Atlas
Annual Thinking LAb on Fibromyalgia Syndrome
3rd edition

GUBBIO
PARK HOTEL CAPPUCCINI
23-25 MAGGIO 2024

# Tecniche innovative per il trattamento del dolore cronico

Valeria Giorgi, MD

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# Tecniche innovative: requirements

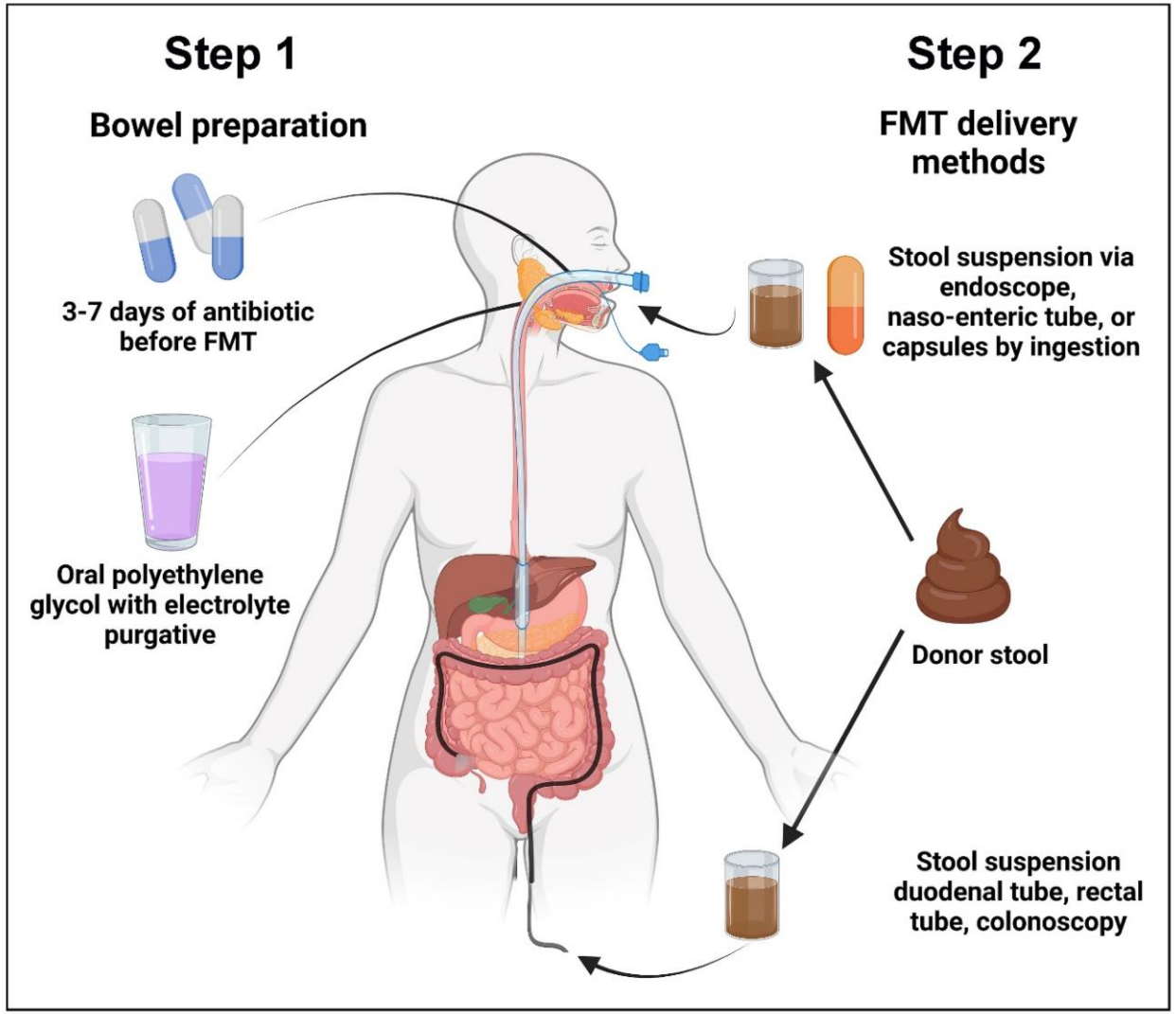
- Utilizzabili in clinica
- Non troppo costose
- Facili da prescrivere

# Trapianto fecale

# Trapianto fecale

- C. difficile infection
- GVHD
- IBD
- IBS
- Multidrug-resistant organisms
- Metabolic syndrome
- Autism spectrum disorders

multiple sclerosis, PD, …





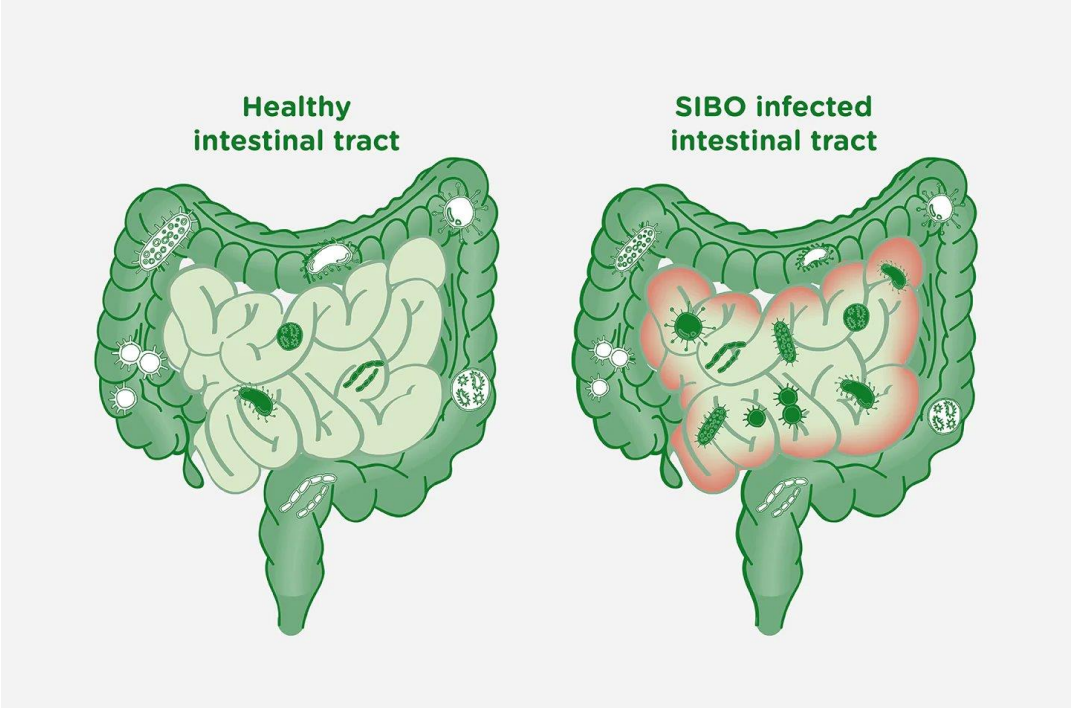

Cancers 2022, 14(3), 691; Annual Review of Medicine 70, 2019

# Trapianto fecale: razionale in FMS

- Intestinal **dysbiosis, SIBO** and increased intestinal **permeability**

Similar mechanisms w/ IBS and Disorders of gut–brain interaction

- immune system, especially the **mast cells** (MCs), along with their products
- receptors, hormones, and neurotransmitters such as serotonin
- **role of the microbiota:** dysbiosis alters the levels of serotonin in the body and can produce hyperstimulation of the autonomic nervous system.






Vasquez, A. Neuroinflammation in fibromyalgia and CRPS is multifactorial. Nat Rev Rheumatol 12, 242 (2016); Seminars in immunopathology 2018, 40(3)

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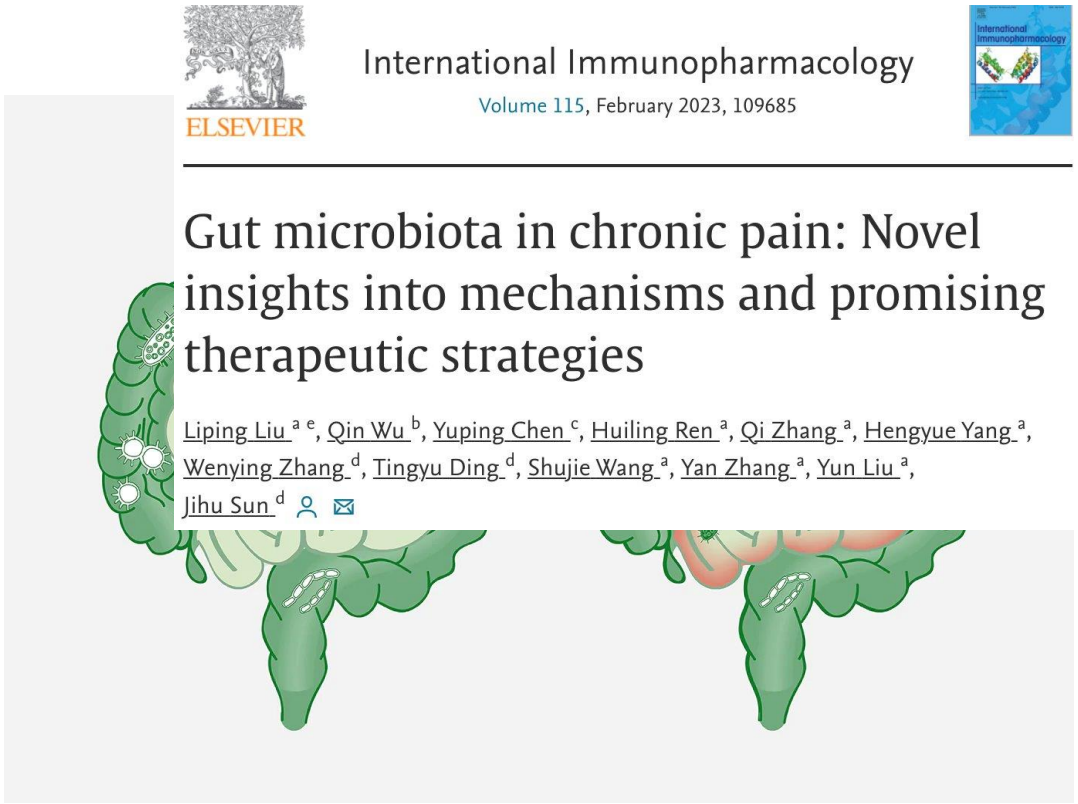


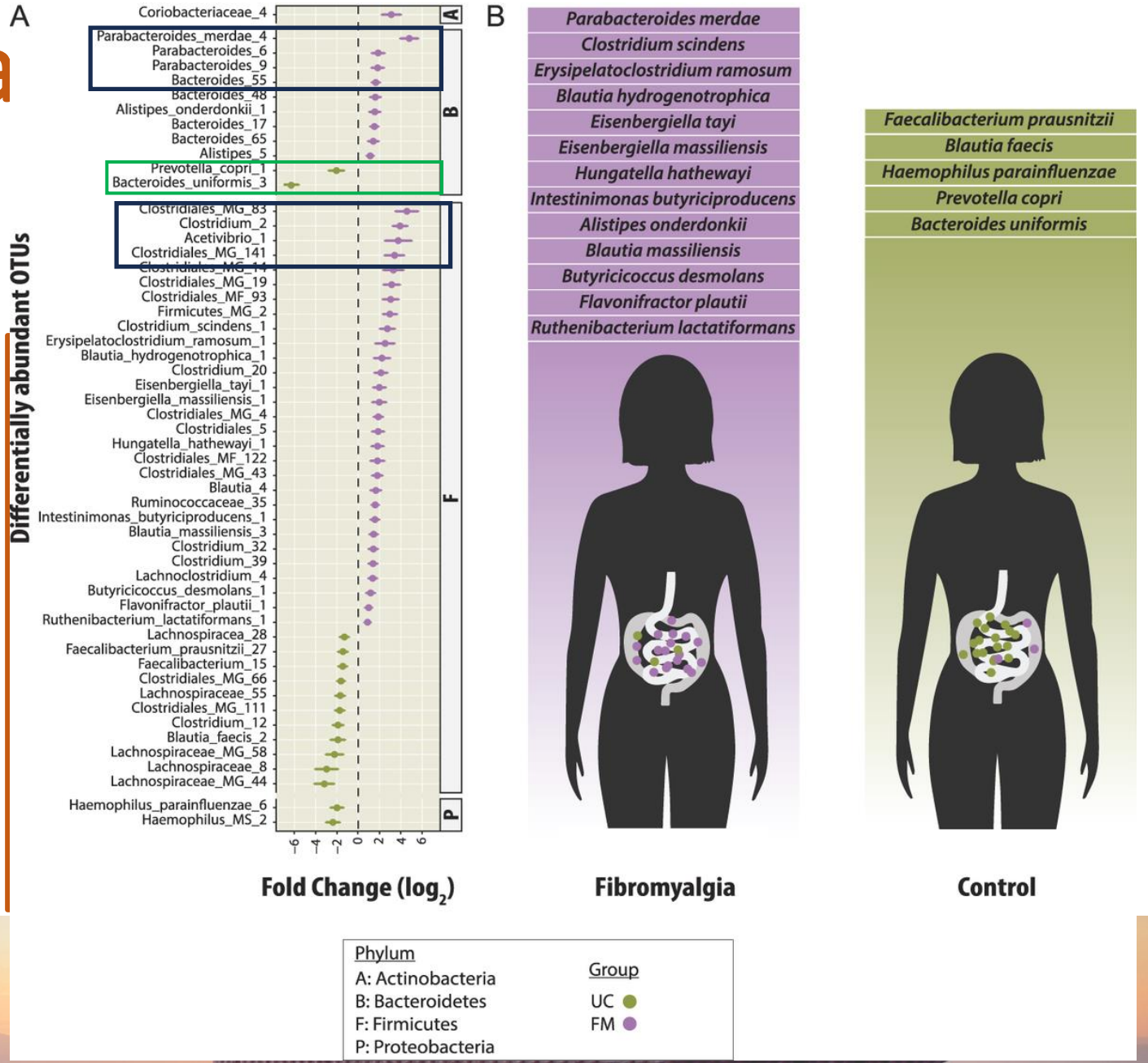



Vasquez, A. Neuroinflammation in fibromyalgia and CRPS is multifactorial. Nat Rev Rheumatol 12, 242 (2016); Seminars in immunopathology 2018, 40(3)

# Trapianto fecale: ra

- **Altered microbiome composition**
  - Histidine\histamine-producing bacteria.

- Altered **BA composition**: α-muricholic acid (αMCA) and alpha and beta-tauromuricholic acid (TMCA α + **β**)






Pain. 2019 Nov;160(11):2589-2602; Pain 2023 , Volume 164 ( 2 ), p e66 – e76

# Trapia

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  - Histidine
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- Altered **BA co**
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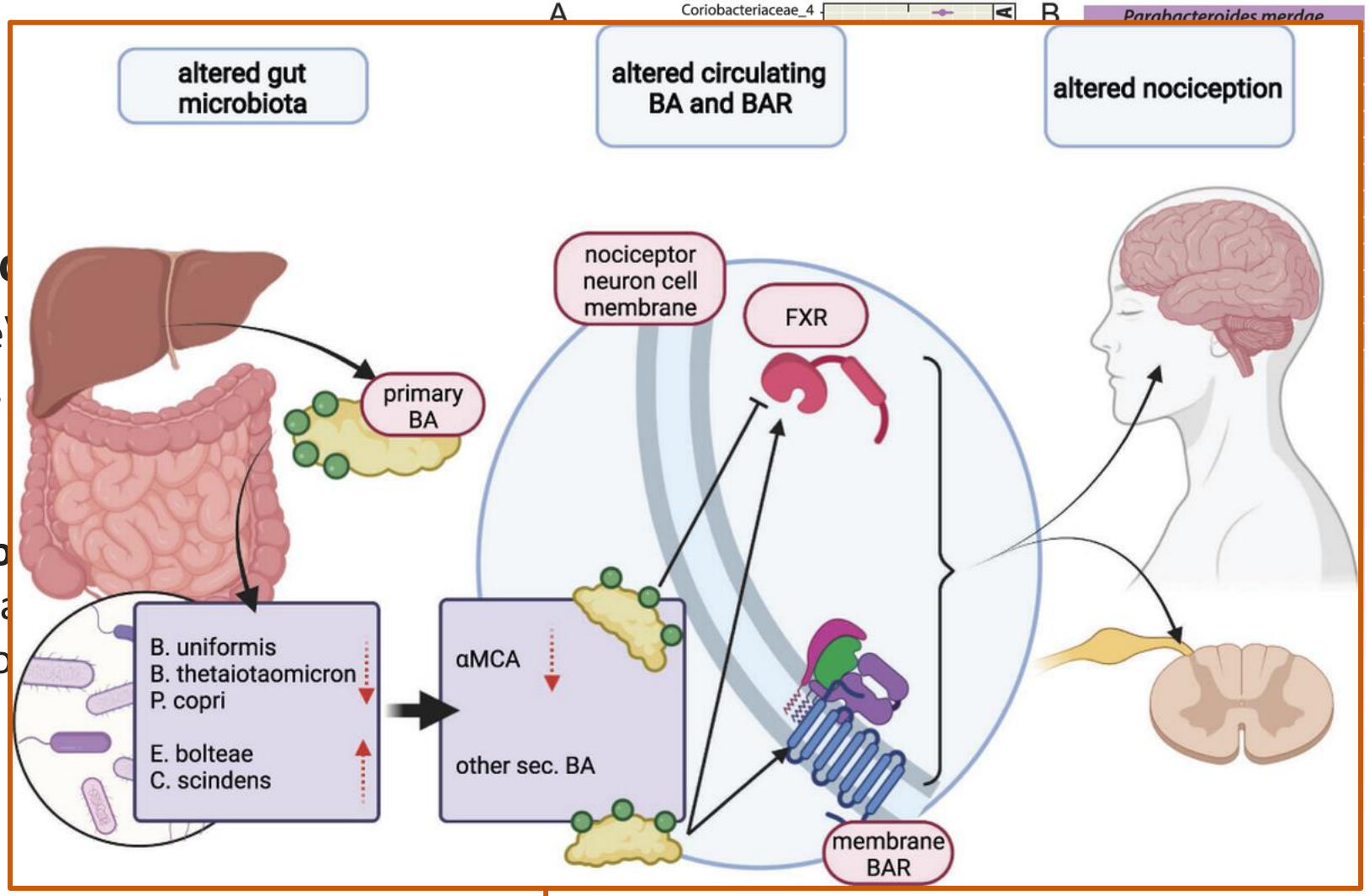






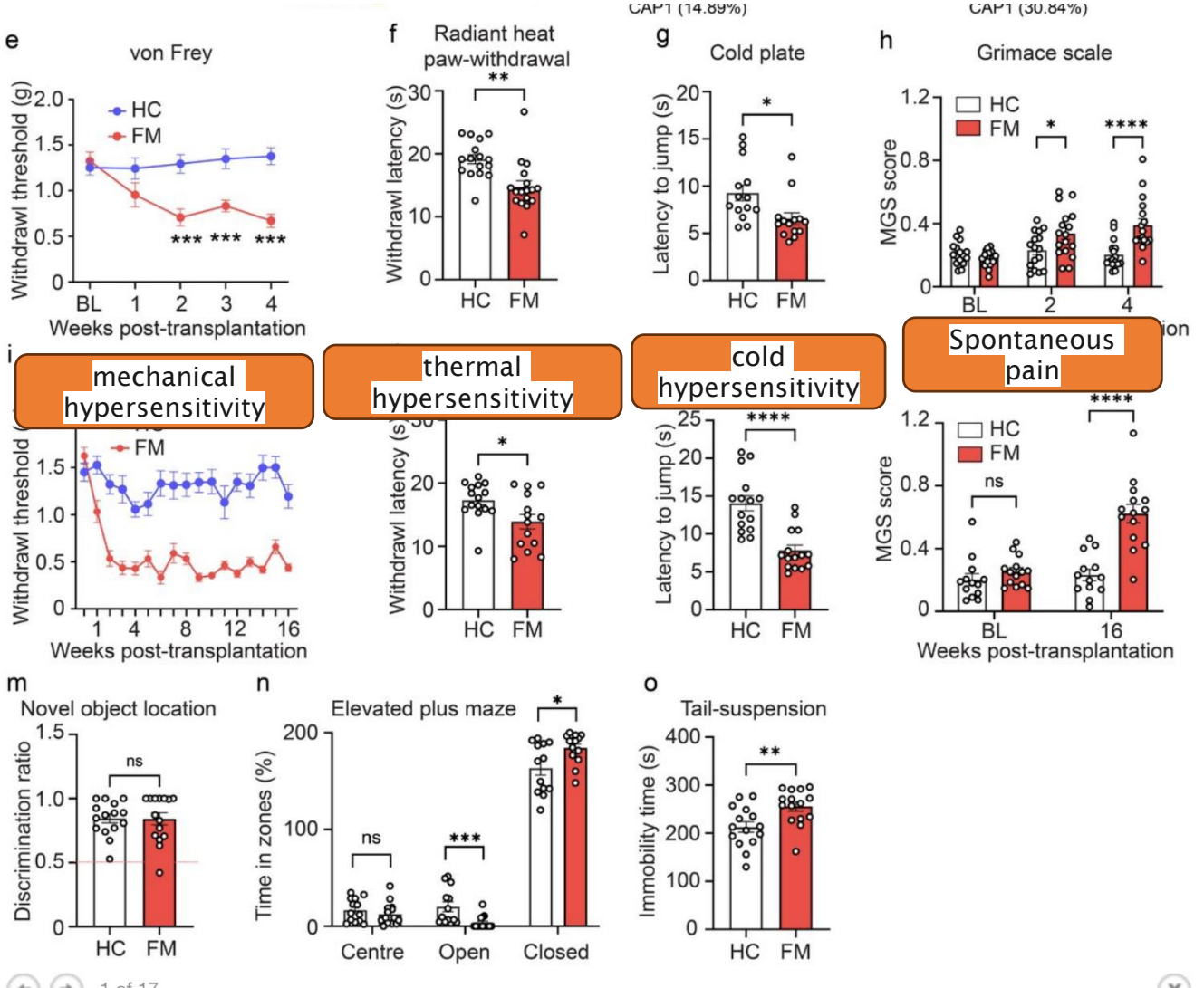



Pain. 2019 Nov;160(11):2589-2602; Pain 2023 , Volume 164 ( 2 ), p e66 – e76

# Trapianto fecale: studio traslazionale

1. **Gut microbiota transplantation from fibromyalgia patients induces pain in mice**
   - primary fibromyalgia, who screened negative for anxiety, depression, IBS
   - microbiota compositional profile was representative of a previously established fibromyalgia signature

No change in memory, anxiety, depression-like behaviour

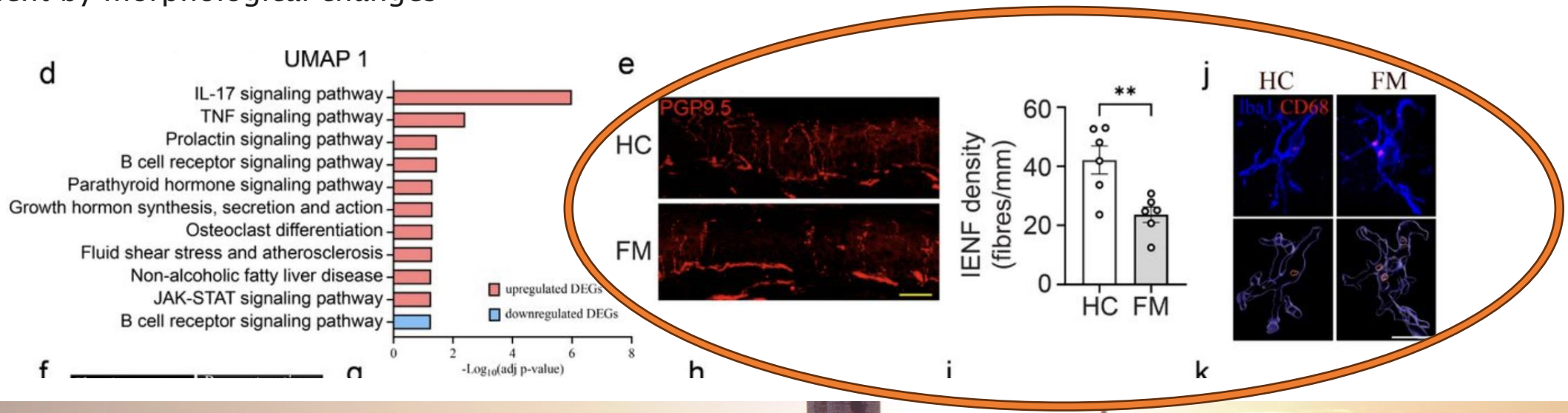





Cai et al., bioRxiv, Gut microbiota promotes pain in fibromyalgia, 2023

# Trapianto fecale: studio traslazionale

- **Increased** proportion of classical **monocytes** compared to mice that received healthy control FMT
- Analysis of differentially expressed genes within this cellular population showed **enrichment for IL-17 and TNF signaling pathways,**
- **Immune-related changes** were also present in other cell types, including intermediate/non-classical monocytes, memory/plasma B cells, DC, Treg, and B cell-like T cells (Supplementary Table 3). The **proportion of memory B cells was decreased** in fibromyalgia FMT-recipient mice
- In fibromyalgia FMT-recipient mice, **microglia were present in a reactive state** in the lumbar dorsal spinal cord as evident by morphological changes



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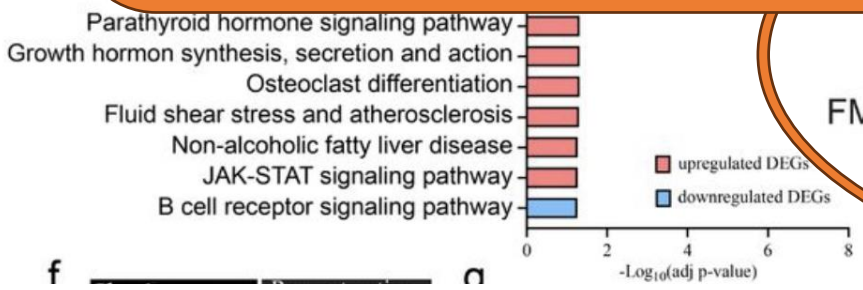
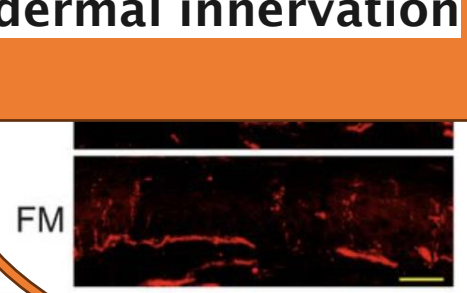
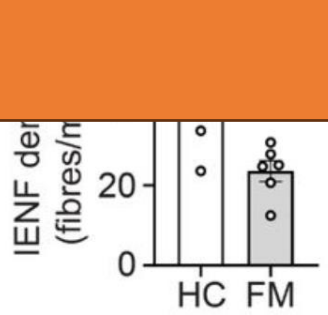
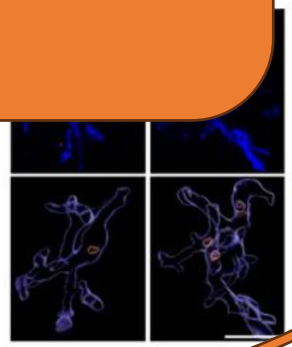
- **Increased** proportion of classical **monocytes** compared to mice that received healthy control FMT
- Analysis of differentially expressed genes within this cellular population showed **enrichment for IL-17 and TNF signaling pathways**
- **Immune-re** ocytes. memory/p **ory B cells was**
- In fibromva al cord as evident

Collectively, these results show that the transplantation of fibromyalgia microbiota into germ-free mice induces multisystemic effects, including **altered metabolic profile, low-grade inflammation, and reduced epidermal innervation**



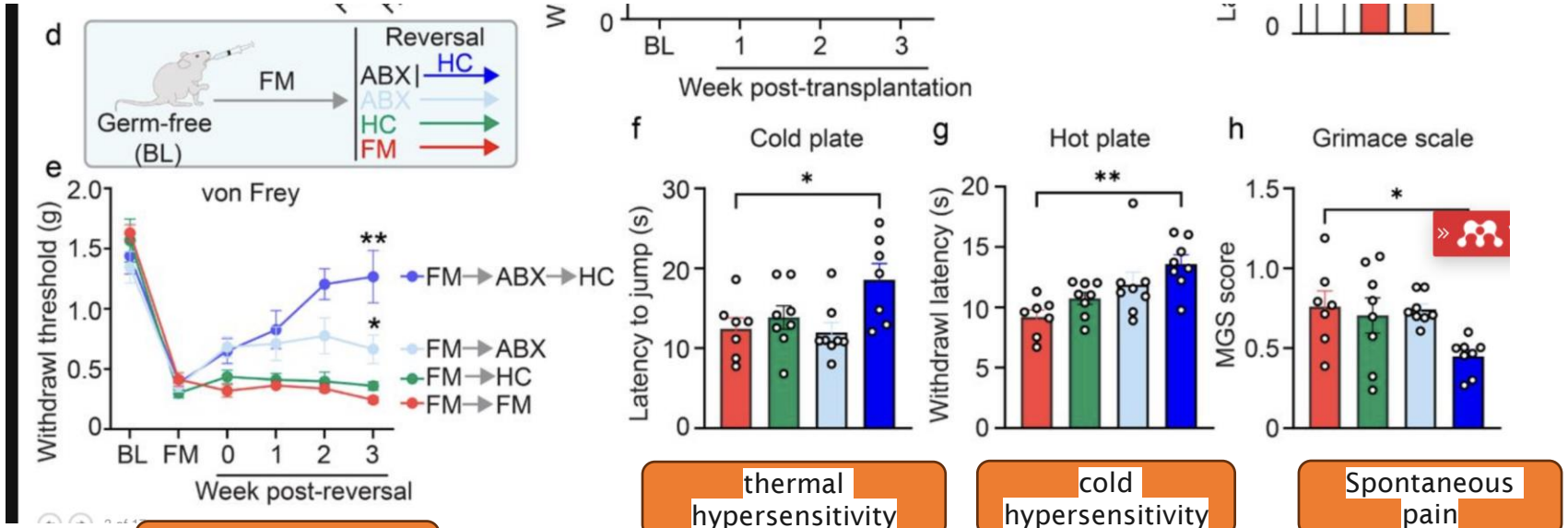


Cai et al., bioRxiv, Gut microbiota promotes pain in fibromyalgia, 2023

# Trapianto fecale: studio traslazionale

2. **La sintomatologia si è in seguito normalizzata con un nuovo trapianto** di **microbiota fecale da soggetto sano**.

Notably, healthy control FMT into fibromyalgia microbiota-recipient mice without prior suppression of gut communities with antibiotics failed to alleviate pain

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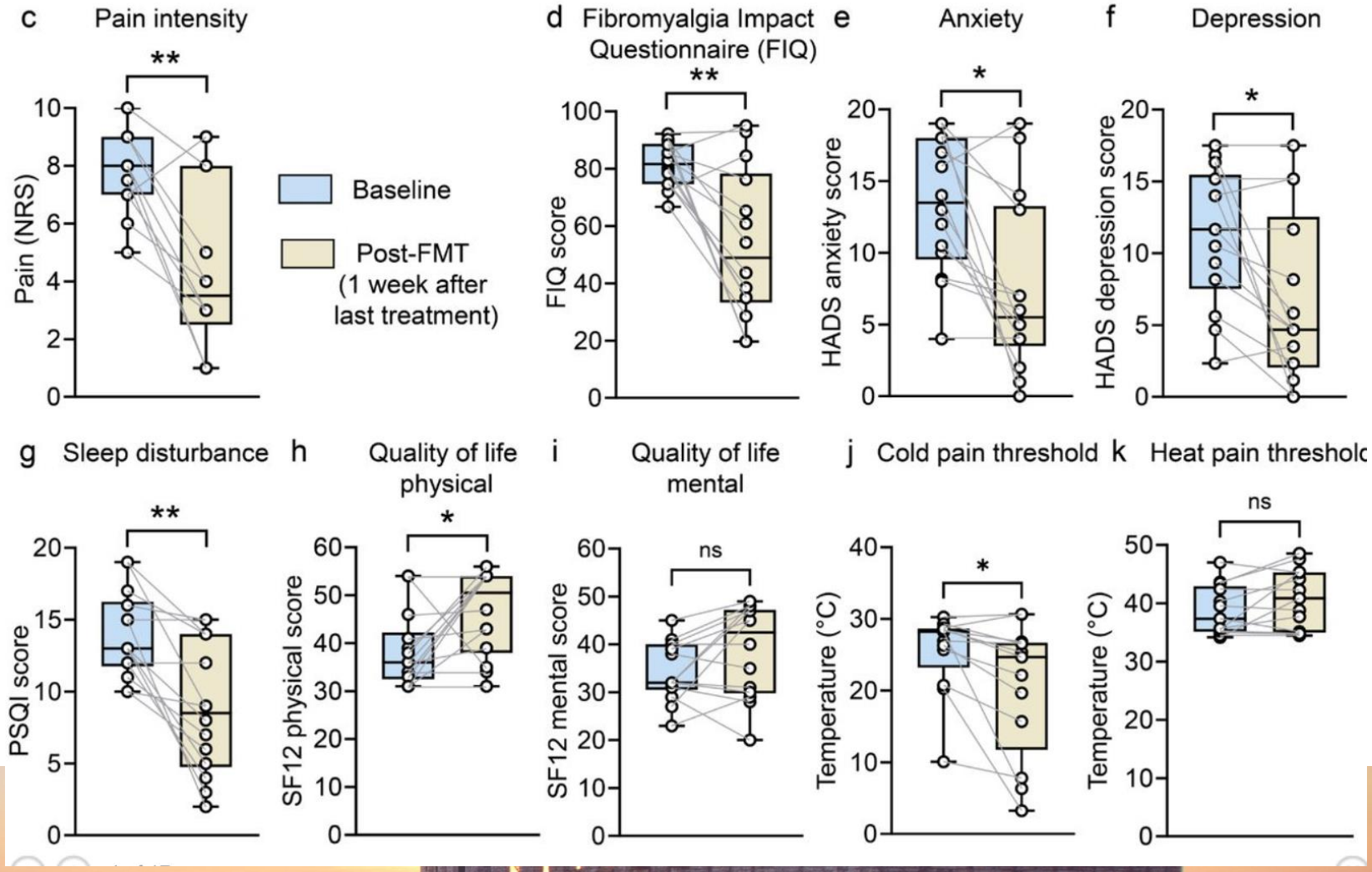
# Trapianto fecale: studio pilota

**3. Open-label, pilot study** to investigate the effect of FMT from healthy individuals on the symptoms of fibromyalgia in **humans** (n.17)

- Following depletion of the endogenous microbial communities using antibiotics and bowel cleansing, each patient received five FMTs, once every two weeks, via oral administration of encapsulated transplants from healthy donor
- One week after the last FMT

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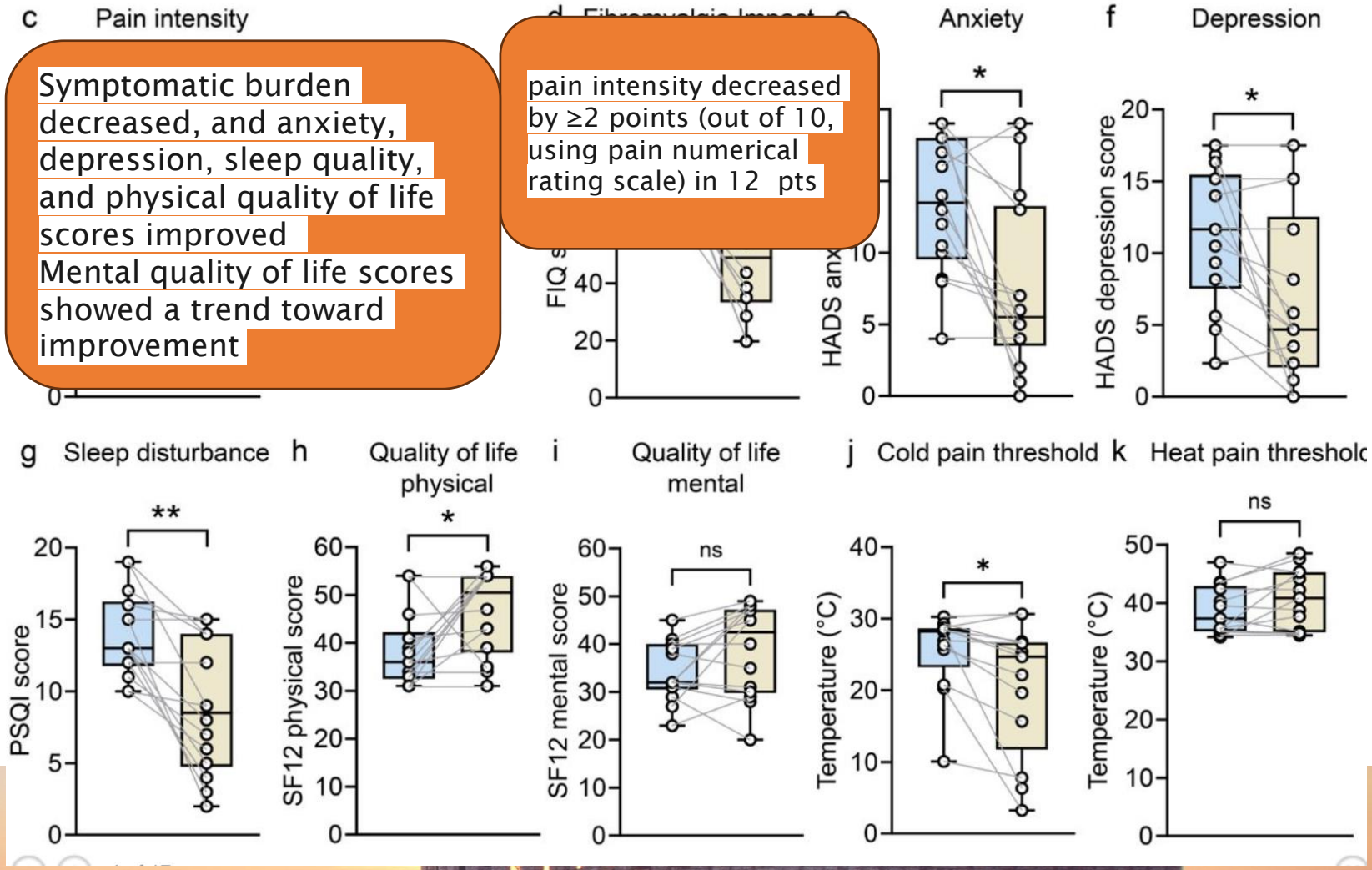
- One week after the last FMT

Symptomatic burden decreased, and anxiety, depression, sleep quality, and physical quality of life scores improved
Mental quality of life scores showed a trend toward improvement

pain intensity decreased by ≥2 points (out of 10, using pain numerical rating scale) in 12 pts




Cai et al., bioRxiv, Gut microbiota promotes pain in fibromyalgia, 2023

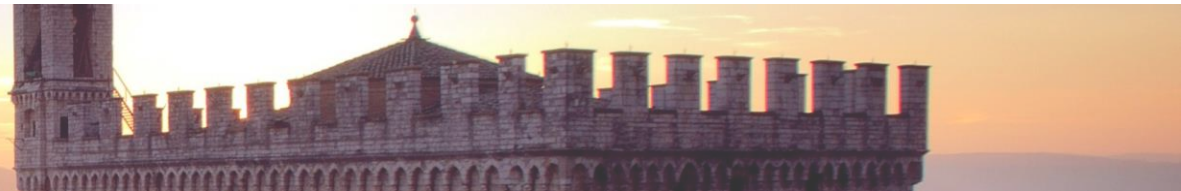
# Realtà virtuale

# Realtà virtuale

- Tecnologia che utilizza software e hardware per creare **un'esperienza simulata** che può **imitare o sostituire la realtà fisica**.
- Gli utenti possono essere **immersi** in ambienti tridimensionali generati al computer e **interagire** con essi utilizzando dispositivi come visori VR, guanti sensoriali o controller di movimento.
- L'esperienza è di fatto vissuta come realistica (studi di neuroimaging)

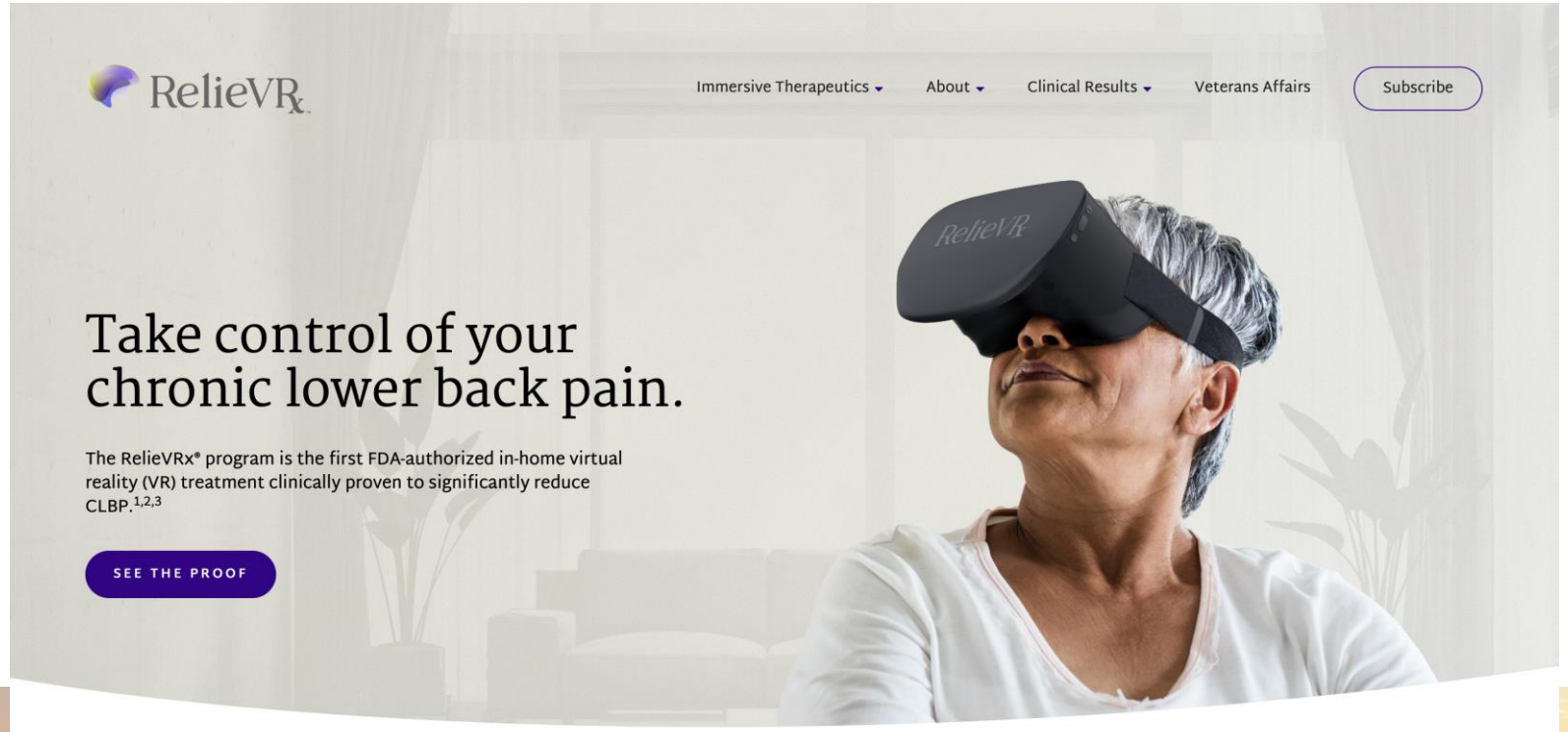
- *VR ANALGESIA*





# Realtà virtuale

November of 2021, the FDA authorized the marketing of a prescription home-use VR device to help reduce chronic low back pain




The RelieVRx program is a non-pharmacologic form of chronic lower back pain relief

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Journal of Medical Internet Research | Journal Information | Browse Journal | Su

**Published on 22.2.2021 in Vol 23, No 2 (2021): February**

Preprints (earlier versions) of this paper are available at https://preprints.jmir.org/preprint/26292, first published December 23, 2020.



## An 8-Week Self-Administered At-Home Behavioral Skills-Based Virtual Reality Program for Chronic Low Back Pain: Double-Blind, Randomized, Placebo-Controlled Trial Conducted During COVID-19

Laura M Garcia [1]; Brandon J Birckhead [1]; Parthasarathy Krishnamurthy [2]; Josh Sackman [1]; Ian G Mackey [1]; Robert G Louis [3]; Vafi Salmasi [4]; Todd Maddox [1]; Beth D Darnall [4]

Atlas Annual Thinking LAb on Fibromyalgia Syndrome 3rd edition

## The RelieVRx Program

The RelieVRx program engages pain centers through various ways:

Mindful Escapes

Pain Education

Diaphragmatic Breathing

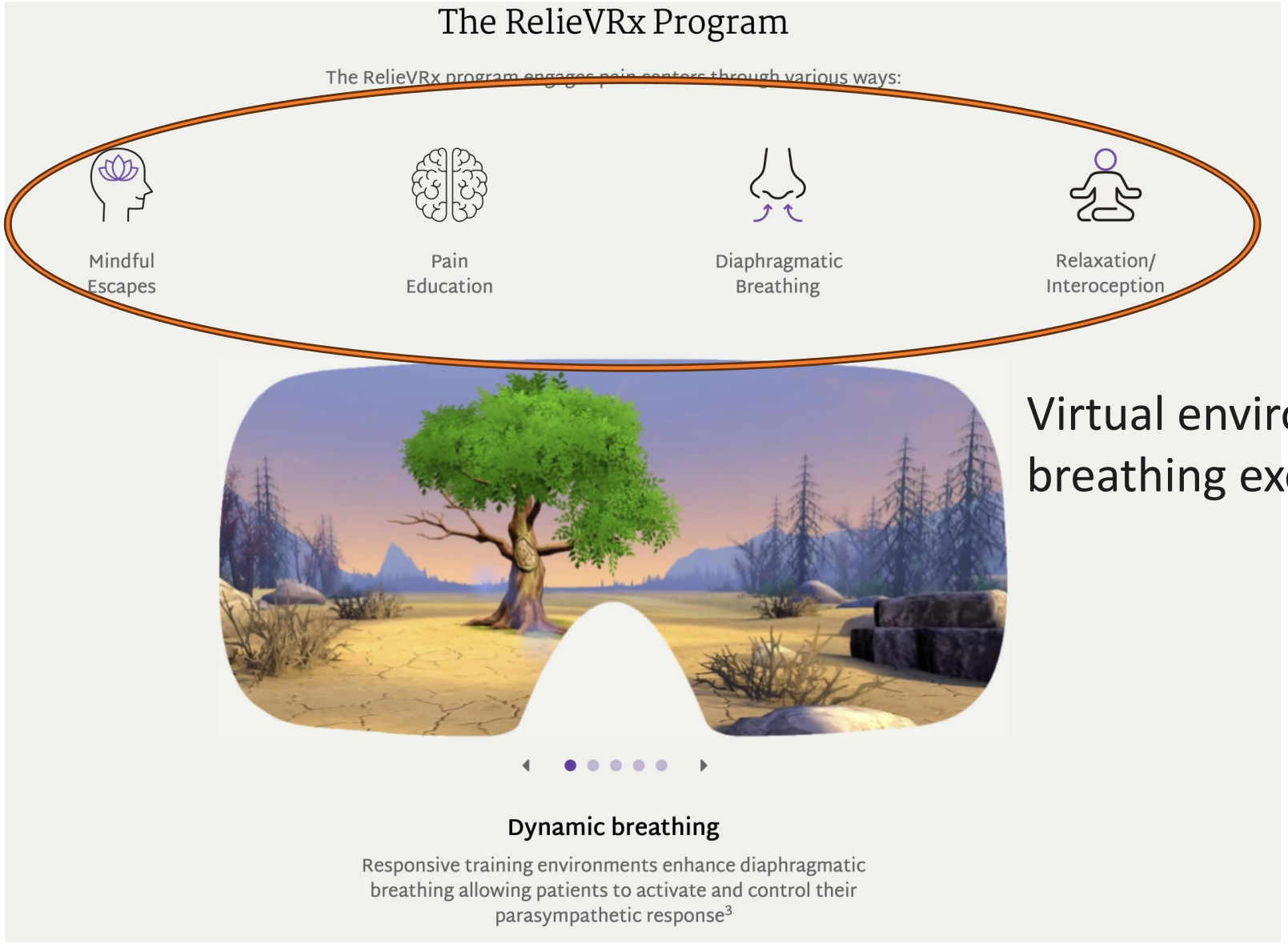
Relaxation/ Interoception

**Dynamic breathing**

Responsive training environments enhance diaphragmatic breathing allowing patients to activate and control their parasympathetic response[3]

Virtual environments: serene nature settings, breathing exercises, narration about pain

VR treatment is self-administered over 56 sessions in the comfort of a patient's home with an average daily session of 6 minutes.

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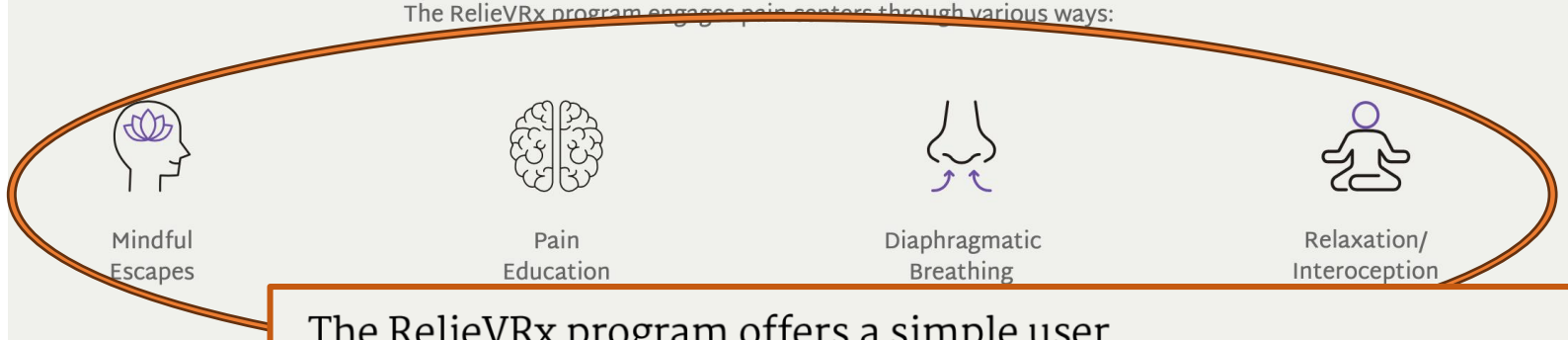


## The RelieVRx program offers a simple user experience at every step of the journey

**1. At prescribing**

After prescribing, the RelieVRx device will ship directly to the patient's home with easy to follow instructions.

**2. Ready to Use**

The RelieVRx device comes ready to use out of the box with preloaded content.

**3. Returning the device**

Patients will then return the device in the original packaging using the provided prepaid return shipping label.

Responsive training environments enhance diaphragmatic breathing allowing patients to activate and control their parasympathetic response[3]

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# Realtà virtuale: FM: Esercizio fisico

- Studies investigating the effect of VR treatment in FM used **non-immersive VR technologies such as exergames** (Collado-Mateo et al., 2017; Garcia-Palacios et al., 2015; Martín-Martínez et al., 2019; Villafaina et al., 2019).

**Nonimmersive VR -> Exergames**

Games for Health

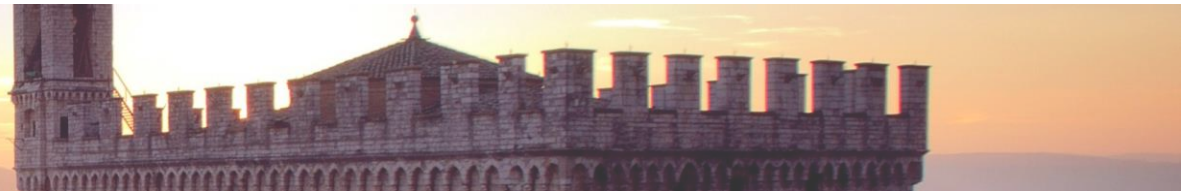
Research Article | NO ACCESS | Published Online: 15 June 2021

**The Effect of Virtual Reality Exercises on Pain, Functionality, Cardiopulmonary Capacity, and Quality of Life in Fibromyalgia Syndrome: A Randomized Controlled Study**

**Authors**: Musa Polat, MD, Abdulvahap Kahveci, MD, Birsen Muci, PhD, Zafer Günendi, MD, and Gülçin Kaymak Karataş, MD | AUTHORS INFO & AFFILIATIONS

**Publication**: Games for Health Journal • https://doi.org/10.1089/g4h.2020.0162





# Realtà

- Studies i
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Games for Health

Research Article | NO ACCESS | Pu

**The Effect of Virtual**
**and Quality of Life in**

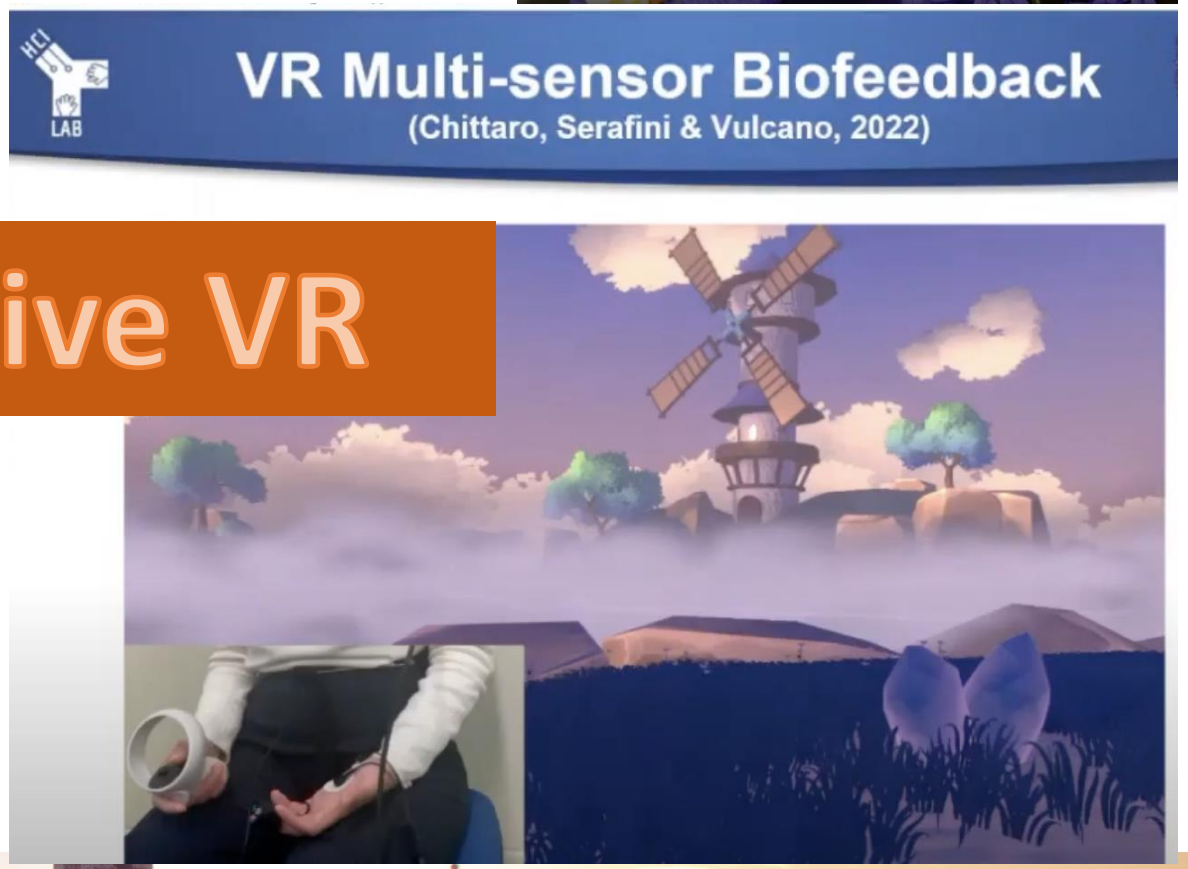
**Authors**: Musa Polat, MD, Abdulvahap Ka

**Publication**: Games for Health Journal •

*Source: worryproofmd.com*

# Realtà virtuale: FM

- Esercizio fisico
- CBT
- Biofeedback multisensoriale


**Immersive VR**

# Realtà virtuale: FM: Esercizio fisico

- EG plus 20 minutes of IVR, twice a week for 8 weeks.
  - IVR: 10 minute dungeon game, the patient was asked to avoid guillotines by tilting …or jump with both legs.

- Aim of **increasing balance and mobility**

Articles

**Effect of fully immersive virtual reality treatment combined with exercise in fibromyalgia patients: a randomized controlled trial**

C. Gulsen PT, MSc, F. Soke PT, PhD, K. Eldemir PT, MSc, Y. Apaydin PT, MSc, C. Ozkul PT, PhD, A. Guclu-Gunduz PT, Professor & ...show all

Pages 256-263 | Accepted 18 May 2020, Published online: 09 Jul 2020

Cite this article https://doi.org/10.1080/10400435.2020.1772900 Check for updates

Exercise+IVR group showed significant improvement compared to the EG regarding pain, kinesiophobia, fatigue, level of physical activity, and mental component of quality of life ($p < .05$)

# Realtà virtuale: FM: CBT

Cyberpsychology, Behavior, and Social Networking > Vol. 16, No. 3

Research Article | NO ACCESS | Published Online: 15 March 2013

## Virtual Reality in the Treatment of Fibromyalgia: A Pilot Study

**Authors**: Cristina Botella, PhD, Azucena Garcia-Palacios, PhD, Yolanda Vizcaíno, BA, Rocio Herrero, BA, Rosa Maria Baños, PhD, and Miguel Angel Belmonte, MD | AUTHORS INFO & AFFILIATIONS

**Publication**: Cyberpsychology, Behavior, and Social Networking • https://doi.org/10.1089/cyber.2012.1572

- 1 sessions of group (ten hour group sessions, ) **ith the support of** an adaptive virtual environment containing a specific content for developing rela ation and mindfulness s ills.
- ong term benefits at months

supported training in slo breathing.

# Realtà virtuale: VR-based biofeedback

Original Article | Open Access

**Virtual Reality–Based Biofeedback and Guided Meditation in Rheumatology: A Pilot Study**

R. Swamy Venuturupalli, Timothy Chu, Marcus Vicari, Amit Kumar, Natalie Fortune, Ben Spielberg

First published: 11 November 2019 | https://doi.org/10.1002/acr2.11092 | Citations: 23

- 20 participants, rheumatoid arthiritis (RA), lupus, and fibromyalgia.

- **Guided meditation (GM) environment**, + **respiratory biofeedback** (BFD) environment.

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2023.

**Virtual Reality Meditation for Fatigue in Persons With Rheumatoid Arthritis: Mixed Methods Pilot Study**

Nathan J Dreesmann [1,2]; Diana Buchanan [3]; Hsin-Yi Jean Tang [3]; Thomas Furness III [4]; Hilaire Thompson [3]

- High Acceptability
- Positive subjective experience
- **Anxiety** was significantly reduced immediately following an GM environment – but not after respiratory BFD. This was inconsistent with results from previous studies and may be a result of the small sample size.
- **Acute pain relief** occurs after immersive respiratory biofeedback and, to a lesser extent, immersive GM.
- The order of intervention did not have a significant effect

# Realtà virtuale: meccanismi

- Active **distraction**.
  - attention is required for pain and exists in limited supply
  - VR is thought to be more effective than traditional methods of distraction because of its immersive property
  - high immersion level produces more pain reduction than lower ones (Shahrbanian et al., 2012).

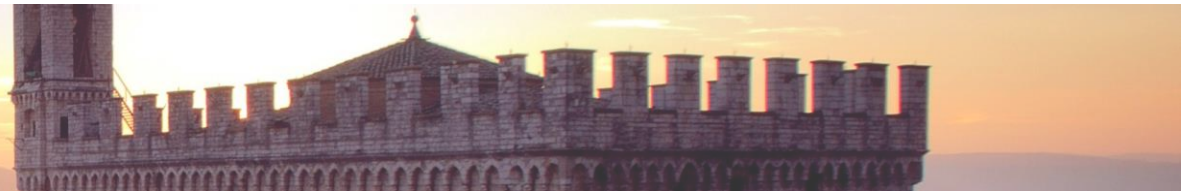
Goal -> **increase user's immersion**

CAVE:

- VR distraction is a more appropriate procedure for specific moments such as when a patient is undergoing a painful medical procedure (experiencing acute pain).
- Chronic pain -> distraction may not always be an effective technique for such a multidimensional condition.



Pain Med, 2018; 19(1)



# Realtà virtuale: meccanismi

- **Neurophysiologic** changes
  - Studies investigating active participation in VR to improve perception of control over pain
    - Loreto-Quijada et al. and Shiri et al. both used techniques that transitioned from visuals representing feelings of pain to visuals representing feelings of calm and comfort or happiness.
  - CBT



Pain Med, 2018; 19(1)

# Psychedelic-Assisted Therapy

# Psychedelic-Assisted Therapy

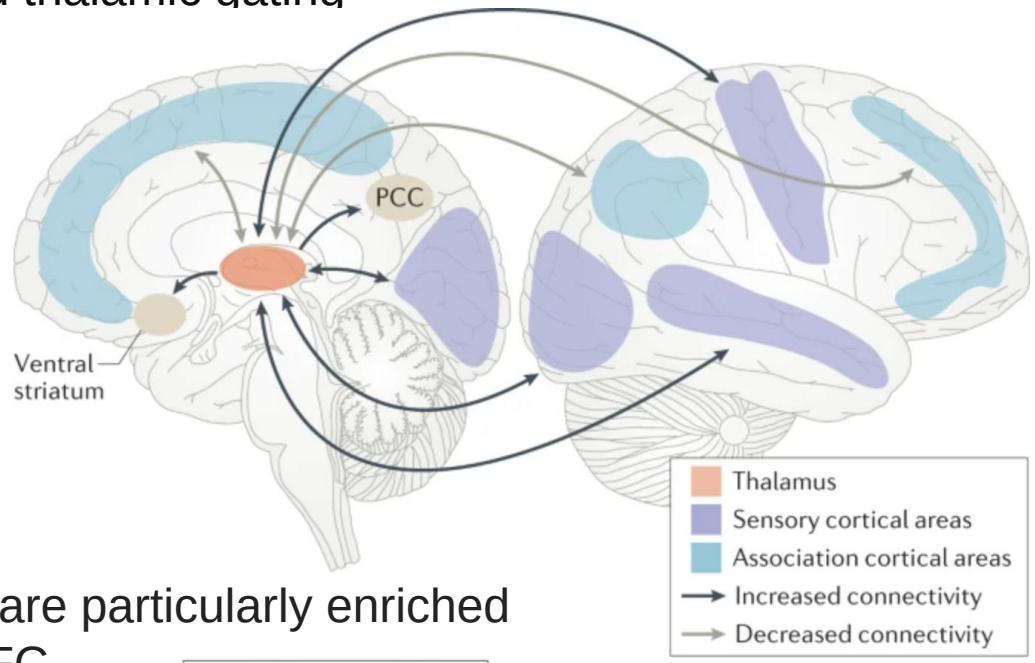
- **Serotoninergic psychedelics**
  - LSD, Psylocibin, DMT, (MDMA)
  - Mostly act through serotonin receptors | **2A** receptor agonism
  - Many psychedelic drugs also have high affinities for 5-HT2B and 5-HT2C receptors & other GPCR



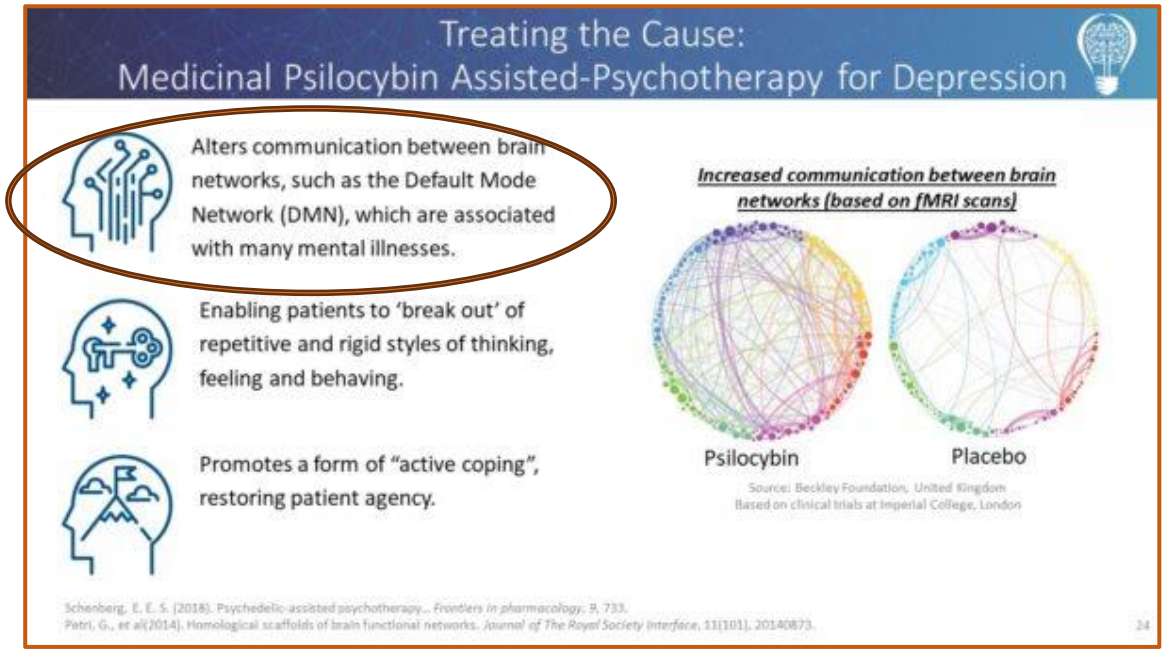
Nature Neuroscience volume 25, pages 1407–1419 (2022);
Nature Reviews Neuroscience volume 21, pages 611–624 (2020)

# Psychedelic-Assisted Therapy: Mechanisms

Widespread changes in neural activity, particularly within the **cortico-striato-thalamo-cortical loops,** Which play crucial roles in regulating perception, cognition, and behavior. | Increased cortical activity, altered thalamic gating




5-HT2A are particularly enriched in the PFC






Nature Neuroscience volume 25, pages 1407–1419 (2022); Nature Reviews Neuroscience volume 21, pages 611–624 (2020); Mindmedicineaustralis.org.au

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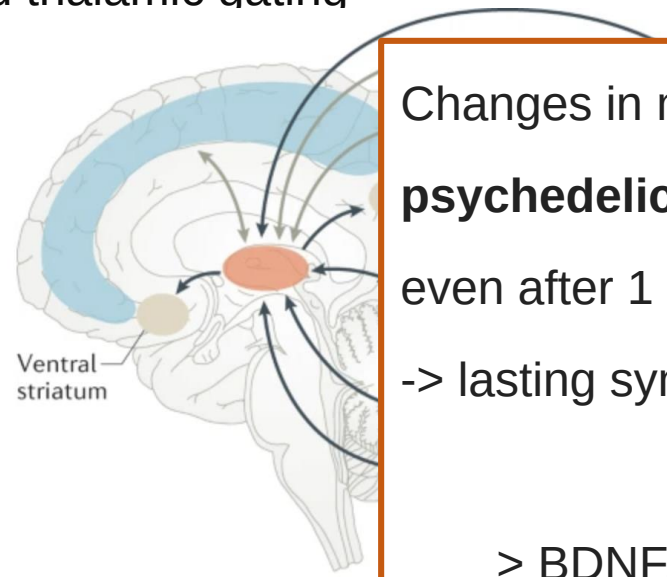



Changes in measures of connectivity ->

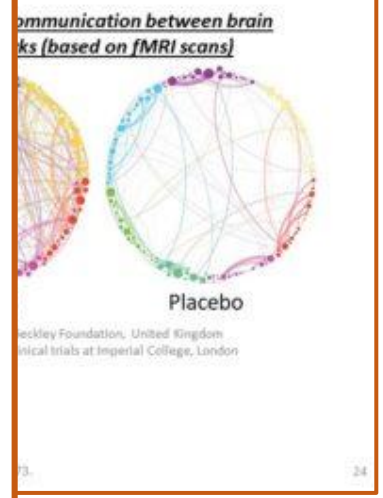
**psychedelic-evoked neural plasticity** (neuroplastic adaptation)

even after 1 administration

-> lasting symptom improvements

> BDNF, AMPA and NMDA-driven neuroplasticity

Treating the Cause:
Medicinal Psilocybin Assisted-Psychotherapy for Depression




5-HT2A are particularly enriched in the PFC

Decreased connectivity



Nature Neuroscience volume 25, pages 1407–1419 (2022); Nature Reviews Neuroscience volume 21, pages 611–624 (2020); Mindmedicineaustralis.org.au

# PAT: Depression

- 8 studies
- A significant decrease of depressive symptoms was found from day 1 to 6 months after psychedelic sessions (drug administration + psychological support).
- No serious adverse effect was reported in all included studies.
- To our knowledge, ketamine is the only treatment which had shown relative similar results

BAP British Association for Psychopharmacology

Impact Factor: **4.1** / 5-Year Im

Restricted access | Review article | First published online May 25, 2020

**Efficacy of psychedelic treatments on depressive symptoms: A meta-analysis**

Bruno Romeo, Laurent Karila, [...], and Amine Benyamina +1 View all authors and affiliations

Volume 34, Issue 10 | https://doi.org/10.1177/0269881120919957

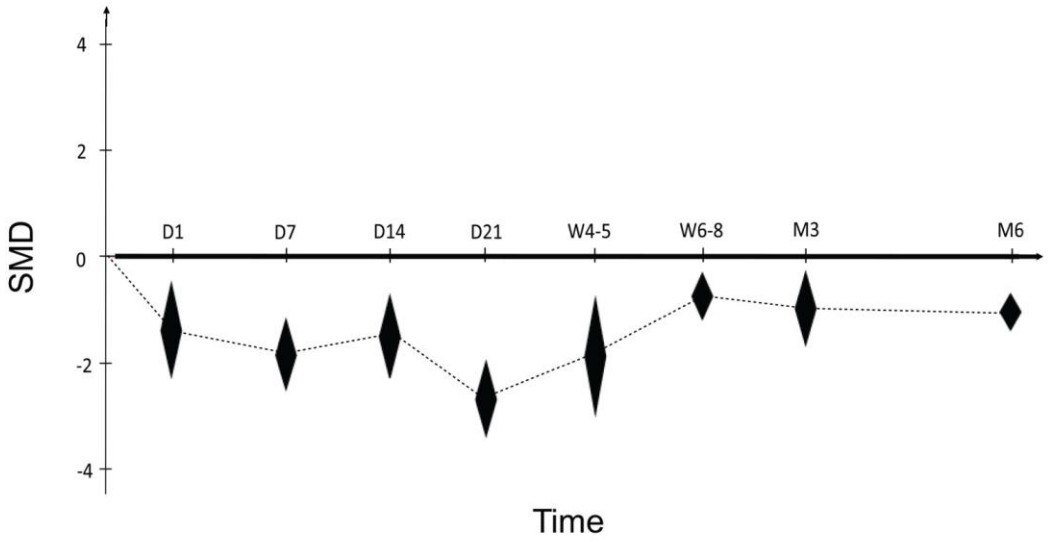



**Figure 1.** Time-course of overall standardized mean differences (SMD) between baseline and each time point of depressive score.

# PAT: Depression

- In the meta-analysis of 7 randomised controlled trials, symptom reduction was significantly indicated in three timepoints out of four, including 1-day, 1-week, and 3–5 weeks, with the exception of the 6–8 weeks follow-up point which was less conclusive.

Contents lists available at ScienceDirect

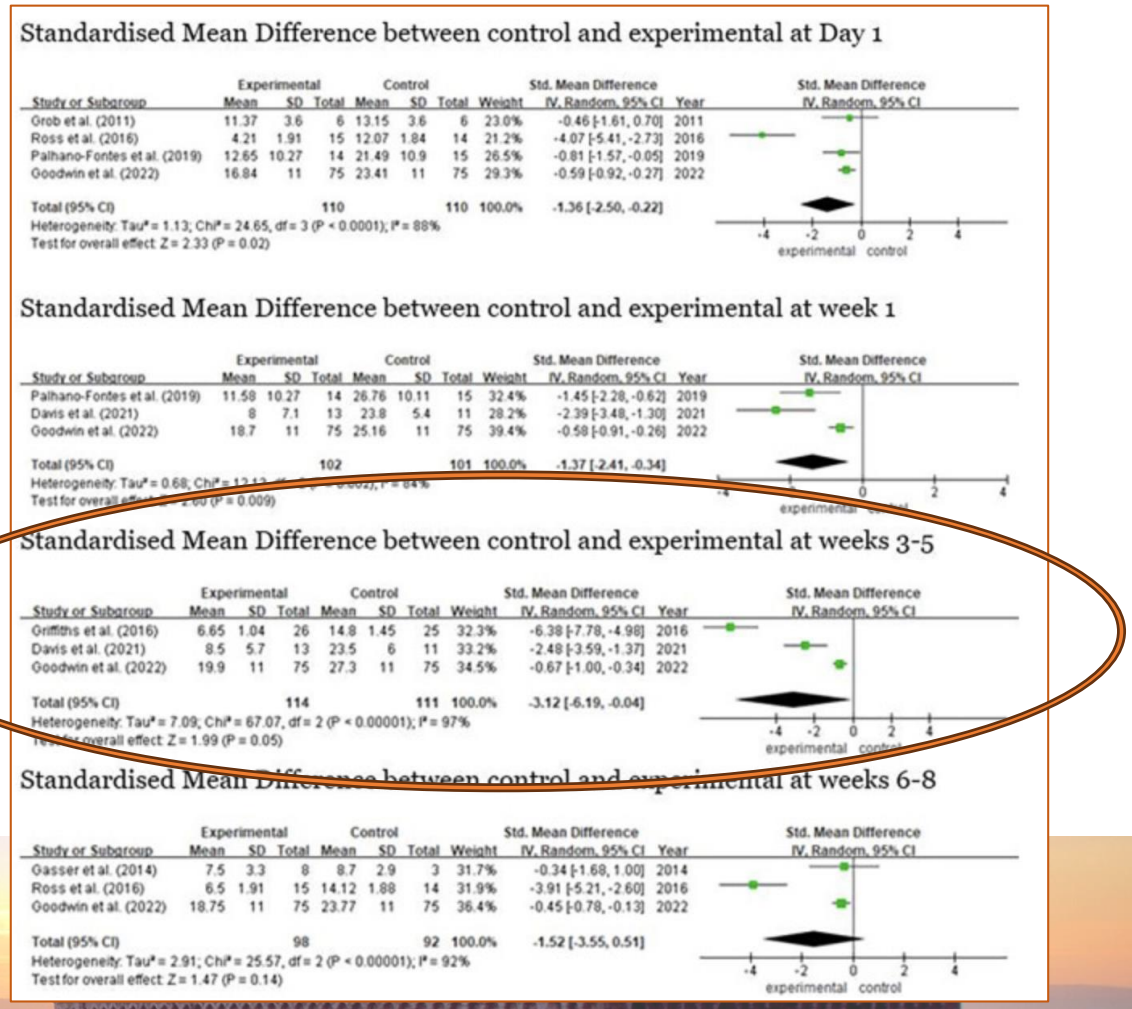
Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review Article

**Psychedelic therapy for depressive symptoms: A systematic review and meta-analysis**

Kwonmok Ko [a,*], Emma I. Kopra [a], Anthony J. Cleare [a,b,c], James J. Rucker [a,b,c]




Atlas Annual Thinking LAb on Fibromyalgia Syndrome 3rd edition

# PAT: PTSD

ORIGINAL RESEARCH article

Front. Psychiatry, 03 November 2022
Sec. Psychopharmacology
Volume 13 - 2022 |
https://doi.org/10.3389/fpsyt.2022.939302

This article is part of the Research Topic
MDMA-Assisted Therapy for Treatment of PTSD and Beyond

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Article | Open access | Published: 14 September 2023

## MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial

Jennifer M. Mitchell, Marcela Ot'alora G., Bessel van der Kolk, Scott Shannon, Michael Bogenschutz,

## Potentially traumatic events, post-traumatic stress disorder and post-traumatic stress spectrum in patients with fibromyalgia

C. Conversano[1], C. Carmassi[2], C.A. Bertelloni[2], L. Marchi[1], T. Micheloni[1], M.G. Carbone[2], G. Pagni[2], C. Tagliarini[2], G. Massimetti[2], L. Bazzichi[3], L. Dell'Osso[2]

nature > nature reviews rheumatology > perspectives > article

Perspective | Published: 05 December 2022

## Emotion regulation and the salience network: a hypothetical integrative model of fibromyalgia

Ana Margarida Pinto, Rinie Geenen, Tor D. Wager, Mark A. Lumley, Winfried Häuser, Eva Kosek, Jacob N. Ablin, Kirstine Amris, Jaime Branco, Dan Buskila, João Castelhano, Miguel Castelo-Branco, Leslie J. Crofford, Mary-Ann Fitzcharles, Marina López-Solà, Mariana Luís, Tiago Reis Marques, Philip J. Mease, Filipe Palavra, Jamie L. Rhudy, Lucina Q. Uddin, Paula Castilho, Johannes W. G. Jacobs & José A. P. da Silva

reported disability associated with
in CPGS subscales for *pain inter*
overall CPGS *severity grade* w
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the medium pain cluster (*n* =

5% (*n* = 24)
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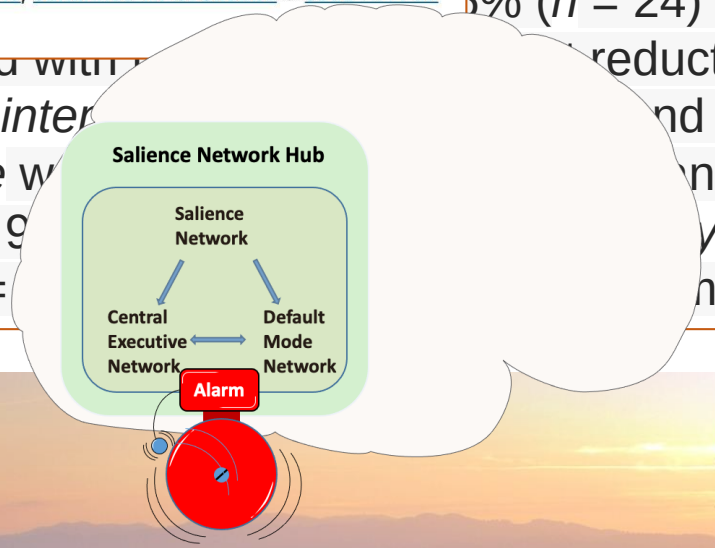


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Volume 154, Issue 8, August 2013, Pages 1216-1223

## Posttraumatic stress disorder in fibromyalgia syndrome: Prevalence, temporal relationship between posttraumatic stress and fibromyalgia symptoms, and impact on clinical outcome

Winfried Häuser [a b], Alexandra Galek [a b], Brigitte Erbslöh-Möller [c], Volker Köllner [d], Hedi Kühn-Becker [e], Jost Langhorst [f], Franz Petermann [g h], Ulrich Prothmann [i], Andreas Winkelmann [j], Gabriele Schmutzer [k], Elmar Brähler [k], Heide Glaesmer [k]

Baseline | After session 1 | After session 2 | After session 3

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# Psychedelic-Assisted Therapy: Mechanisms

- In **fMRI** studies in healthy volunteers, psilocybin and MDMA **attenuate amygdala reactivity** to negative and neutral stimuli and increase activity in the frontal cortex, modulating circuitry that can become dysregulated following trauma (Kraehenmann et al., 2015; Feduccia et al., 2018).
- Reduced amygdala reactivity in response to affective stimuli and associated negative affect was decreased **1-week** post psilocybin administration in healthy volunteers (Barrett et al., 2020).
- In PTSD, psilocybin may also inhibit fear responses during the revisiting of traumatic material.

Systems involved in emotional processing and memory are modulated by MDMA

# PAT and chronic pain: Applications

- Phantom limb pain
  - Already in 1960s and 70s
- **Headache**
  - randomized, double-blinded, placebo-controlled study of psilocybin for **cluster** headaches in 2022
  - Psylocibin may reduce the frequency of migraine headaches
- **Neuropathic** pain
  - Case series (Pain 2023). low-dose psylocibin  Patients reported up to 80–100% pain relief lasting anywhere from 3–4 hours to 2–4 weeks. However, the analgesic effect in 1 subject persisted for weeks suggesting a possible mechanism downstream of direct 5-$HT_{2A}$ agonism that may involve central modulation of nociception and synaptic plasticity
- **Fibromyalgia**
  - Only **survey** (Glynos et al. J Psychoactive Drugs) - Of the 354 participants surveyed, 29.9% had reported use of a psychedelic with 59.4%, 36.8%, and <3% having a neutral, positive, or negative perceptions, respectively, on their impact of health and pain. Interestingly, 12 participants reported intentional use for treating chronic pain, with 11 noting improvement in pain symptoms
  - ONGOING 3 trials: 2 open label and 1 RCT
- Other **case reports** (CRPS, low back pain, spinal cord injury)

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METHODS article

Front. Psychiatry

Sec. Psychopharmacology

Volume 15 - 2024 |

doi: 10.3389/fpsyt.2024.1320780

This article is part of the Research Topic

Down the rabbit hole – the psychological and neural mechanisms of psychedelic compounds and their use in treating mental health and medical conditions

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## Study Protocol for "Psilocybin in patients with fibromyalgia: Brain biomarkers of action"

Provisionally accepted

# Psychedelic analgesic mechanisms

- Modulation of bottom-up nociception
- Anti-inflammatory properties
  - Serotonergic agonism from psychedelics has th… in…
    necrosis factor-α (TNF-α), nuclear factor-κB and…
- Impact on nega… s r…
- Cognitive and …
- Neuroplastic effects

Critical role of the 5-$HT_{2A}$ R **in the nociceptive transmission** through the spinal cord their activation can inhibit the descending nociceptive transmission in states of chronic and neuropathic pain

**5-HT2A receptors are expressed in neurons in the dorsal root ganglia (DRG)** - one of the analgesic properties of psilocybin, for instance, are believed to be mediated by **downregulation** of 5-HT2A receptor in the DRG.

emerging evidence in animal models that 5-$HT_{2A}$ agonists have powerful anti-inflammatory effects by reducing inflammatory cascades mediated by pro-inflammatory cytokines


Modulation of the gut microbiome by psychedelics may influence immune functions.



From taboo to treatment: The emergence of psychedelics in the management of … pain and opioid use disorder." British Journal of Clinical Pharmacology (2023).
«Are psychedelic medicines the reset for chronic pain…?» Zai et al., … Neuropharmacology 2023

# Psychedelic analgesic mechanisms

Neuropharmacology
Volume 233, 1 August 2023, 109528

## Are psychedelic medicines the reset for chronic pain? Preliminary findings and research needs

Farah Z. Zia [a], Michael H. Baumann [b], Sean J. Belouin [c d m], Robert H. Dworkin [e f], Majid H. Ghauri [g h], Peter S. Hendricks [i], Jack E. Henningfield [j k], Ryan K. Lanier [j], Stephen Ross [l], Ann Berger [m]

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- Cognitive and
- Neuroplastic effects

models that 5-$HT_{2A}$ agonists have powerful anti-inflammatory effects by reducing inflammatory cascades mediated by pro-inflammatory cytokines

Immunology Letters
Volume 228, December 2020, Pages 45-54

## Psychedelics as a novel approach to treating autoimmune conditions

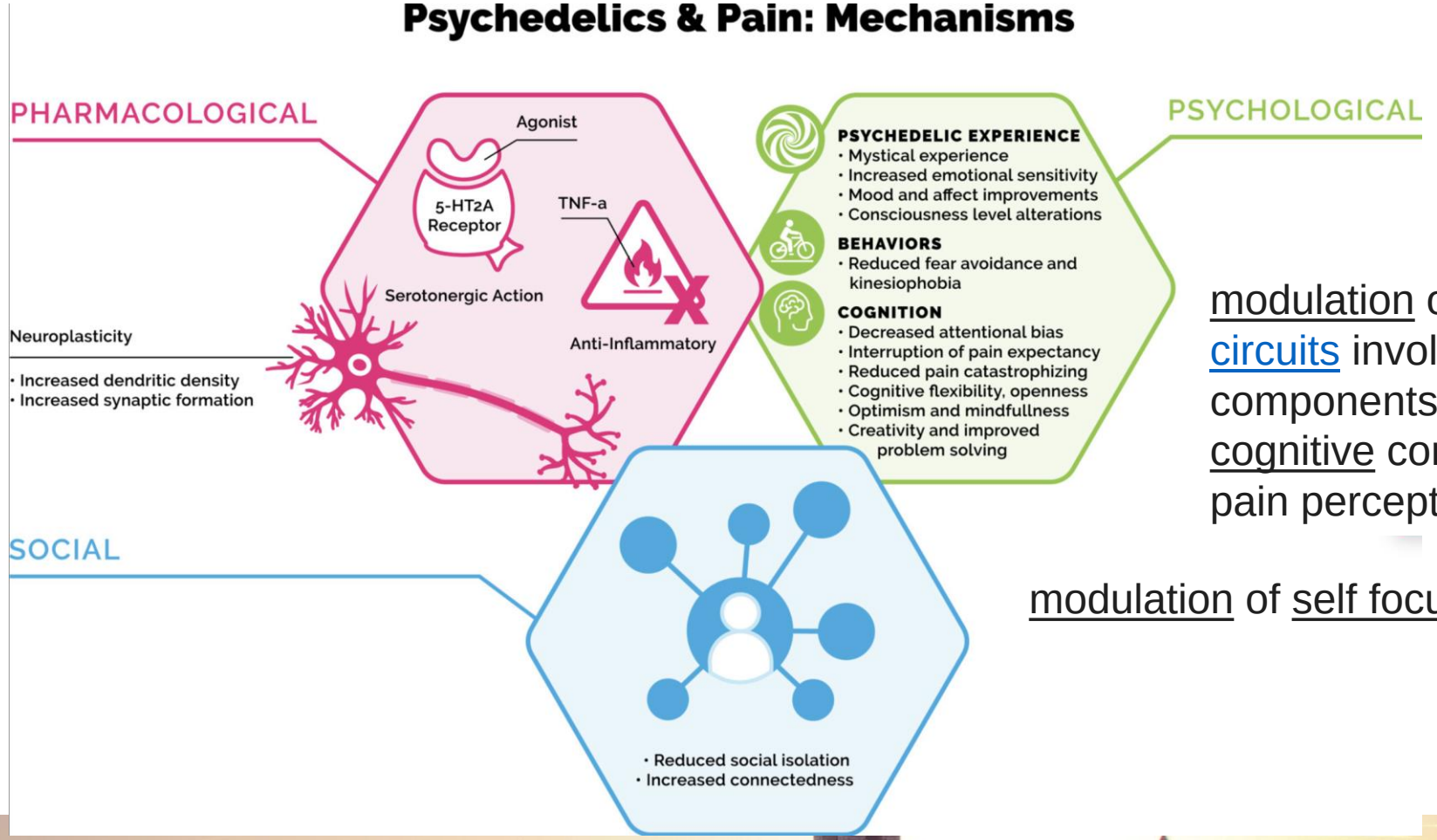
Caitlin Thompson [a], Attila Szabo [b c]

Modulation of the gut microbiome by psychedelics may influence immune functions.



From taboo to treatment: The emergence of psychedelics in the management of pain and opioid use disorder." British Journal of Clinical Pharmacology (2023).
«Are psychedelic medicines the reset for chronic pain…?» Zai et al., Neuropharmacology 2023

# Psychedelic analgesic mechanisms




modulation of neural circuits involved in the affective components, alterations in cognitive components involved in pain perception

modulation of self focus

# PAT for chronic pain: therapeutic model

- Necessity to adapt the psychiatric model of PAT application to chronic pain
- For some conditions, such as cluster headache and migraine, the drug alone, at smaller doses with subtle subjective effects, may have therapeutic benefit.

- It is vital to reconsider the current emphasis on more resource-intensive psychedelic-assisted psychotherapy and advocate for a more flexible, diversified, and pragmatic role of psychedelics in this group of medical conditions.

- Priorities for future research include identifying **ideal dosing parameters** (How much drug should be administered, and when?), **elucidating mechanisms of action** (How do psychedelics work?) and delineating the influence of extra-pharmacologic factors (What might be therapeutic other than the drug itself?), all in the service of advancing therapeutic benefit.
    - The lack of specificity of the popular term ‘microdosing,’ for instance, generates confusion. It encapsulates a range of potential regimens from a single sub-psychedelic dose in one’s lifetime to daily small doses for the rest of one’s life, which are starkly differing scenarios with very different pharmacokinetic and pharmacodynamic consequences.

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# Tecniche innovative per il trattamento del dolore cronico

Valeria Giorgi, MD

Unità di Ricerca Clinica, Gruppo Ospedaliero Moncucco, Lugano, CH