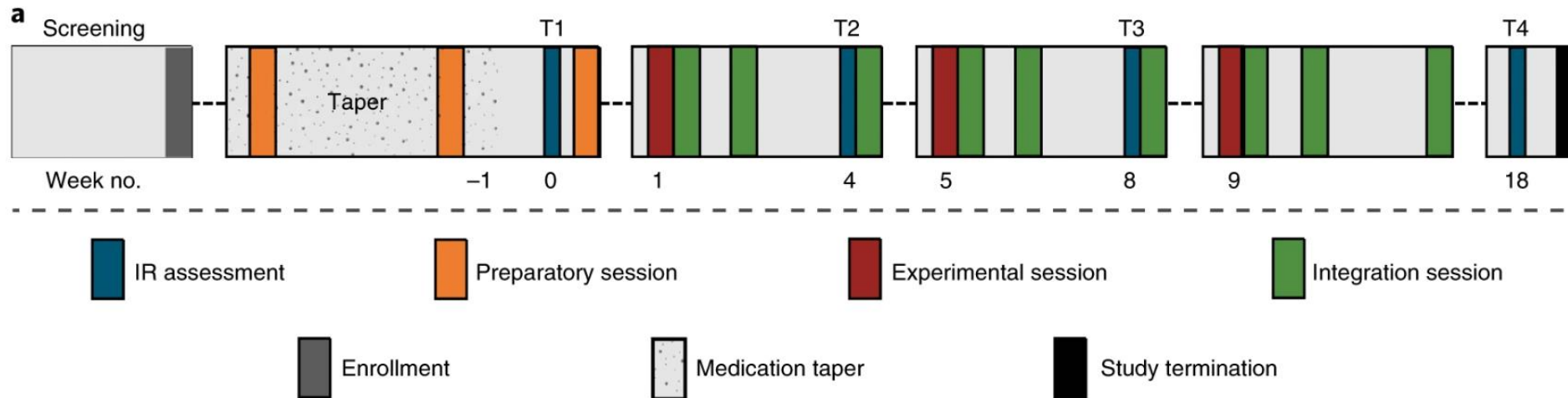
ARTICLES

<https://doi.org/10.1038/s41591-021-01336-3>

Check for updates

OPEN

MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study



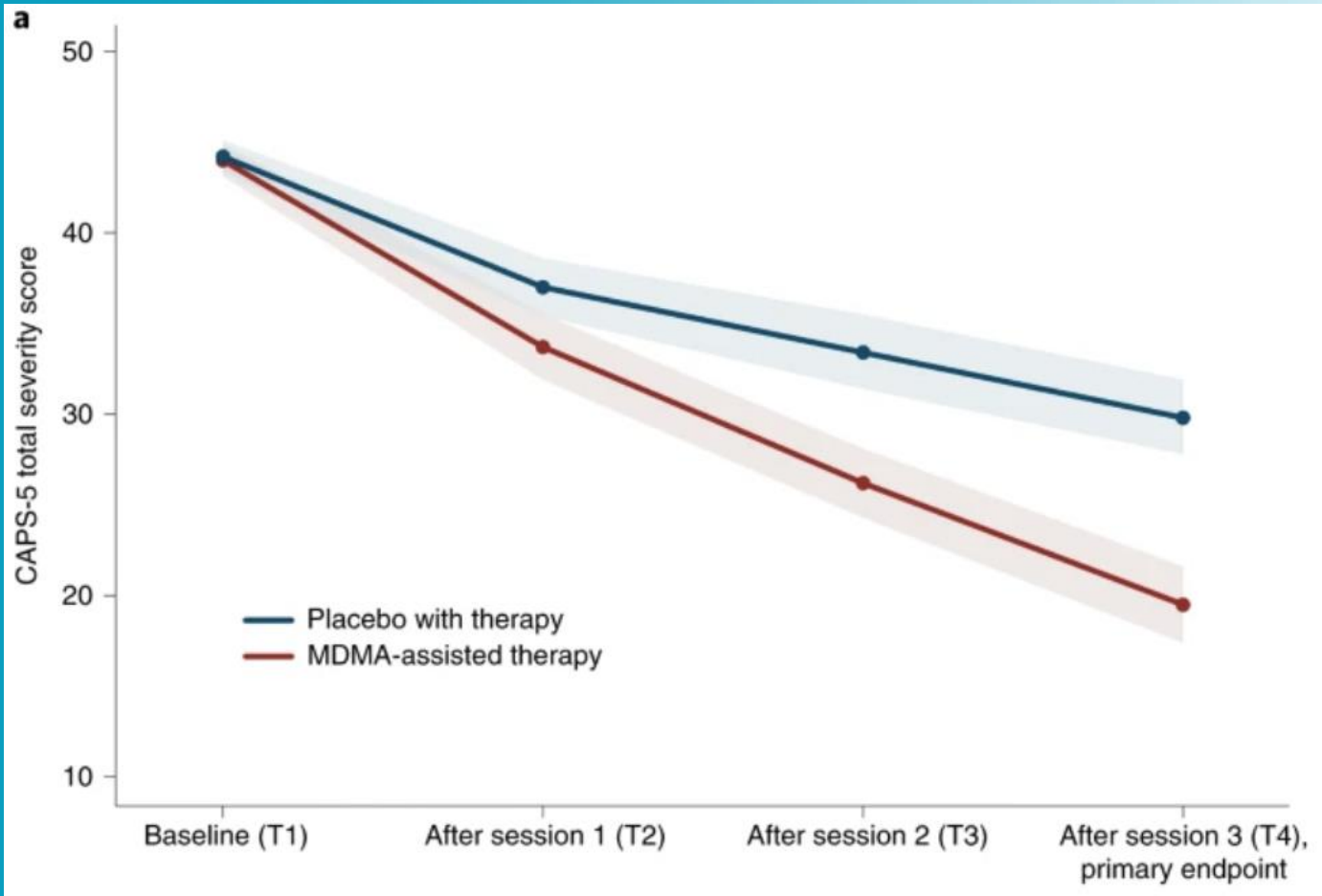
Mitchell, et al. 2021

MDMA-Assisted Therapy for PTSD



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- Reduced severity scores on the structured Clinically Administered PTSD Scale (CAPS-5)
- Despite recent setbacks, MDMA may be eventually FDA-approved for PTSD

Mitchell, et al. 2021

MDMA-Assisted Therapy for PTSD



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 frontiers | Frontiers in [Psychiatry](#)

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MDMA-assisted therapy is associated with a reduction in chronic pain among people with post-traumatic stress disorder

Christie, et al. 2022

- Analysis of Phase 2 MAPS-sponsored study data
- 84% of PTSD patients reported suffering from pain
- *Significant pain reduction reported for patients in severe and moderate pain subgroups*

Hyperscan Neuroimaging for MDMA-Assisted Therapy in Fibromyalgia



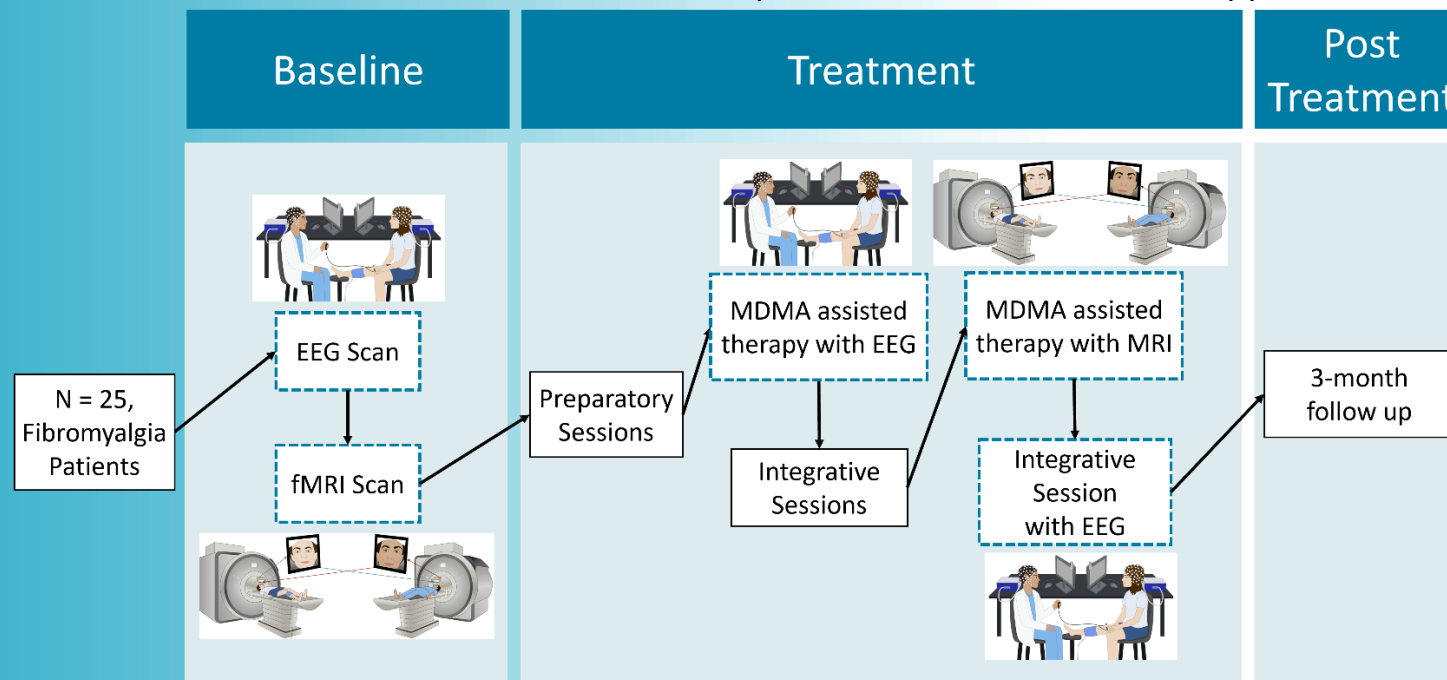
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- Therapeutic alliance: positive patient-clinician relationship → acknowledged as an essential component for MDMA-assisted therapy (*preparatory sessions build rapport and alliance, MAPS*)

***Our study is now FDA
and IRB approved,
awaiting DEA
approval
(enrollment 2024)***

Hyperscan neuroimaging & MDMA-assisted therapy in Fibromyalgia
→ clinical and brain response to MDMA-assisted therapy



Summary



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- Prior research suggests efficacy of psychedelics for pain
- Hyperscan fMRI and EEG and can be used to study the brain mechanisms supporting pain patient/clinician interactions and therapeutic alliance
- Psychedelics may change how pain patients relate to clinicians and vice versa, enhancing therapeutic alliance and clinical outcomes → establish importance of psychedelic-assisted therapy for chronic pain
- **Future directions:**
 - Mechanisms of action for the “therapy” part of psychedelic-assisted therapy for pain & other disorders
 - What type of guided therapy works best for which patients and with which psychedelic substance?



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Thank You