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

Vitaly Napadow, PhD

Director, Scott Schoen and Nancy Adams Discovery Center for Recovery from
Chronic Pain at Spaulding Rehabilitation Hospital

Director of the Center for Integrative Pain NeuroImaging (CiPNI)
at Martinos Center for Biomedical Imaging at Massachusetts General

Professor of Physical Medicine and Rehabilitation and Radiology,
Harvard Medical School





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?



Mechanisms for developing chronic pain not completely understood → likely involve interplay between

- somatic/visceral afferent input
- peripheral & central sensitization
- emotional state
- behavior & cognition

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

Fear-Avoidance Model of Chronic Pain



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

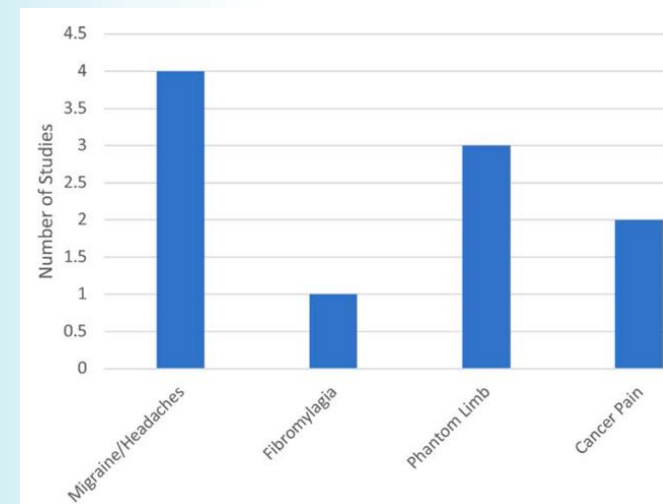
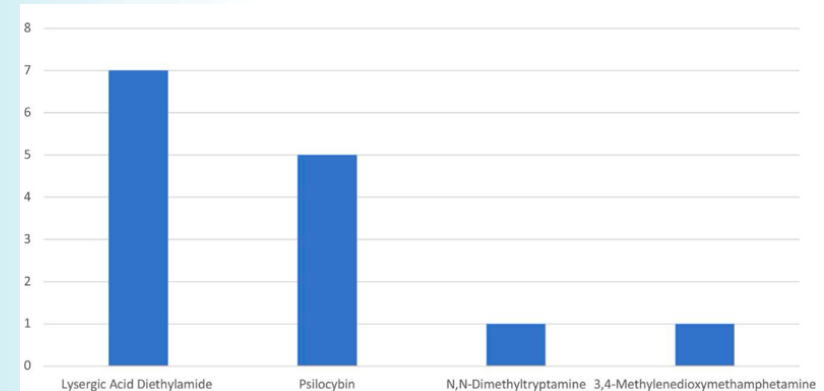


Why Psychedelics for Chronic Pain?

- 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)

Efficacy across different chronic pain conditions: pain relief, shorter cluster periods, reduced frequency/severity of symptoms

→ But: 1960's/1970's studies, newer studies needed

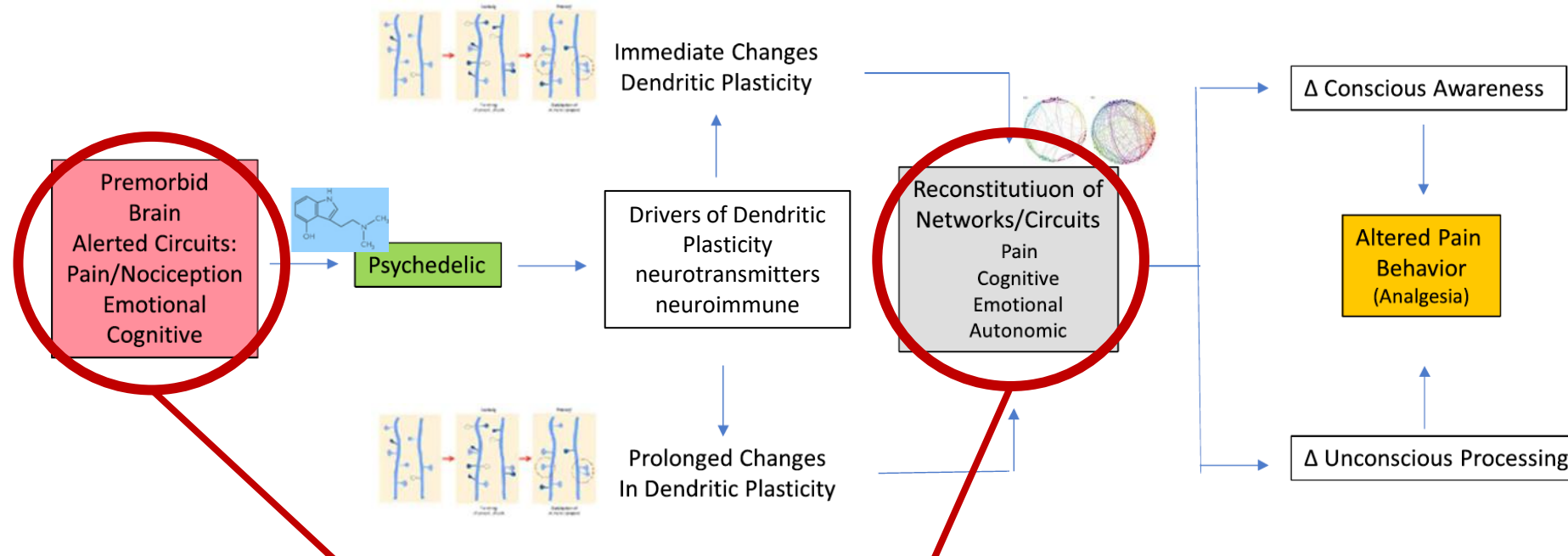


Goel, et al. 2023.

Model: Psychedelics Target Brain Network Plasticity?

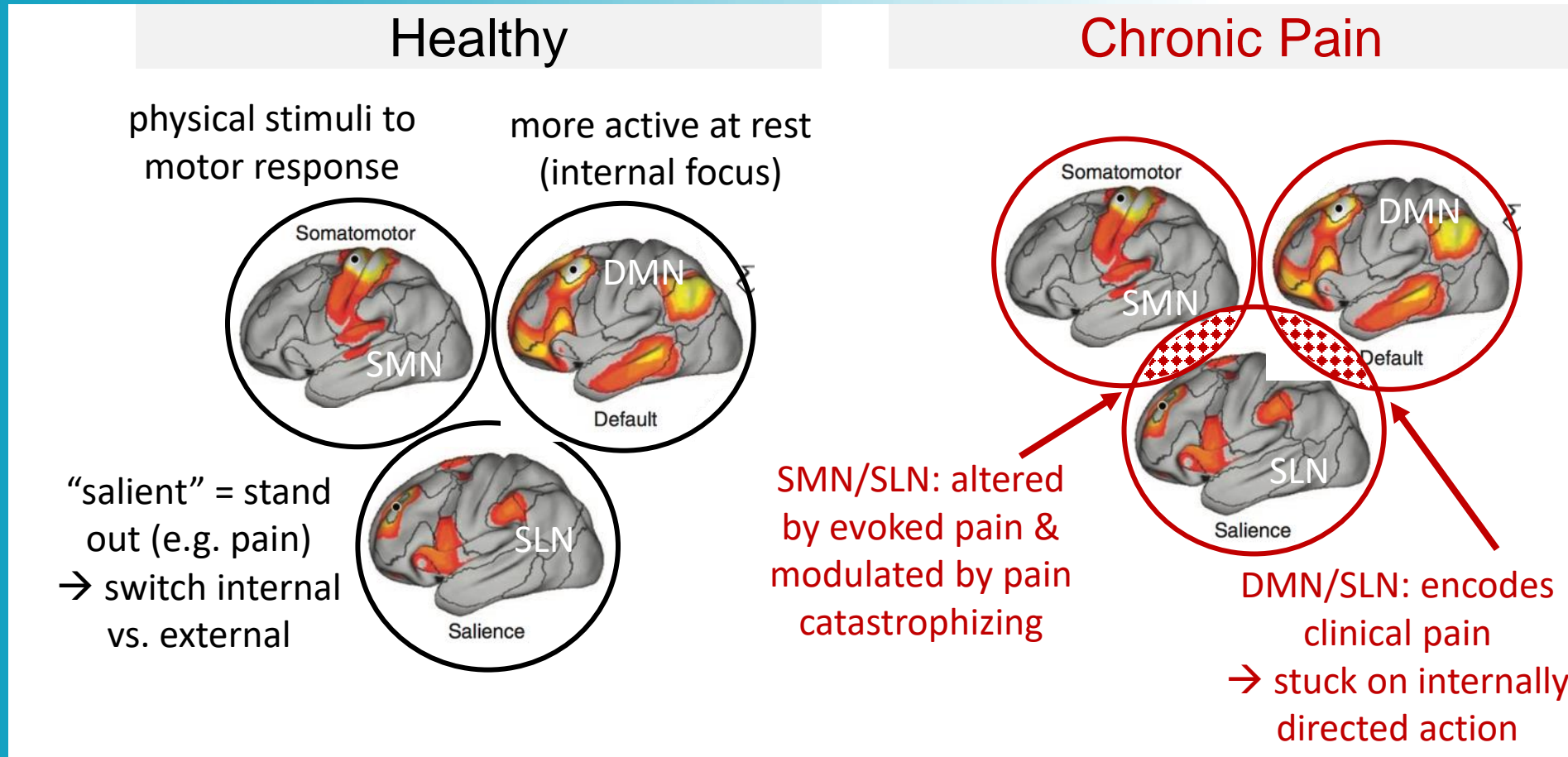


Model “How psychedelics may alter pain behavior”: effects on pain systems (Elman, et al. 2022)



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

Chronic Pain Characterized by Brain Network Enmeshment



Kim, et al. *Pain* 2019.



Chronic Pain Characterized by Brain Network Enmeshment

- Psychedelics-assisted therapy to optimize pain management skills vs. analgesic effects (see PTSD/depression approaches)
 - Psychedelic experience: might induce heightened cognitive clarity and increased emotional receptivity → enhanced/renewed recognition of intrinsic meaning of life, a closer connection to loved ones, nature and religion?
 - Potential cognitive reattribution processes that target dysfunctional thoughts towards pain (i.e., catastrophizing)
 - **Boosting therapeutic alliance** i.e., a positive patient-clinician relationship → increased range of positive emotions, interpersonal trust, and heighten state of empathic rapport





Therapeutic Alliance Important for Pain and Depression

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



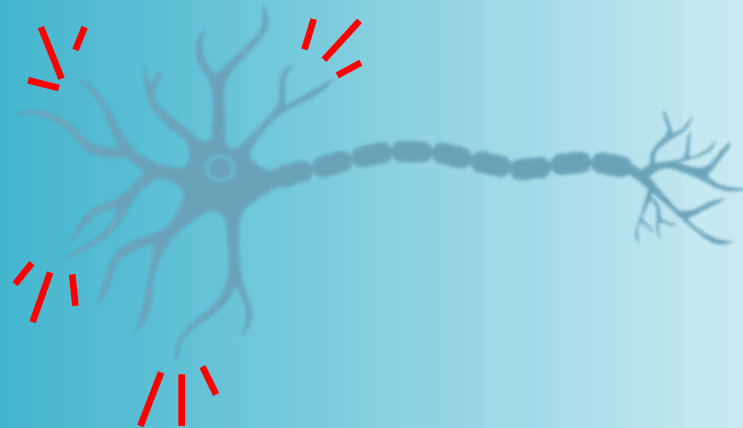
Upregulating Neuroplasticity for Enhanced Therapy



psychedelics



neuroplasticity



guided therapy



How to investigate the neural mechanisms supporting guided therapy and patient/clinician therapeutic alliance?

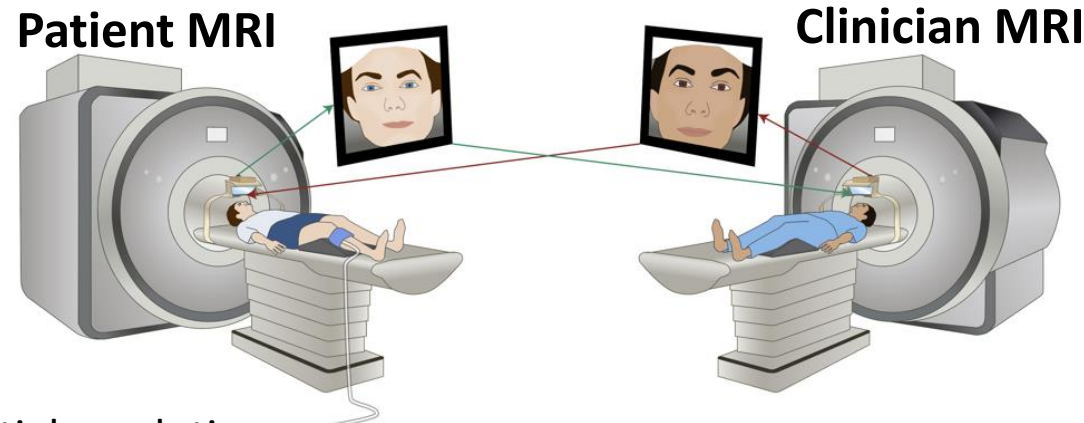


Hyperscanning Brain Mechanisms of Therapeutic Alliance



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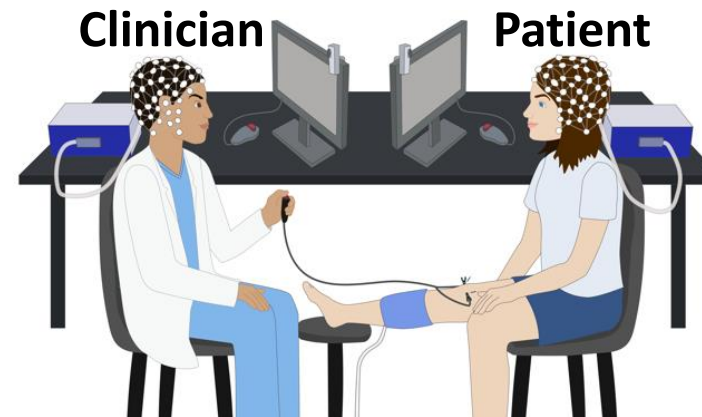
Arvina Grahl, PhD
(SRH/Harvard)

MRI: high spatial resolution

→ precise location of involved
brain regions

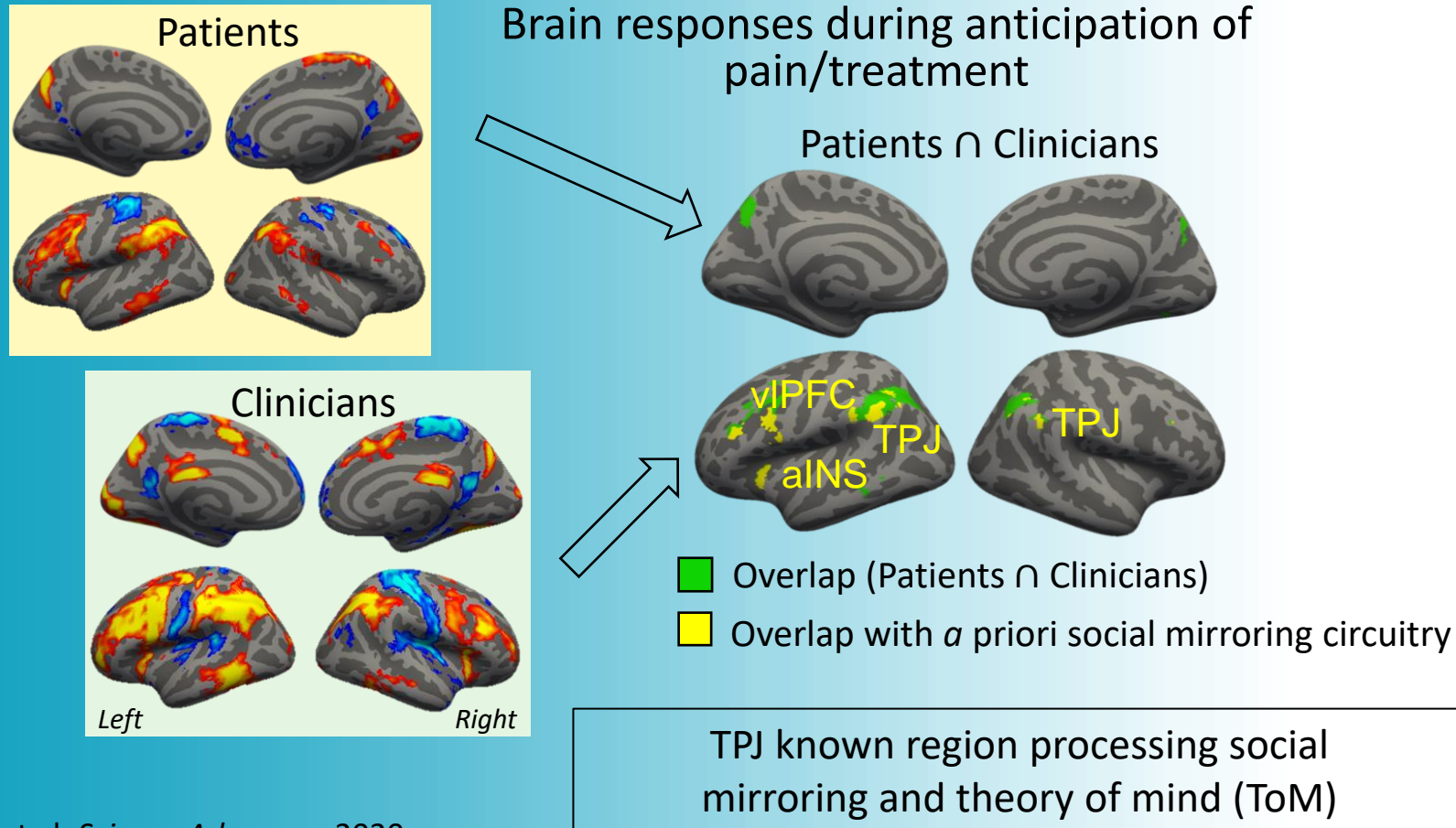
EEG: high temporal resolution

→ temporal dynamics of
underlying processes



Alessandra Anzolin,
PhD (SRH/Harvard)

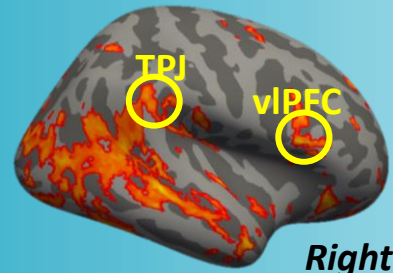
Hyperscanning Brain Mechanisms of Therapeutic Alliance



Hyperscanning Brain Mechanisms of Therapeutic Alliance



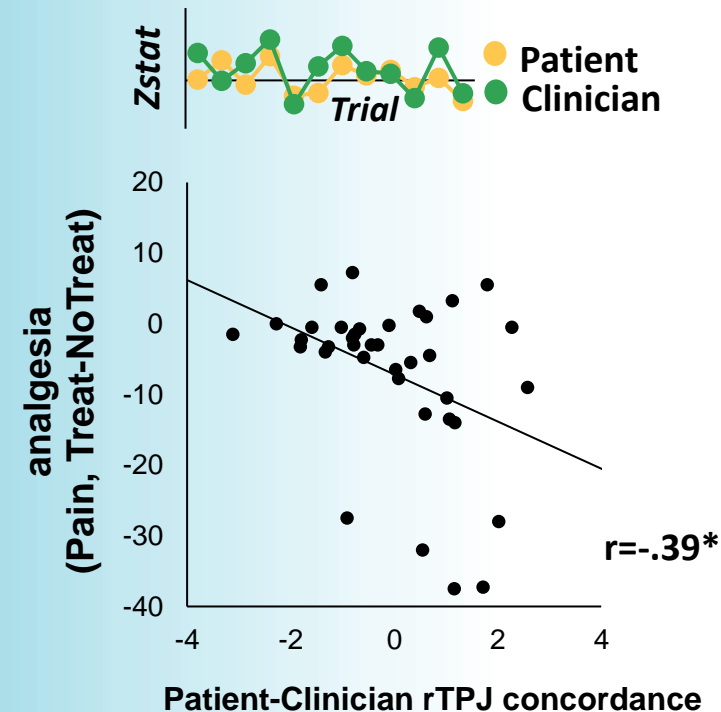
Clinicians' dynamic concordance
with patients' rTPJ



Social Interaction > No Interaction

Summary: 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



Hyperscanning MDMA-Guided Therapy for Pain



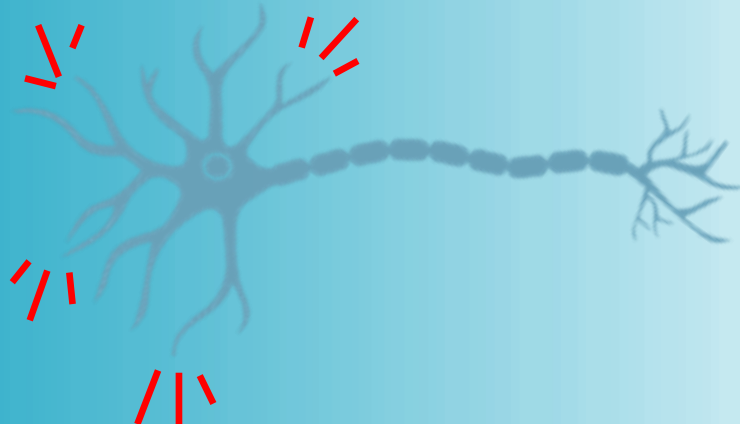
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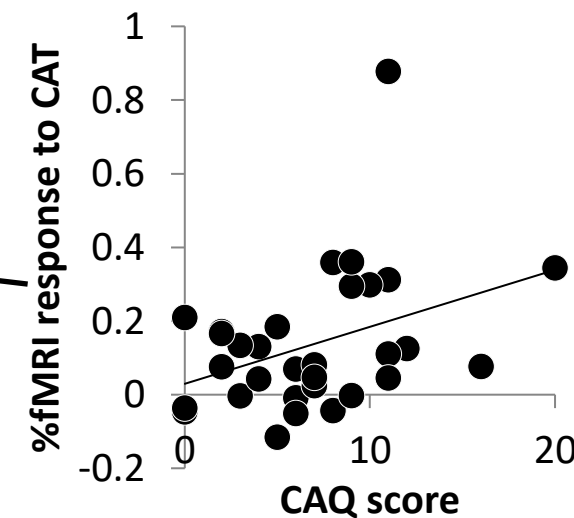
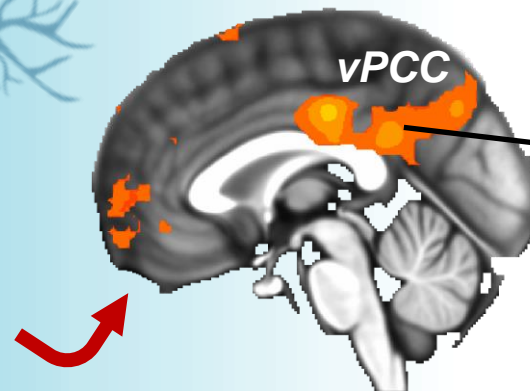
pro-social
psychedelic
(MDMA)



neuroplasticity



guided therapy



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



MDMA-Assisted Therapy for PTSD

nature
medicine

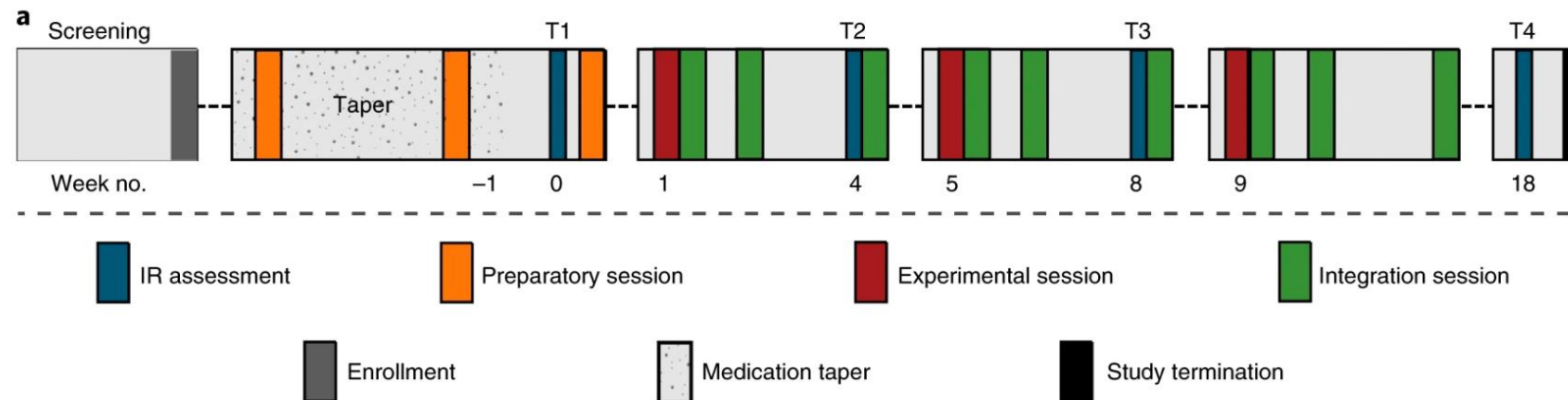
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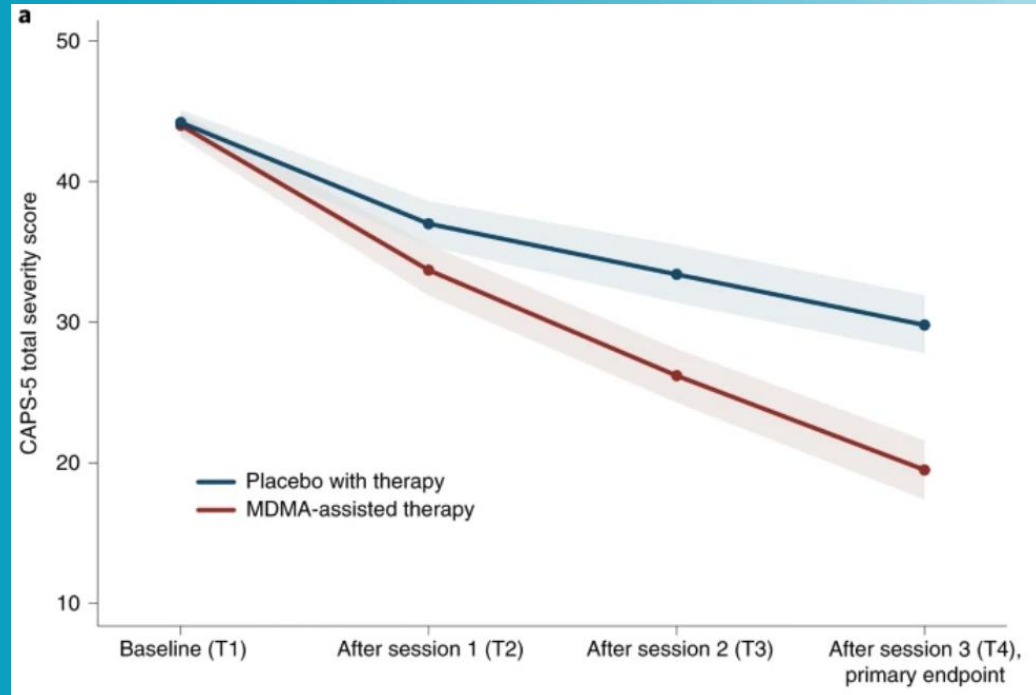
MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study



Mitchell, et al. 2021.



MDMA-Assisted Therapy for PTSD



- Reduced severity scores on the structured Clinically Administered PTSD Scale (CAPS-5)
- “By about the end of 2023, MDMA is very likely to become FDA-approved for PTSD” – Kelan Thomas, PharmD, Touro Univ., *Pharmacy Times*

Mitchell, et al. 2021.

MDMA-Assisted Therapy for PTSD Pain



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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

OPEN ACCESS

EDITED BY

Peter Schuyler Hendricks,
University of Alabama at Birmingham,
United States

REVIEWED BY

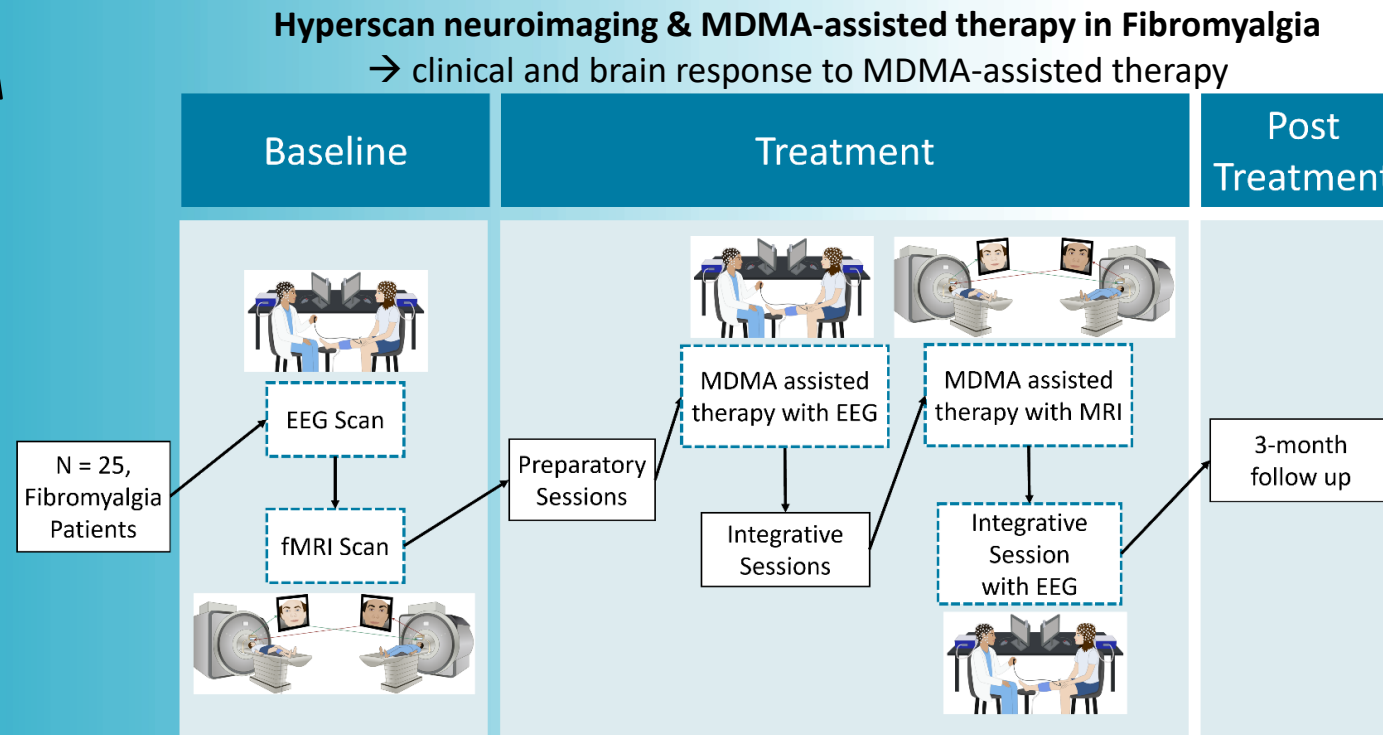
- Analysis of Phase 2 MAPS-sponsored study data
- 84% of PTSD patients reported suffering from pain
- *Significant pain reduction reported for patients in severe and moderate pain subgroups*

Christie, et al. 2022.

Hyperscan Neuroimaging & MDMA-Assisted Therapy in Fibromyalgia

- Therapeutic alliance: positive patient-clinician relationship → acknowledged as an essential component for MDMA-assisted therapy

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





Summary

- Hyperscan fMRI and EEG and can be used to study the brain mechanisms supporting pain patient/clinician interactions and therapeutic alliance
- The psychedelic experience may change how pain patients relate to clinicians and vice versa, potentially enhancing therapeutic alliance and clinical outcomes → establish importance of guided therapy for chronic pain in psychedelic medicine
- **Future directions:**
 - What type of guided therapy works best with which psychedelic substance?
 - What is role of short-term vs long-term therapy for brain and clinical outcomes?
 - If "connection" is the essential ingredient, what characteristics of therapists allow for better alliance during psychedelic medicine?





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Thank You