



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

Psilocybin-Assisted Therapy for Irritable Bowel Syndrome

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Disclosures



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I have the following relevant financial relationship with a commercial interest to disclose:

Tryp Therapeutics: Research funding

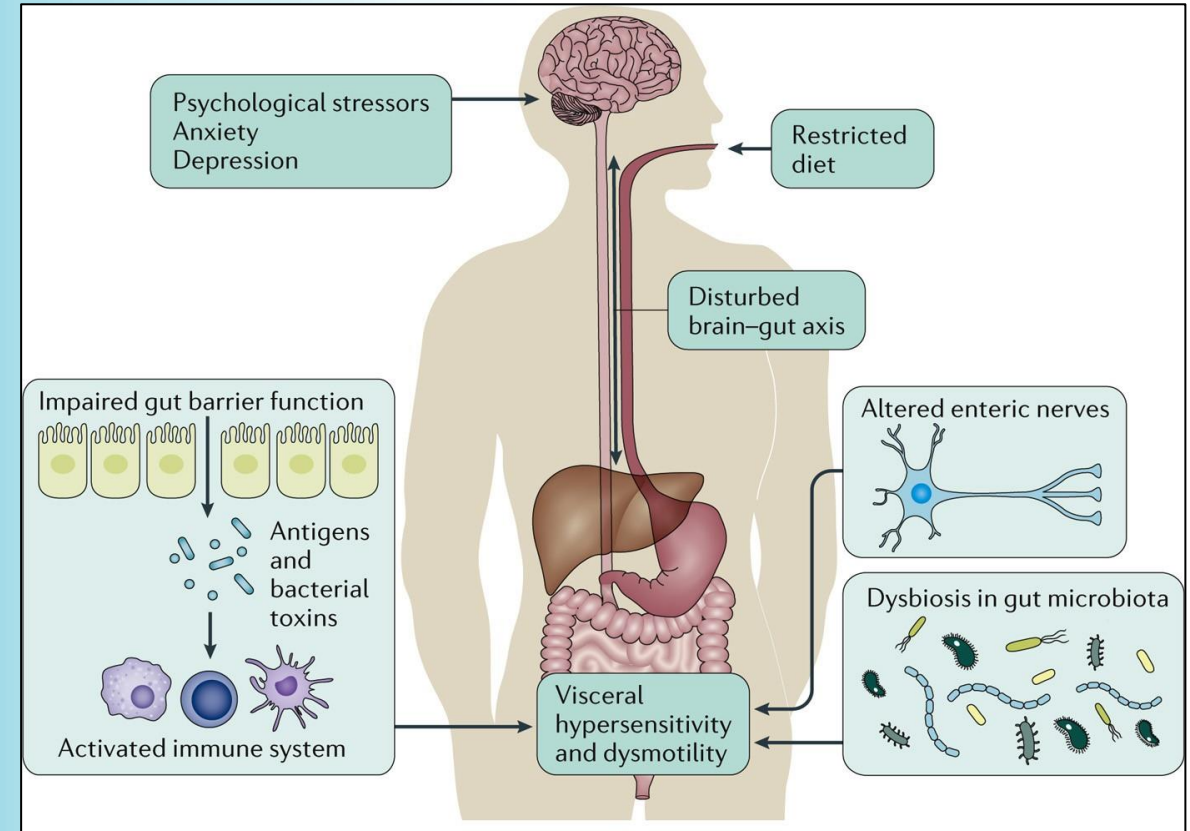


Agenda

- Rationale of psychedelic-assisted therapy (PAT) in disorders of gut-brain interaction (DGBI)
- Preliminary data

IBS is a prevalent pain disorder with psychiatric comorbidities

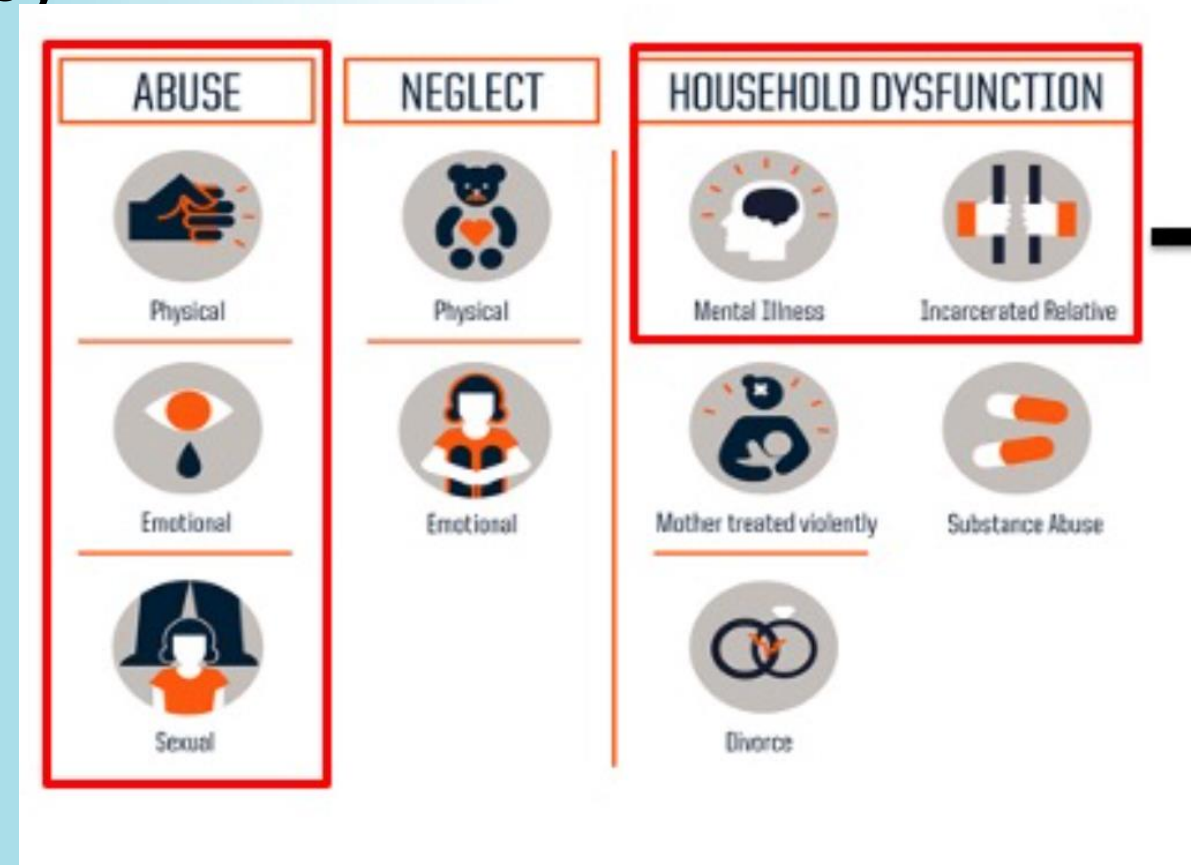
- **5 – 10%** of the population
- Abd. pain + gut motility/defecation changes
- **2-3X** as likely as gen pop to have anxiety and/or depressive disorder
- Visceral hypersensitivity: lower threshold for pain in GI tract



Zamani 2019, *Aliment. Pharmacol Ther.*
Spiller & Major 2016, *Nat. Rev. Gastro*

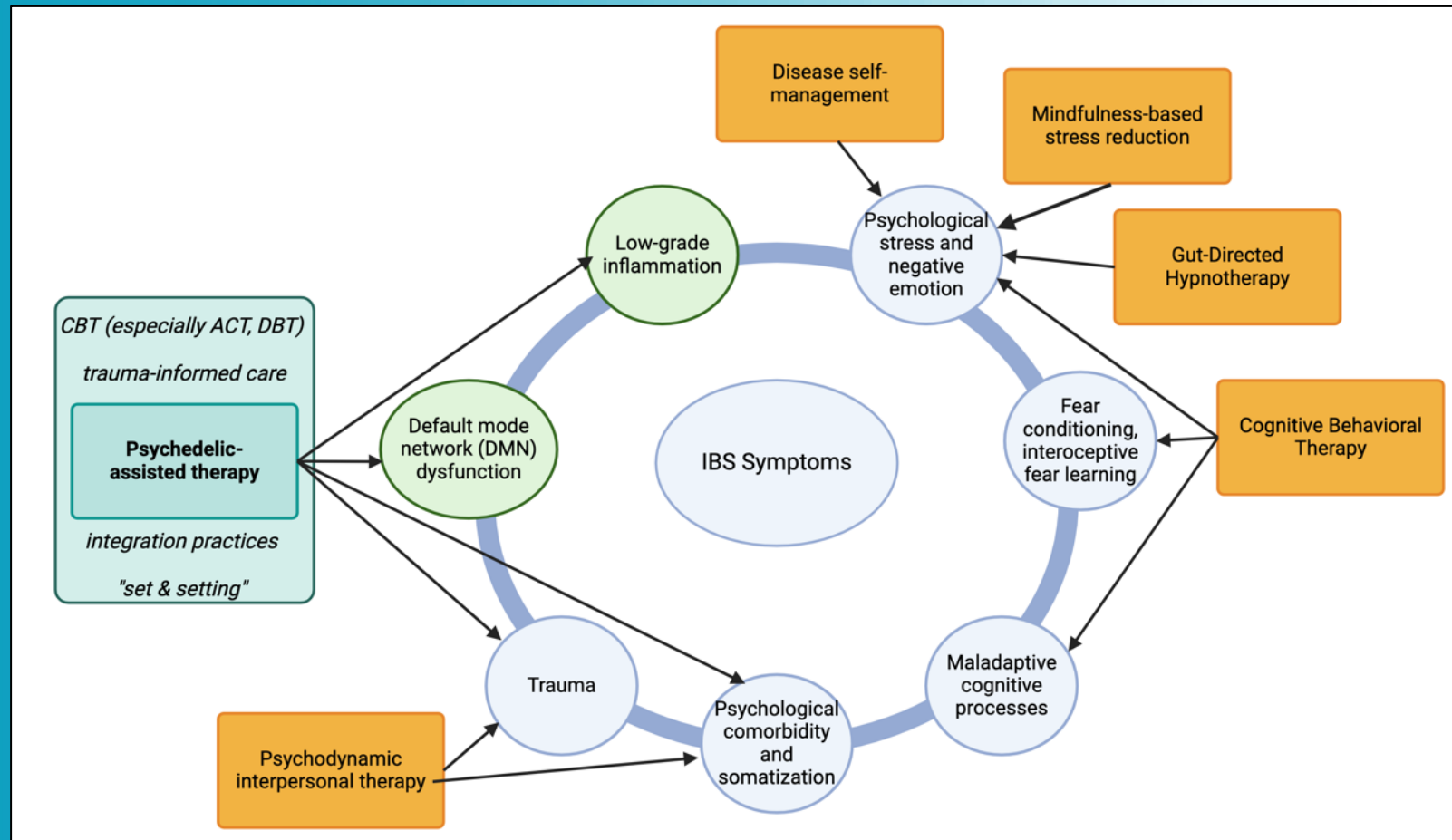
Trauma predisposes to visceral hypersensitivity

- Trauma (esp. early life) causes changes to ENS-CNS interplay
 - 80% of patients with IBS have 1+ adverse childhood event (ACE)
 - More ACE → higher risk of IBS



Park et al 2016, *Neurogastro.*

Targets of brain-gut behavioral therapies & PAT



Mauney *et. al.*, under review



PAT for IBS: A Phase 2a Pilot RCT

- **Single-center, feasibility pilot**
 - 14 participants (open label)
 - Inclusion criteria: Treatment-refractory IBS, age 21+
- **Intervention:** Two sessions of 25mg psilocybin-assisted psychotherapy (~ACT) + prep/integration vs. waitlist control
- **Outcomes:**
 - Primary outcomes: safety, feasibility
 - Mixed methods

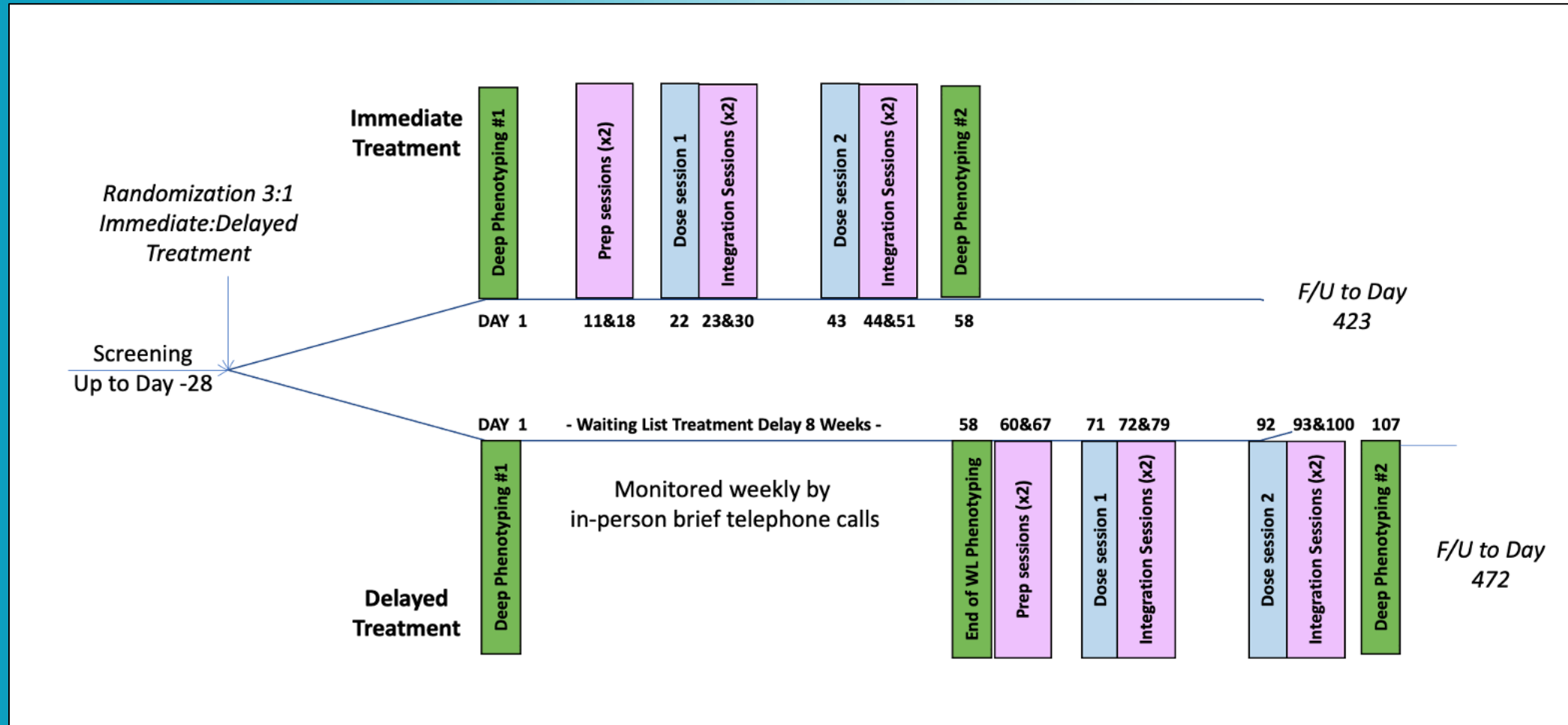


Exploratory Outcomes





PAT for IBS: Study Schema





Preliminary Outcomes

Screened 144 participants, enrolled 7, 4 completed 2x doses:

- **PAT1: 40s F, clinician, Asian**
- PAT2: 50s F, clinician, white
- PAT3: 30s F, clinician, white
- PAT4: 30s M, business, white

Randomized to immediate treatment



PAT1 Dosing Days

Mystical Experiences Questionnaire (MEQ): unity/sacredness; positive mood; transcendence of time/space; ineffability

	Time Point	MEQ (Raw)	MEQ (%)	"Complete" Mystical Exp?
PAT1	Dose 1	104	69%	Yes
	Dose 2	125	83%	Yes
	Change from Dose 1	21		



PAT1 Dosing Days

Challenging Experiences Questionnaire (CEQ): grief, fear, death, insanity, isolation, physical distress, and paranoia.

	Time Point	MEQ (Raw)	MEQ (%)	"Complete" Mystical Exp?	Challenging Experiences	CEQ %
PAT1	Dose 1	104	69%	Yes	97	75%
	Dose 2	125	83%	Yes	91	70%
	Change from Dose 1	21			-6	



PAT1 Dosing Days Qualitative Themes

1. Emotional processing, grief, personal/family relationships
2. Imagery of natural world related to love and pain processing



PAT1 Dosing Days Qualitative Themes

1. Emotional processing, grief, personal/family relationships
2. Imagery of natural world related to love and pain processing

I became a tree—Kind of a tree of life, but more focused on love. Kind of maternal love? I was a really big tree, but also kind of agile. **There was an incredible current of love running through me—it was bottomless and infinite, with so much energy. I could impact the energy and love to everyone around me, and there were countless brightly colored flowers all throughout my branches.**

This heron was ancient and very wise. **He taught me to take my IBS pain and discomfort, and turn it inside out, and push it out. I had a small, soft bird belly. I could take the sensations and turn them inside out, and they left my body in a shower of small white downy feathers.**



PAT1 Dosing Days Qualitative Themes

1. Emotional processing, grief, personal/family relationships
2. Imagery of natural world related to love and growth
3. Challenges with lack of control over body during session



PAT1 GI & Mental Health Changes

IBS-Symptom Severity Score

- 175–300: moderate severity
 - -300+: severe IBS.
- Reduction of 50pt is clinically significant

	Time Point	IBS-SSS
PAT1	Pre-Intervention	230
	Post-Intervention	119
	Change	-111



PAT1 GI & Mental Health Changes

Visceral Sensitivity Index: GI-Specific Anxiety. E.g., avoidance of restaurants, worry about symptoms

	Time Point	IBS-SSS	VSI
PAT1	Pre-Intervention	230	35
	Post-Intervention	119	18
	Change	-111	-17



PAT1 GI & Mental Health Changes

Patient Global Impression of Change

	Time Point	IBS-SSS	VSI	PGI-C
PAT1	Pre-Intervention	230	35	6
	Post-Intervention	119	18	2
	Change	-111	-17	-4

(b) **PGI-C**

Since the start of the study,
my overall status is:

1: Very Much Improved

2: Much Improved

3: Minimally Improved

4: No Change

5: Minimally Worse

6: Much Worse



PAT1 GI & Mental Health Changes

Acceptance and Action Questionnaire:
measures psychological flexibility; higher
score = worse

	Time Point	IBS-SSS	VSI	PGI-C	AAQ
PAT1	Pre-Intervention	230	35	6	26
	Post-Intervention	119	18	2	30
	Change	-111	-17	-4	4



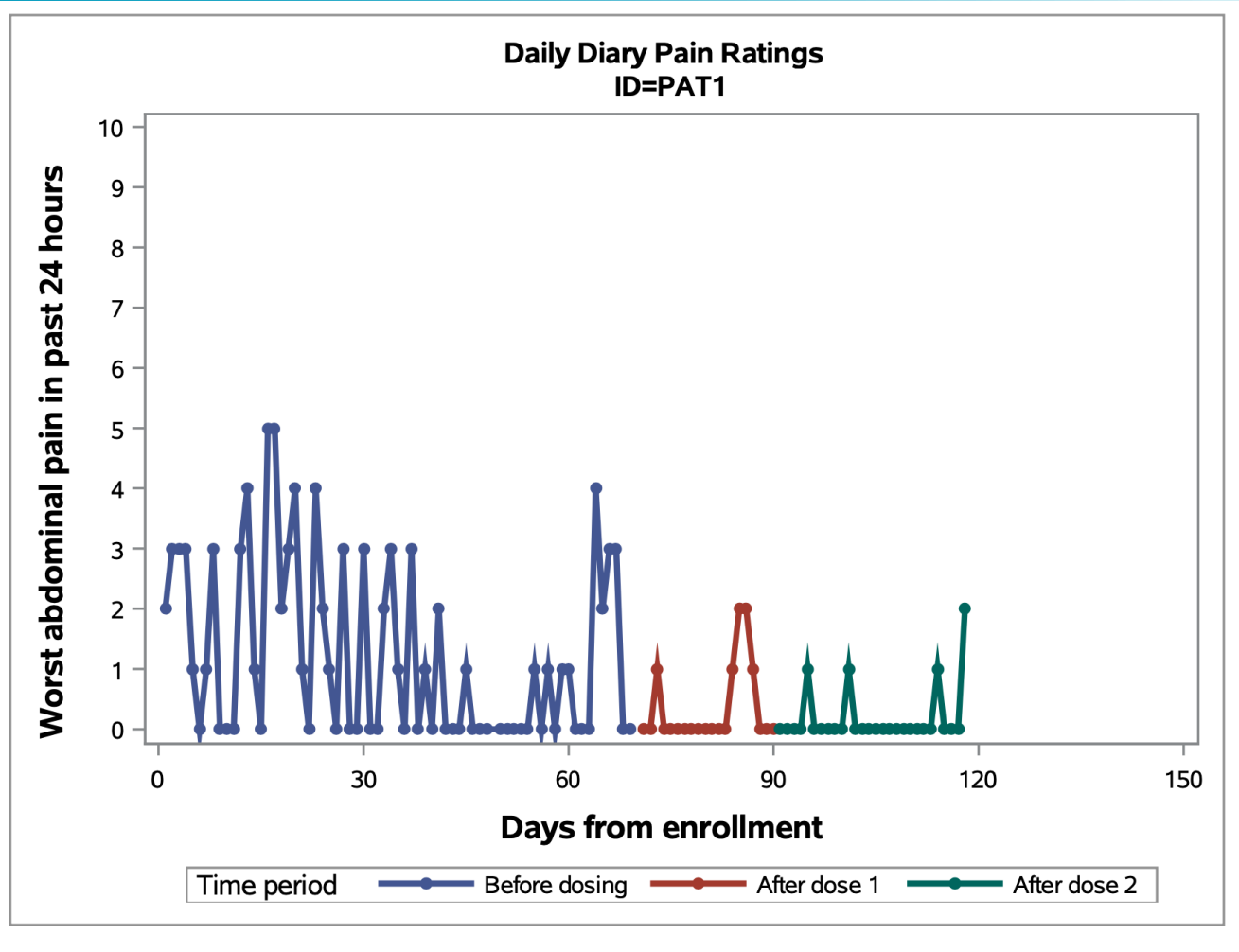
PAT1 GI & Mental Health Changes

Hospital Anxiety and Depression Scores

	Time Point	IBS-SSS	VSI	PGI-C	AAQ	HADS-Anxiety	HADS-Depression
PAT1	Pre-Intervention	230	35	6	26	10	8
	Post-Intervention	119	18	2	30	9	7
	Change	-111	-17	-4	4	-1	-1



PAT1 Pain Diary





Preliminary Outcomes

- PAT1: 40s F, clinician, Asian
- **PAT2: 50s F, clinician, white**
- PAT3: 30s F, clinician, white
- PAT4: 30s M, business, white



PAT2 Dosing Days

	Time Point	MEQ (Raw)	MEQ (%)	"Complete" Mystical Exp?	Challenging Experiences	CEQ %
PAT2	Dose 1	65	43%	No	7	5%
	Dose 2	56	37%	No	2	2%
	Change from Dose 1	-9			-5	



PAT2 Dosing Days Qualitative Themes

1. Dream-like experience

I felt like I was in a long dream and kept waking up – but not completely



PAT2 Dosing Days Qualitative Themes

1. Dream-like experience
2. Emotions (tears) without understanding of cause

“I did quite a bit of crying- sobbing, more like – but I didn’t really feel sad – or if I was, there was no reason”

"I struggled to identify the feelings on even what I wanted/needed in terms of comfort”



PAT2 Dosing Days Qualitative Themes

1. Dream-like experience
2. Emotions (tears) without understanding of cause
3. Feelings of safety and support throughout the day

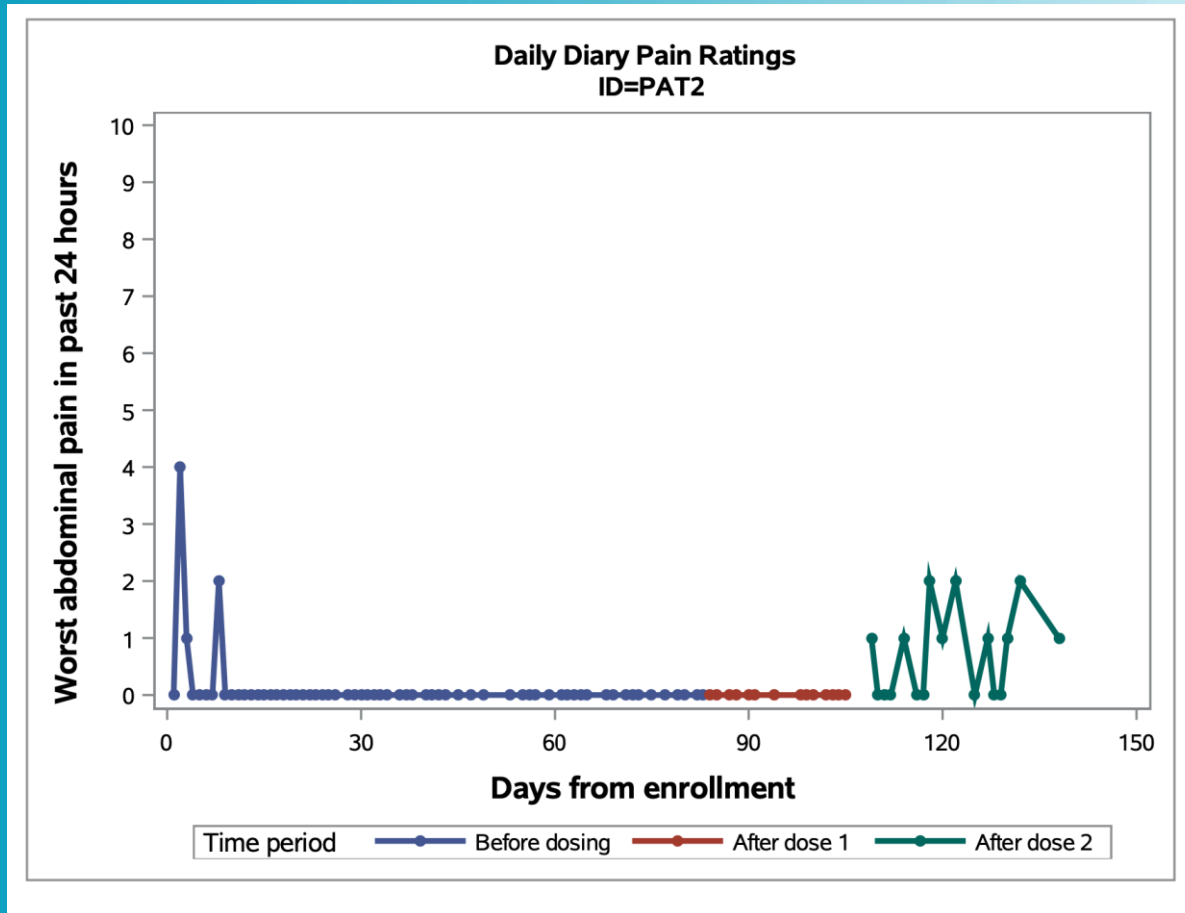


PAT2 GI & Mental Health Changes

	Time Point	IBS-SSS	VSI	PGI-C	AAQ	HADS- Anxiety	HADS- Depression
PAT2	Pre-Intervention	122	35	3	26	16	4
	Post-Intervention	69	18	4	30	11	1
	Change	-53	-17	1	4	-5	-3



PAT2 Pain Diary





Preliminary Outcomes

- PAT1: 40s F, clinician, Asian
- PAT2: 50s F, clinician, white
- **PAT3: 30s F, clinician, white**
- PAT4: 30s M, business, white



PAT3 Dosing Days

	Time Point	MEQ (Raw)	MEQ (%)	"Complete" Mystical Exp?	Challenging Experiences	CEQ %
PAT3	Dose 1	47	31%	No	76	58%
	Dose 2	48	32%	No	90	69%
	Change from Dose 1	1			14	



PAT3 Dosing Days Qualitative Themes

1. Re-experiencing of trauma. Anxiety/shame around lack of control

I am a little bummed that instead of a cosmic, beautiful experience I was reminded of this event that I don't feel like I have the tools to process independently



PAT3 Dosing Days Qualitative Themes

1. Re-experiencing of trauma. Anxiety/shame around lack of control, esp. with past traumatic events
2. Discomfort and challenges staying with uncomfortable experiences/feelings

I'm curious about my experiences of discomfort and why I can't sit with any uncomfortable feelings. I'm also curious about how unprocessed trauma is impacting my life and why I can't just move on. **I know it's important to sit with discomfort but I don't know how and will do anything to avoid being uncomfortable.**



PAT3 Dosing Days Qualitative Themes

1. Re-experiencing of trauma. Anxiety/shame around lack of control, esp. with past traumatic events
2. Discomfort and challenges staying with uncomfortable experiences including dosing experience
3. Challenges with relationships and trust



PAT3 Additional Reflections

Positive	Neutral	Negative
<p>- I do not care at all about IBS symptoms. I am noticing sensations and processing them as sensations rather than pain or indicators of something wrong.</p> <p>- I am not worrying about going to the bathroom before I go or dwelling on it after I go. It is a tiny event in my day rather than something that consumes my thoughts for most of the day</p>		



PAT3 Additional Reflections

Positive	Neutral	Negative
<p>- I do not care at all about IBS symptoms. I am noticing sensations and processing them as sensations rather than pain or indicators of something wrong.</p> <p>- I am not worrying about going to the bathroom before I go or dwelling on it after I go. It is a tiny event in my day rather than something that consumes my thoughts for most of the day</p>	<p>- Less rigid about diet, realizing sometimes comfort food is comforting even if it hurts my tummy</p>	



PAT3 Additional Reflections

Positive	Neutral	Negative
<p>- I can process sensations in my body as sensations rather than pain, Looking at things differently</p> <p>- I do not care at all about IBS symptoms. I am noticing sensations and processing them as sensations rather than pain or indicators of something wrong.</p> <p>- I am not worrying about going to the bathroom before I go or dwelling on it after I go. It is a tiny event in my day rather than something that consumes my thoughts for most of the day</p>	<p>- Less rigid about diet, realizing sometimes comfort food is comforting even if it hurts my tummy</p>	<p>- I feel like my connections to myself and the universe have been severed and I am completely alone</p> <p>- I have all these new, powerful emotions and don't know how to handle them</p>



PAT3 Serious Adverse Event

- Suicidal ideation lasting 6 weeks + post-dose 2
 - → additional integration sessions, medication bridge
 - ED eval, cleared for outpatient
 - Ongoing outside therapy and psych NP
- Reported to IRB and FDA
- Added SI to consent form and added more in-depth interview to screen for add'l psych/psychosocial contraindications

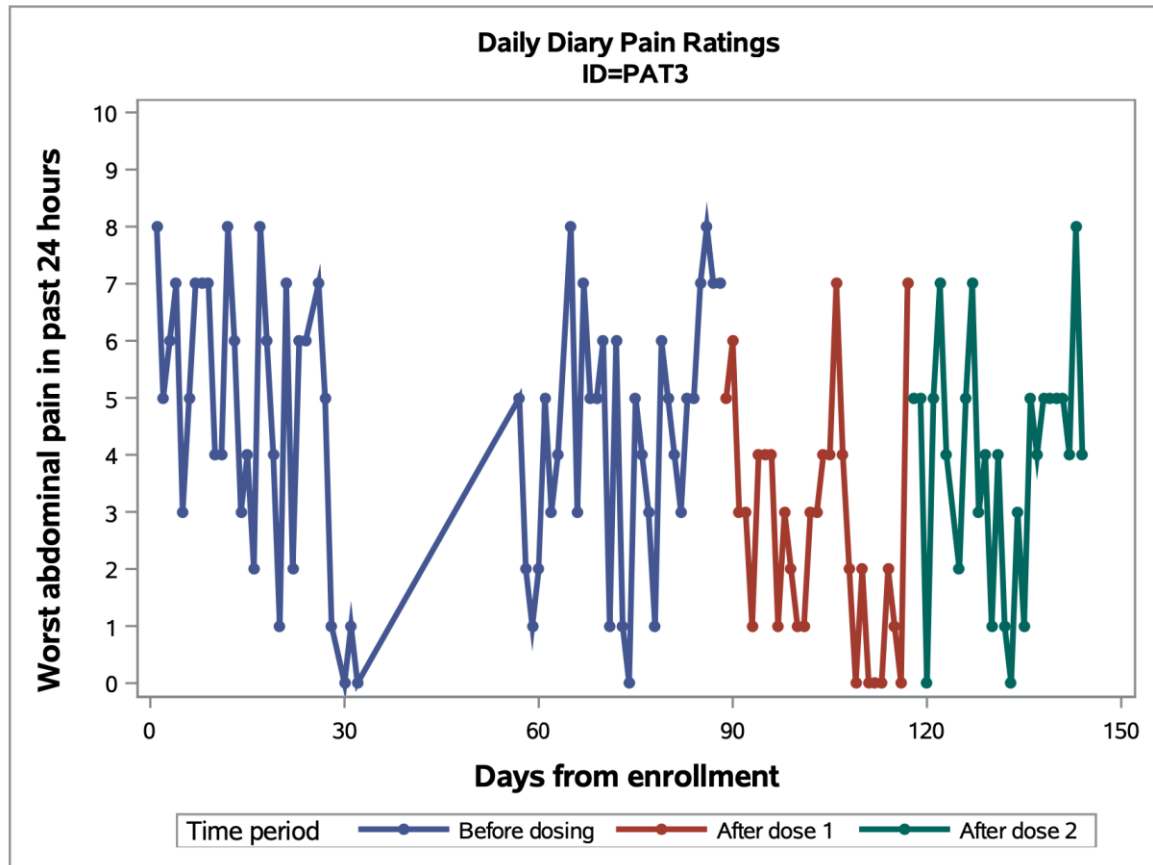


PAT3 GI & Mental Health Changes

	Time Point	IBS-SSS	VSI	PGI-C	AAQ	HADS- Anxiety	HADS- Depression
PAT3	Pre-Intervention	282	64	5	24	6	6
	Post-Intervention	214	50	7	38	20	20
	Change	-68	-14	-2	14	14	14



PAT3 Pain Diary





Preliminary Outcomes

- PAT1: 40s F, clinician, Asian
- PAT2: 50s F, clinician, white
- PAT3: 30s F, clinician, white
- **PAT4: 30s M, business, white**



PAT4 Dosing Days

	Time Point	MEQ (Raw)	MEQ (%)	"Complete" Mystical Exp?	Challenging Experiences	CEQ %
PAT4	Dose 1	55	37%	No	76	58%
	Dose 2	55	37%	No	90	69%
	Change from Dose 1	0			>	



PAT4 Dosing Days Qualitative Themes

1. Paranoia

My entire sense of realness in the world was deconstructed layer-by-layer and eventually vanished. I **thought I was a test subject in an intergalactic simulation - an organism laying permanently in a bed, being dosed and analyzed** - perhaps with thoughts being loaded into me - for reasons unclear



PAT4 Dosing Days Qualitative Themes

1. Paranoia
2. Connection of emotions to somatic symptoms

It seems notable that I had these intensely powerful experiences across both medication days but never cried or burst out in rage. **I wonder to what extent I feel feelings with my body instead of feeling them with my mind.** I noticed that [the therapist] often asks, "how are you feeling?" and **I usually answer with some physical indicator and not how my emotions feel**



PAT4 Dosing Days Qualitative Themes

1. Paranoia
2. Connection of emotions to somatic symptoms, wondering about applicability of dosing day experiences to everyday life
3. Approaching exploration with curiosity

Eventually there was a strong image of a purple and black industrial shapes... This felt like a scary experience was forthcoming. I braced for it **and tried to remind myself that of the two options - (1) shudder and turn away or (2) try to look at it with curiosity - curiosity would be better.**

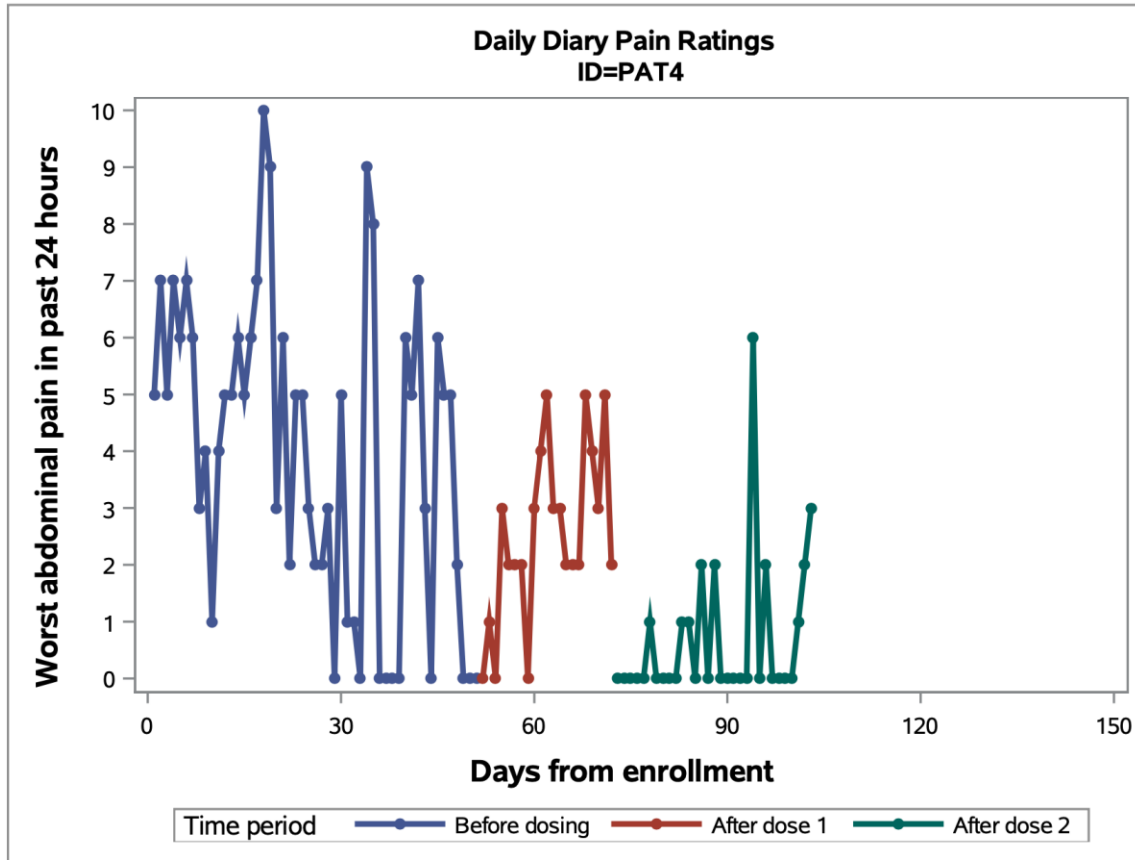


PAT4 GI & Mental Health Changes

	Time Point	IBS-SSS	VSI	PGI-C	AAQ	HADS- Anxiety	HADS- Depression
PAT4	Pre-Intervention	217	62	4	8	6	3
	Post-Intervention	231	60	3	11	4	2
	Change	14	-2	-1	3	-2	-1

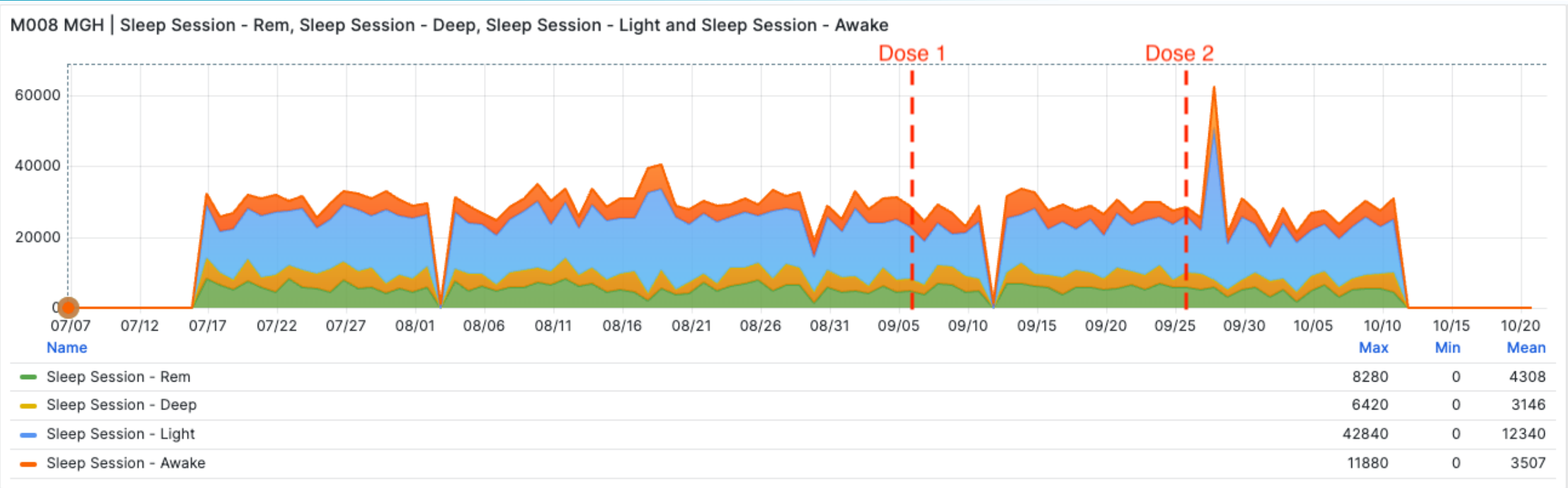


PAT4 Pain Diary



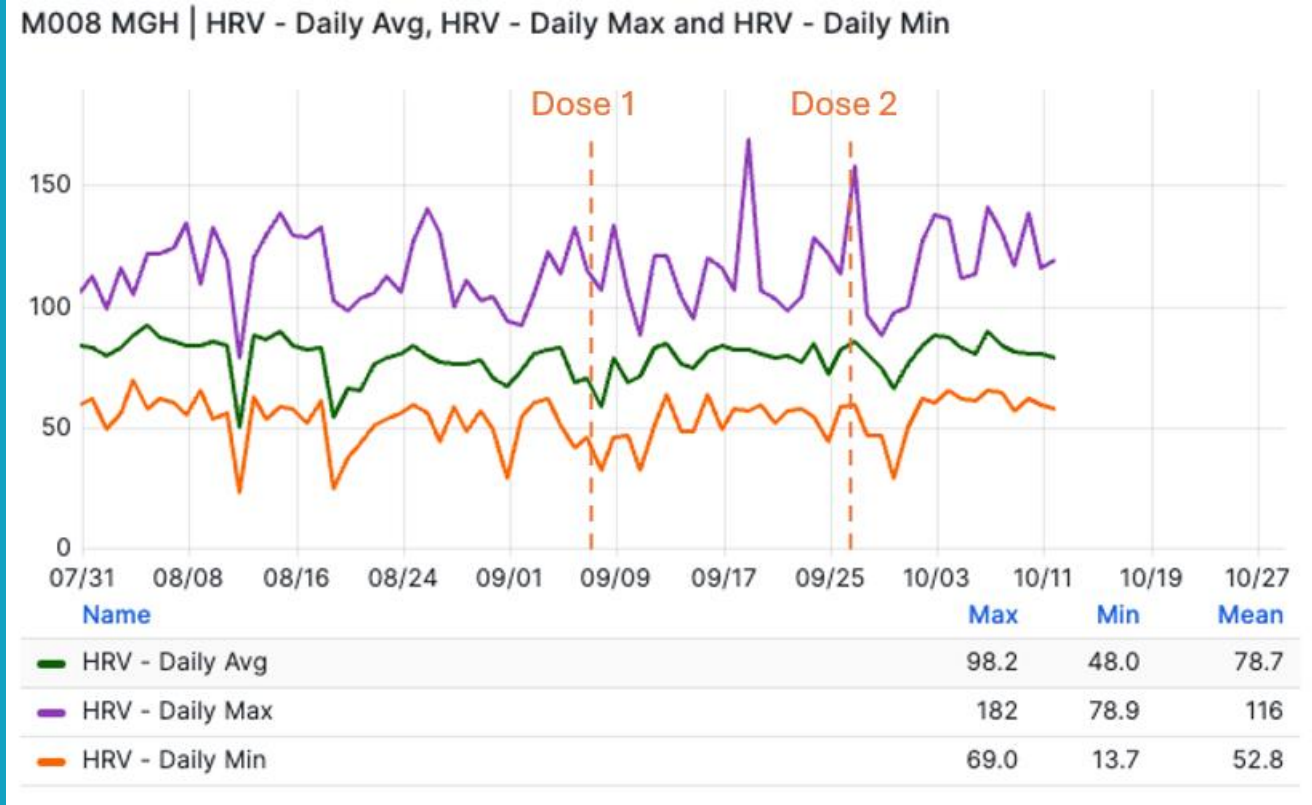


PAT4 Watch Data: Sleep



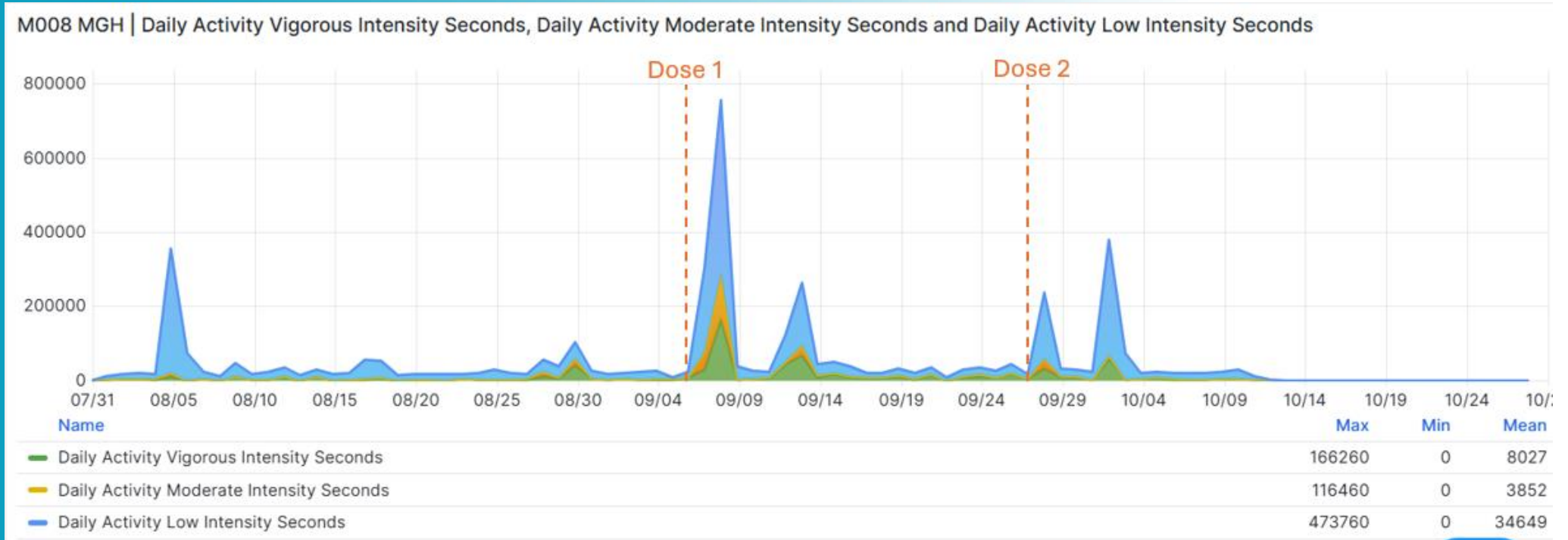


PAT4 Watch Data: HRV



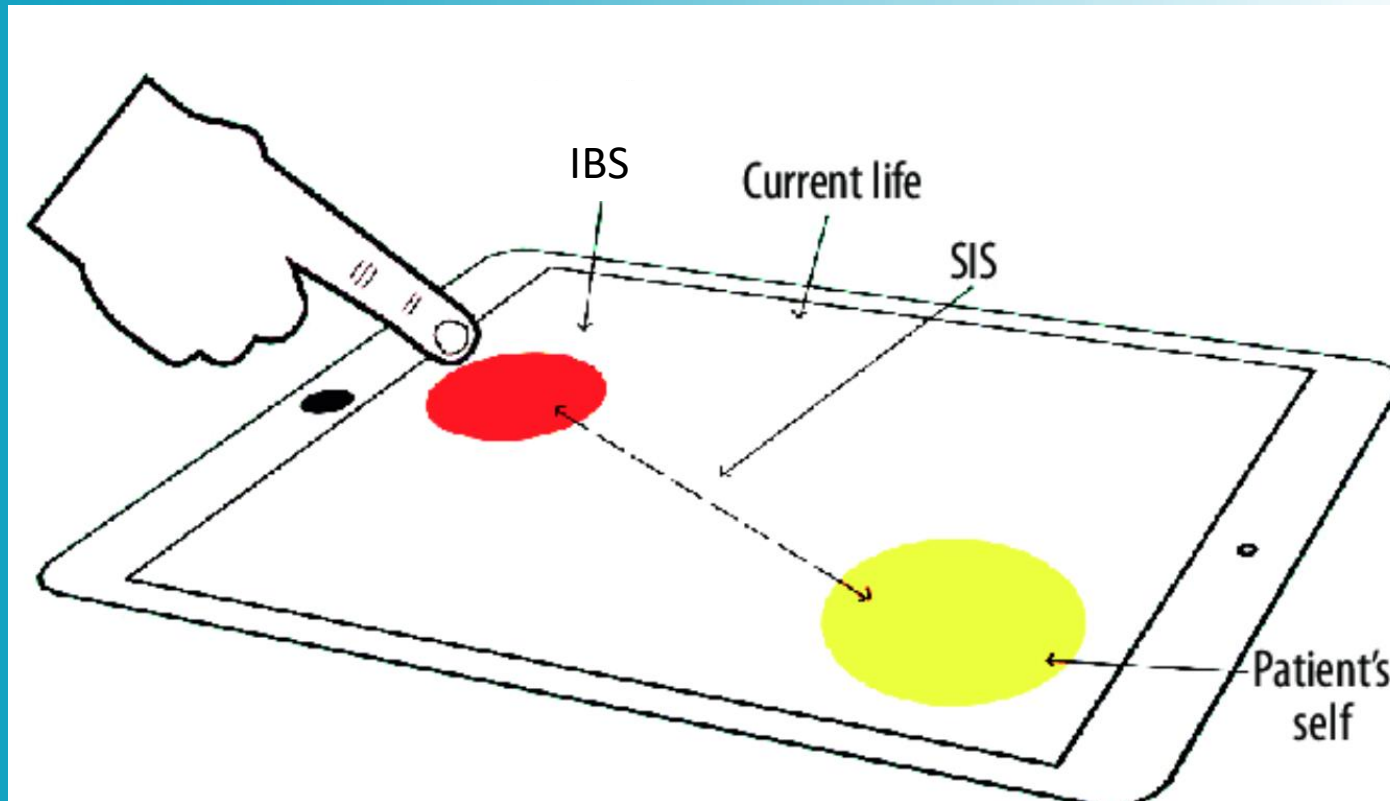


PAT4 Watch Data: Activity





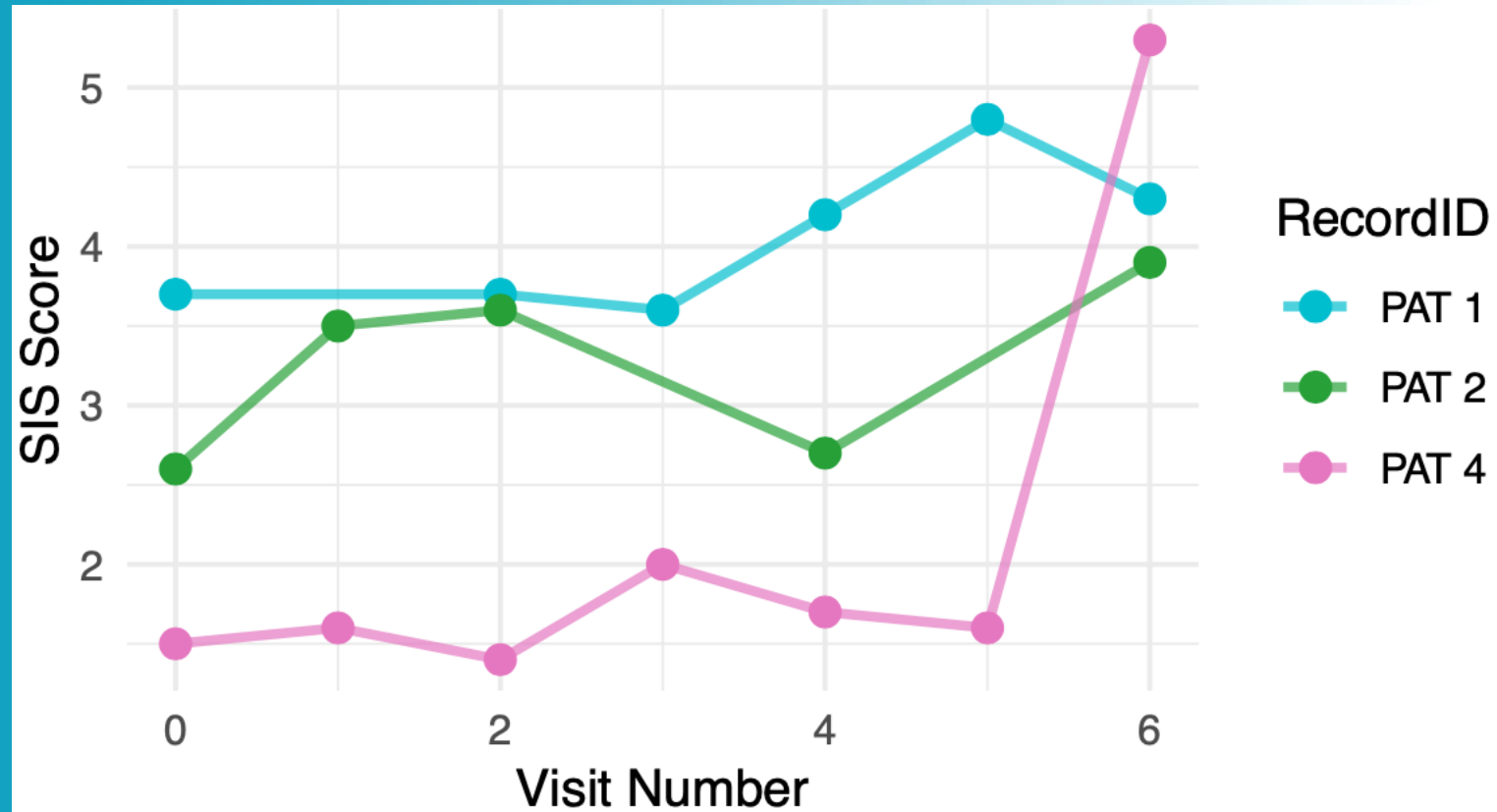
Self-Illness Separation



Adapted from Kabar *et. al.* 2018

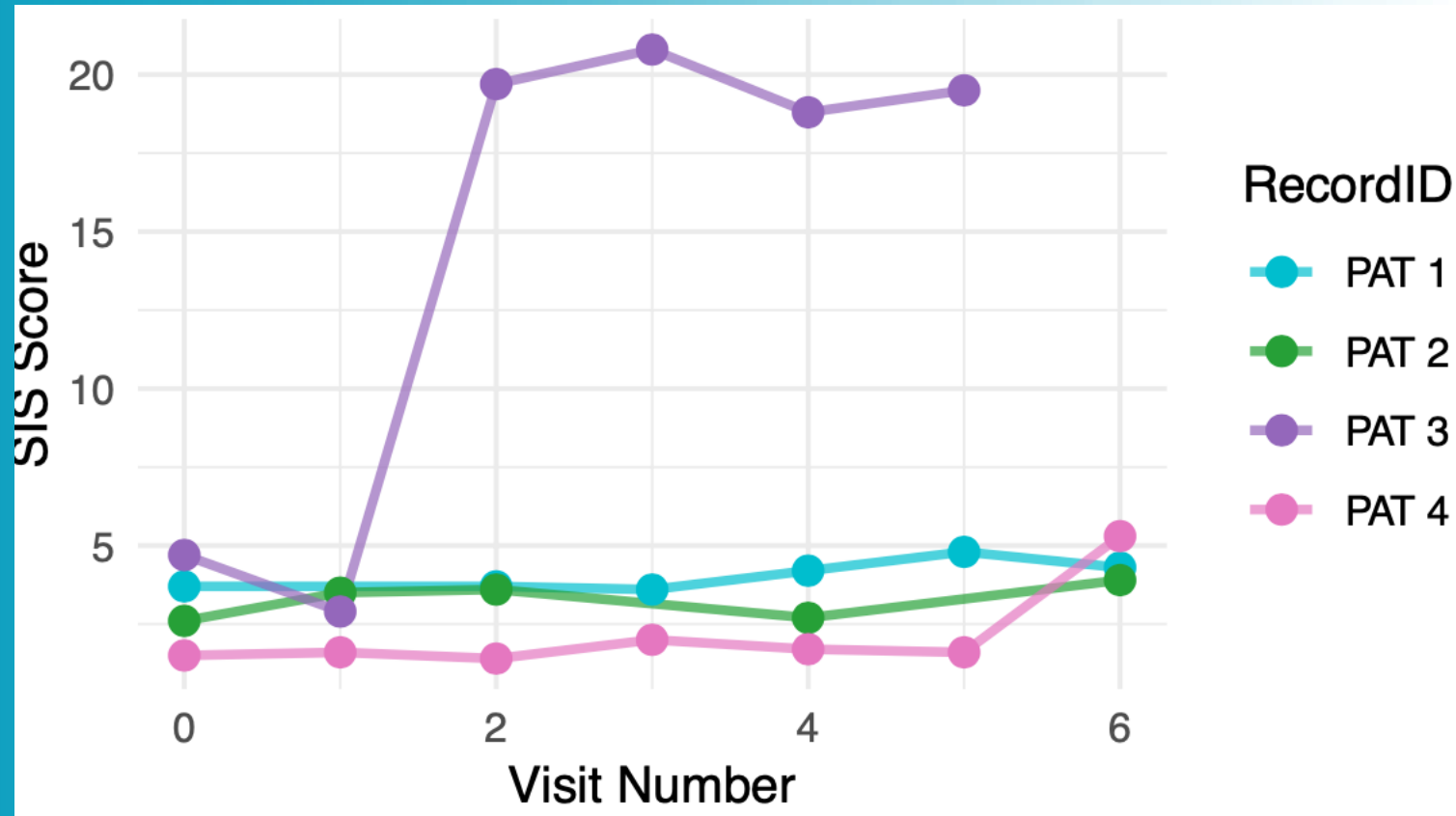


SIS Over Time



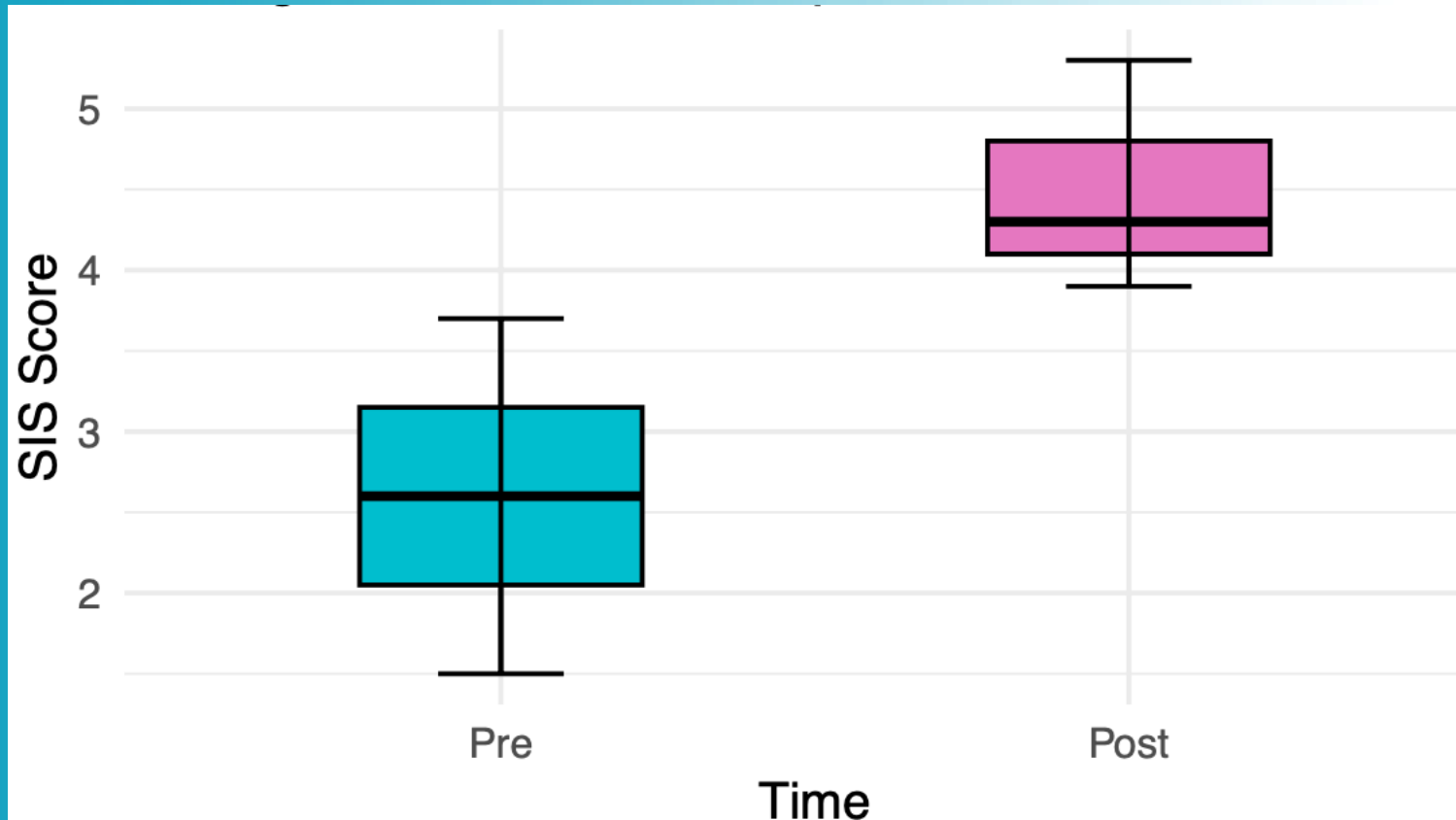


SIS Over Time (+PAT3)



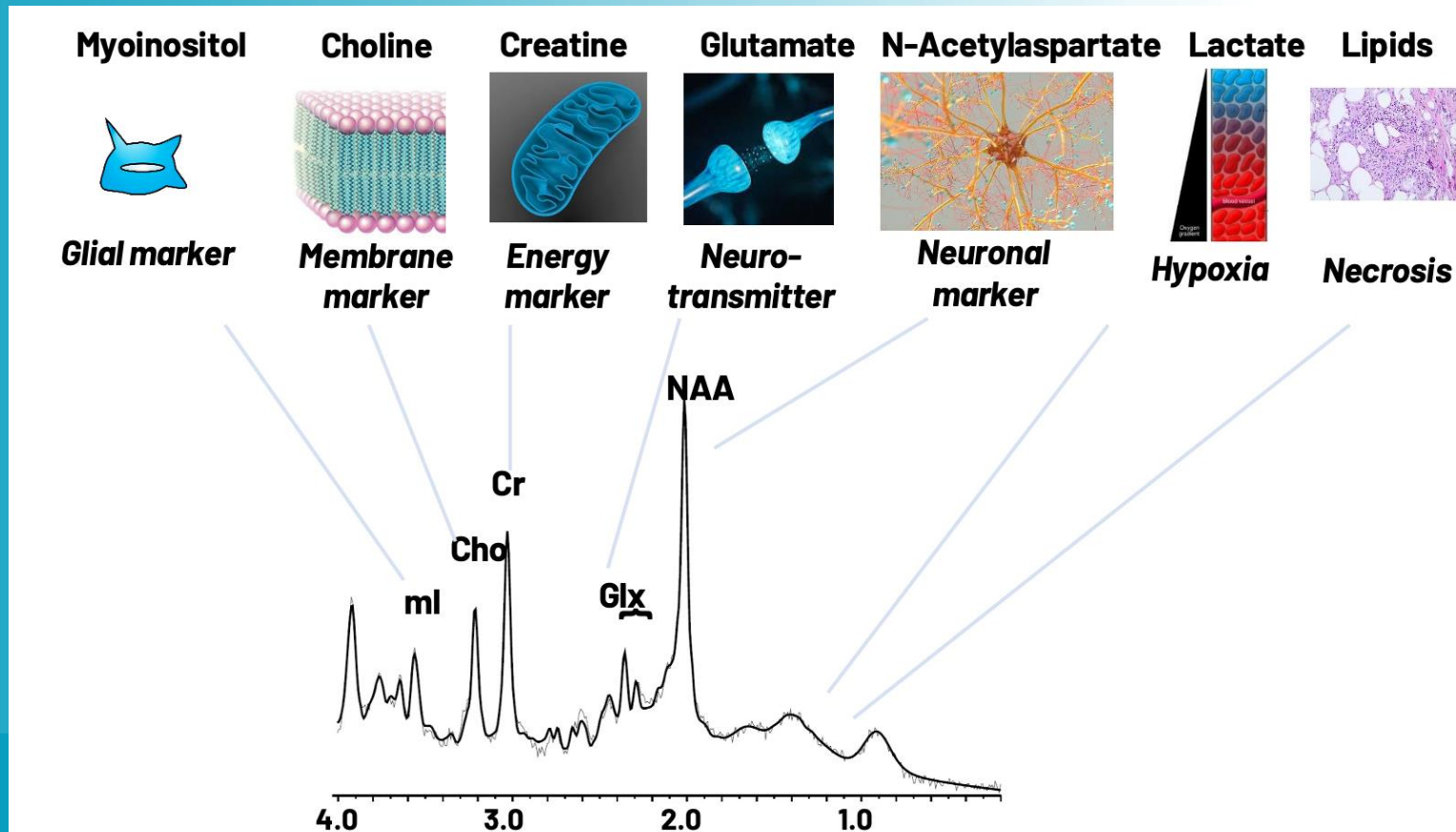


Change in Self-Illness Separation Score



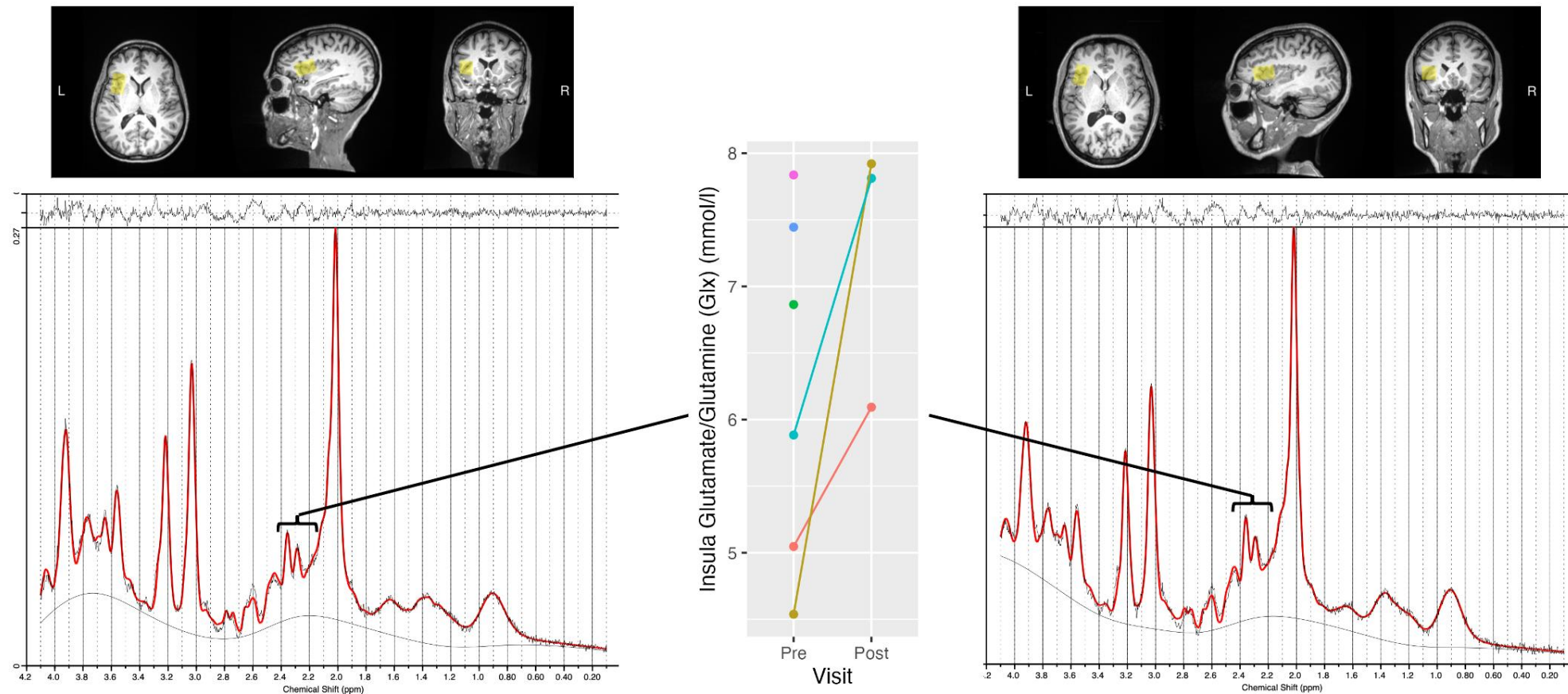
^1H magnetic resonance spectroscopy (MRS) background

- Spectroscopy allows us to measure the neuro-chemical state of the brain (concentrations of neurotransmitters, metabolites, etc.)



Increases in anterior insula Glx concentration pre-/post-

- Anterior insula: emotional processing, self-awareness, pain processing





Qualitative Interviews Post-Study (n=3)

1. Increased feelings of openness & flexibility
2. Importance of therapy model (integration/prep, dyad)
 1. Lack of interest in group therapy
 2. Interest in more guidance/IBS-specific approaches
3. Challenges reducing expectancy



Preliminary Conclusions

1. Feasible & physiologically safe
 - Risk of destabilization, especially in patients with a trauma history & little psychological-mindedness.
2. Extremely variable intensity of dosing experiences
3. Promising data that PAT can decrease IBS symptoms and GI-specific anxiety (3/4 patients) -- ?not mediated by psych. flexibility
4. Decreases in depression and anxiety indices (3/4 patients)



Research priorities in PAT/DGBI

- Managing/incorporating GI “side effects”
- Matching patient + drug + therapy – cyclic vomiting, functional dyspepsia, ARFID
- Future directions: motility (including basic science), food diaries, mediating effect of trauma history



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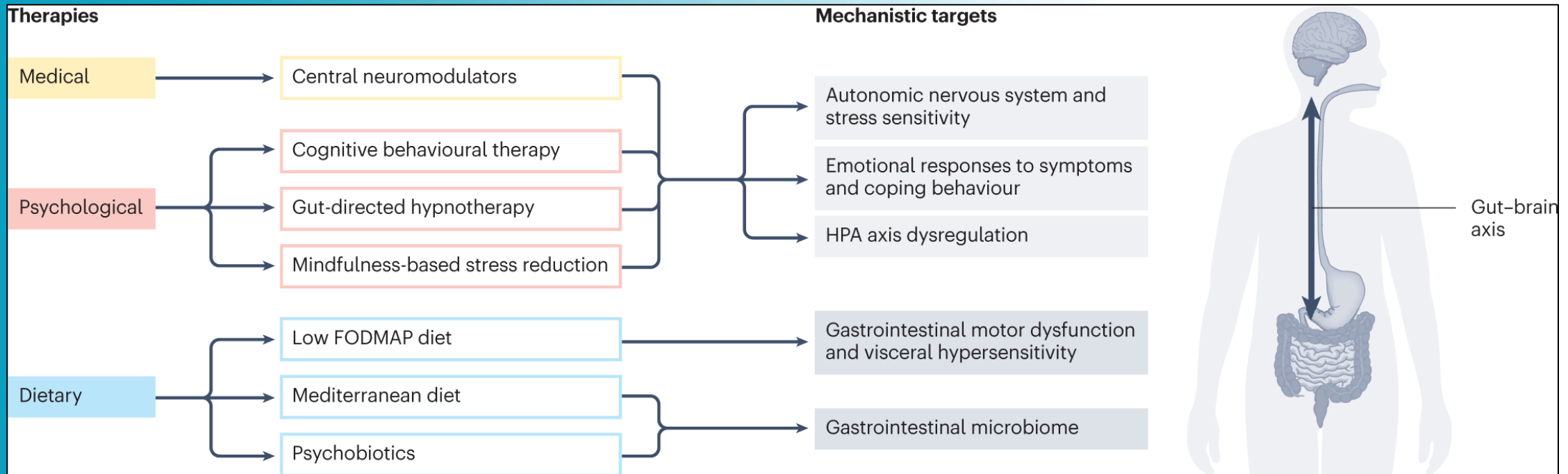
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Extant IBS therapies target the gut-brain axis



Staudacher 2023, *Nat. Rev. Gastro*

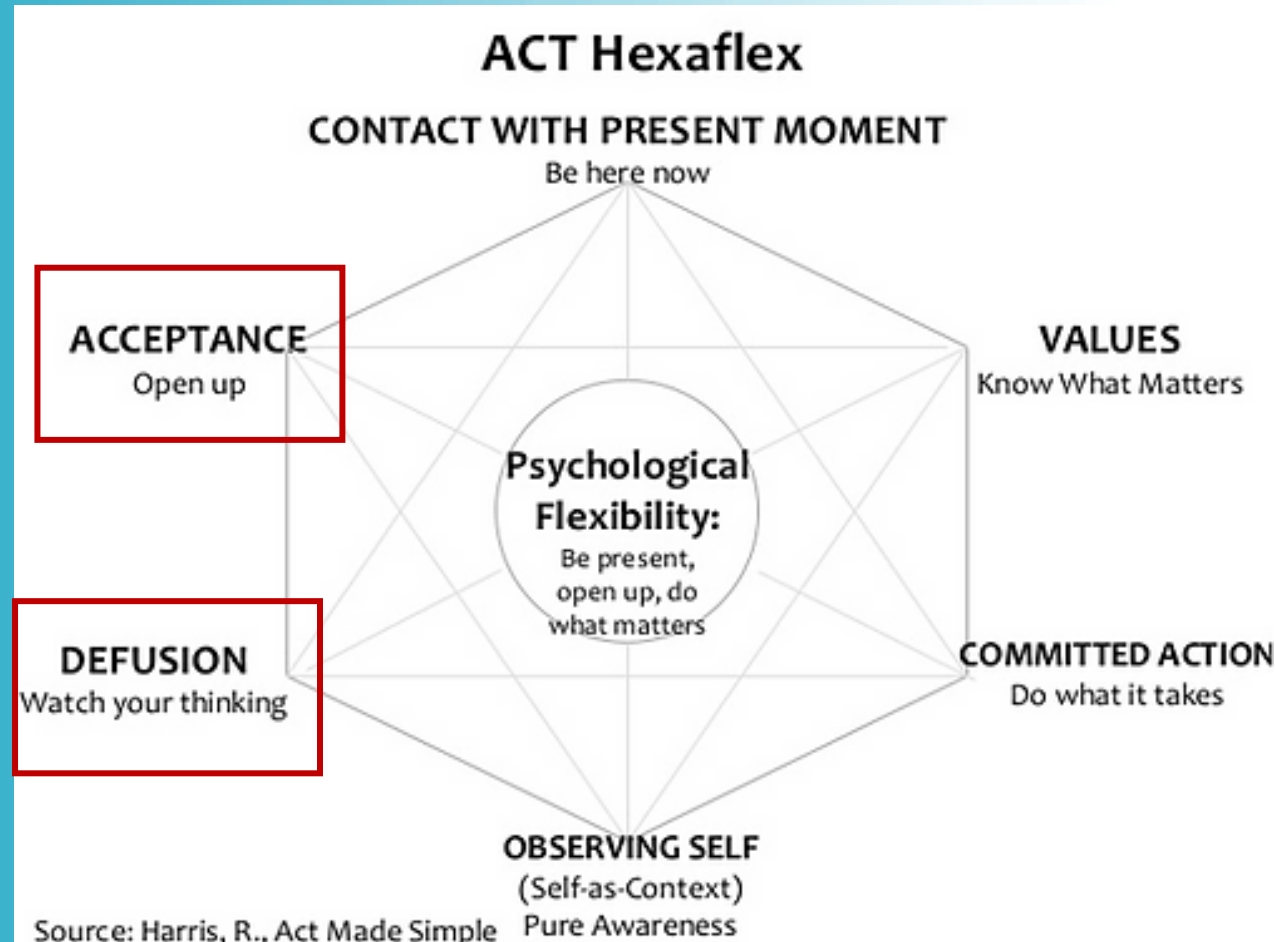


PAT may uniquely modulate the enteric environment

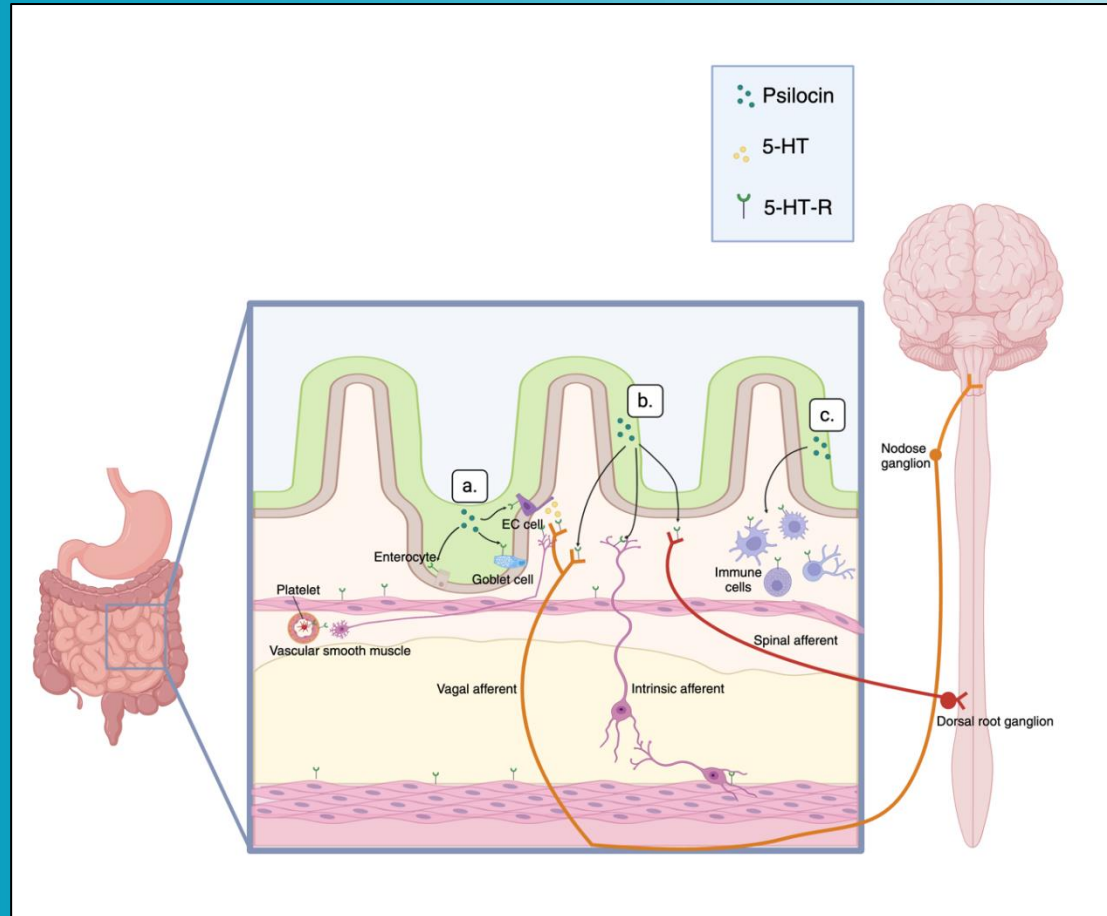
- Serotonergic signaling in the gut
 - Motility, inflammation
- Anti-inflammatory effects
- Endocannabinoid system
- Microbiome changes



PAT for IBS: Therapeutic Approach



Potential targets of psilocin in the gut

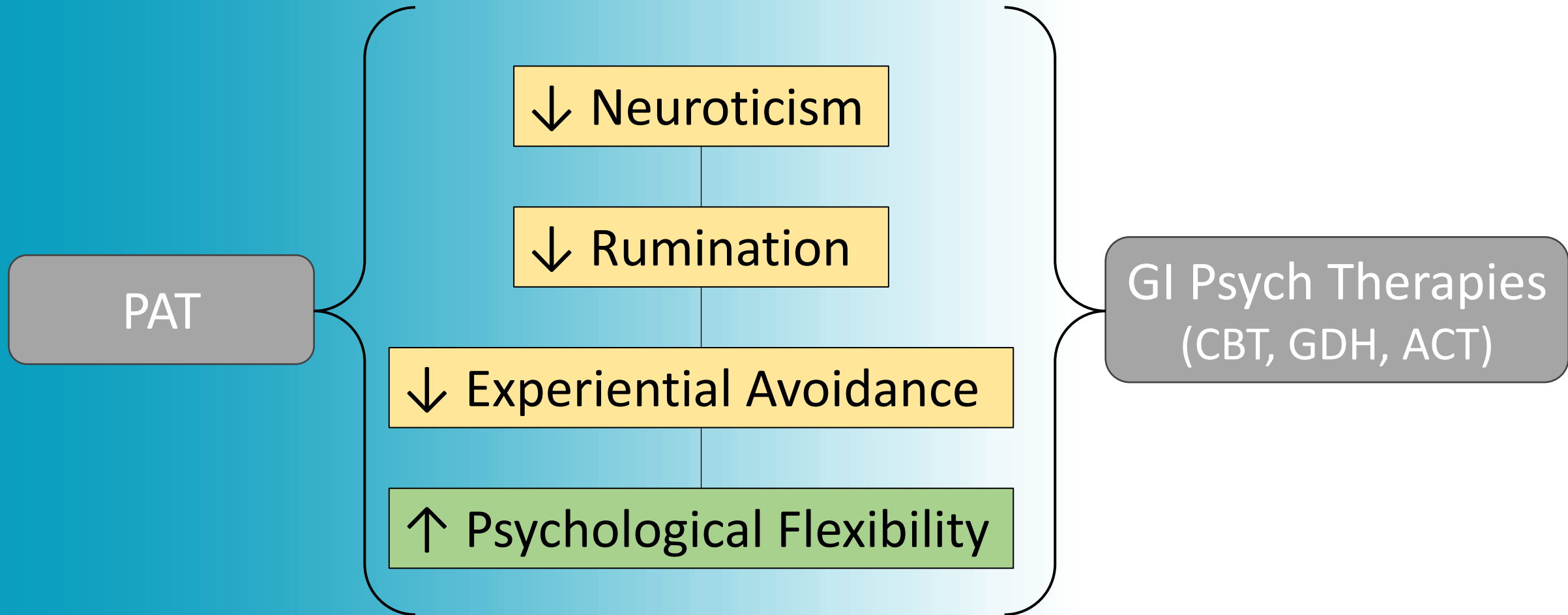


- a) 5HT-R on enterocytes, goblet cells, EC cells → gut permeability, mucus layer, intrinsic serotonin release
- b) 5HT-R on vagal/intrinsic/spinal afferents → visceral sensation, motility. ?Neuroplastic effects.
- c) 5HT-R in the gut (T-cells, mast cells, macrophages, dendritic cells) → anti-inflammatory

Mauney *et. al.*, under review



Psychological mechanisms are shared in PAT and extant IBS therapies





Central targets are shared in PAT and extant IBS therapies

