The potential of psilocybin-assisted therapy for anorexia nervosa

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Disclosures

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  - New York State Psychiatric Institute
  - Steven and Alexandra Cohen Foundation
  - Reunion Neuroscience
  - Cybin Inc.

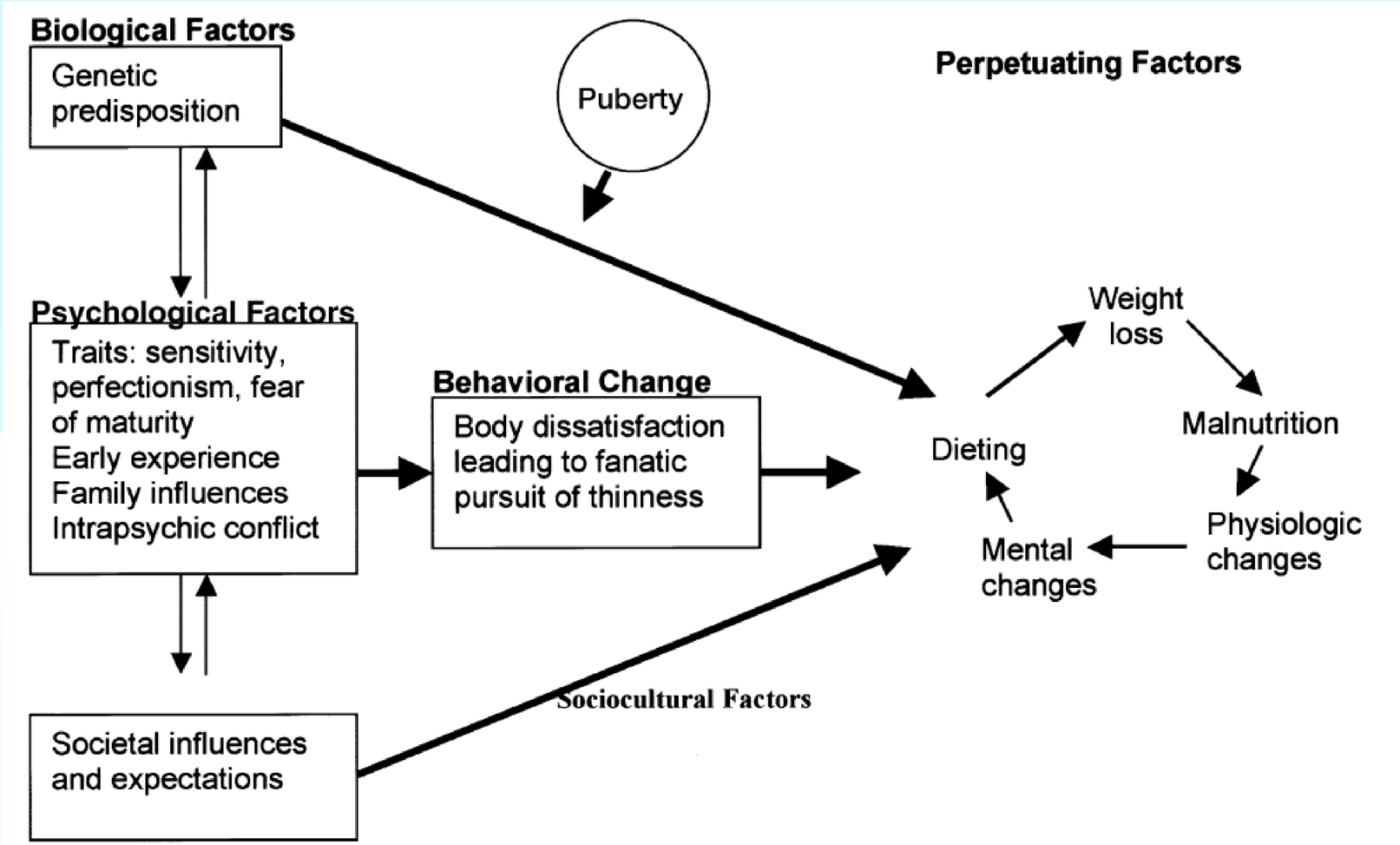
Overview

- Background and rationale on psilocybin for anorexia nervosa (AN)
- Population-specific treatment considerations
- Data from a pilot study of psilocybin for people with (AN)

Anorexia nervosa

- Anorexia nervosa (AN) is a behavioral disorder characterized by caloric restriction, fear of gaining weight, and disturbance in perception of one's weight or shape.
- **Highest mortality** of any psychiatric illness (10%)
- Phenomenological parallels to anxiety and addiction
- Complicated by physiological sequelae of **starvation**
  - Gastrointestinal, cardiac, hepatic, renal dysfunction

Pathophysiology of AN is still not fully understood



Silber, T. J. (2005). *Advances in pediatrics*, *52*, 49-76.

Standard AN treatment

- Combination of **nutritional rehabilitation** and **psychotherapy** in two phases
    1) Weight restoration
    2) Weight maintenance and relapse prevention
- No type of psychotherapy has been proven to be superior
- Adjunctive pharmacotherapy is employed in some cases as second-line treatment.
- Treatment success is limited by ambivalence to change
    - **Up to ~30-50% relapse** after weight restoration

Psychedelics for AN

- Possible mechanisms by which psilocybin-assisted therapy may be helpful in the treatment of AN
  - AN bears phenomenological similarity to conditions that seem to be improved by psychedelic-assisted therapy
  - ? Direct or indirect effects of 5-HT_{2A} agonism
    - Receptor-level
    - Brain network-level
  - Psychological changes including improved cognitive flexibility, “quantum change”
  - Improvement of co-morbid conditions & quality of life

5-HT functioning in AN

- Evidence for altered serotonergic (5-HT) functioning in AN
  - A study comparing recovered AN patients to healthy controls found decreased 5-HT_{2A} binding in the mesial temporal lobe (hippocampus, amygdala) and pre- and sub-genual anterior cingulate (executive functioning, regulation of emotion) [1]
  - Possible differences in allele frequencies of 5-HT_{2A} promoter polymorphism among AN patients [2]

[1] Frank et al., 2002 Biological Psychiatry, 52(9), 896-906.
[2] Hinney et al., 2000 *European journal of pharmacology*, *410*(2-3), 147-159.

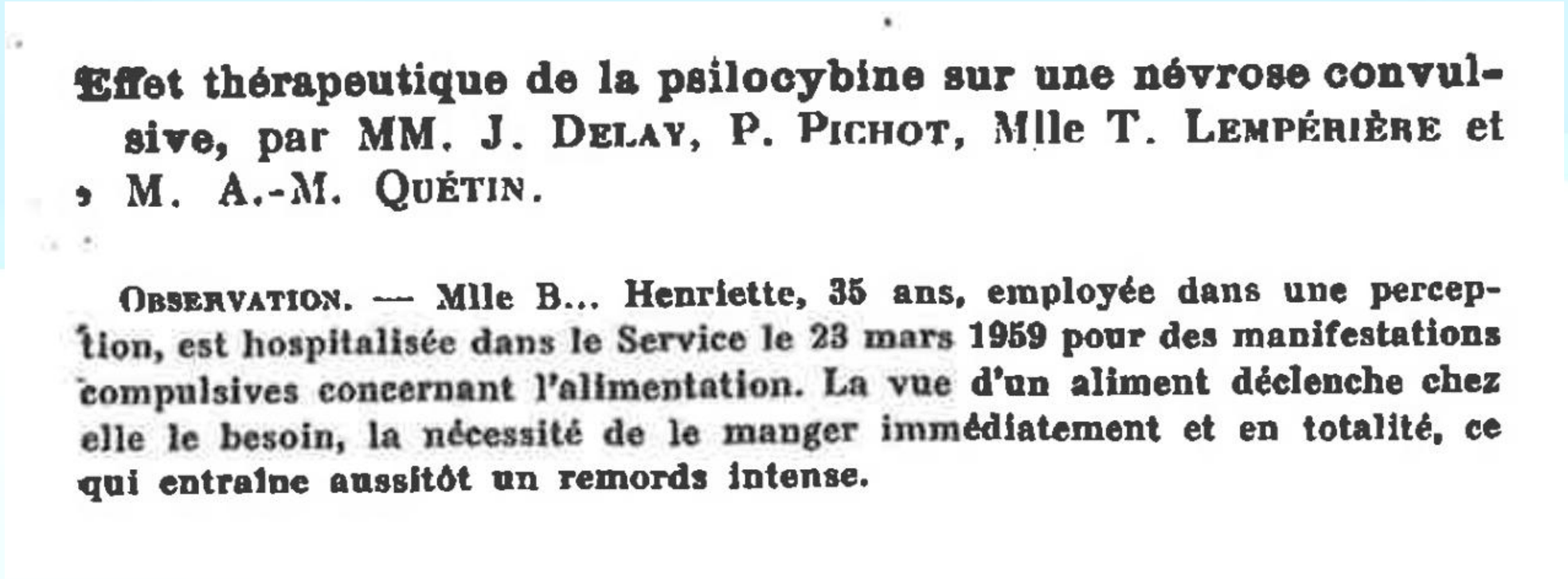
Functional connectivity differences in AN

- Important caveats to imaging research in AN
  - Nutritional status can be confounding
  - Lack of within-subjects studies (i.e. imaging of the same person before and after recovery)
- Patients with AN have increased rsFC in the DMN and the frontoparietal network.[1]
  - Increases in DMN rsFC in AN additionally appear to partially correct after recovery.[2]
- Psilocybin acutely decreases rsFC in the DMN as well as in the amygdala.[3,4]

1 Lee et al. (2014). *Psychiatry Research: Neuroimaging*, *221*(1), 43-48.
2 Boehm et al. (2016) *Journal of Psychiatry and Neuroscience*, *41*(6), 377-385.
3. Carhart-Harris et al. (2012). *Proceedings of the National Academy of Sciences*, *109*(6), 2138-2143.
4 Kraehenmann et al. (2015). *Biological psychiatry*, *78*(8), 572-581.

Existing evidence for psychedelics for people with EDs

Limited literature from the first wave of psychedelic research



Effet thérapeutique de la psilocybine sur une névrose convulsive, par MM. J. DELAY, P. PICHOT, Mlle T. LEMPÉRIÈRE et M. A.-M. QUÉTIN.

OBSERVATION. — Mlle B... Henriette, 35 ans, employée dans une perception, est hospitalisée dans le Service le 23 mars 1959 pour des manifestations compulsives concernant l'alimentation. La vue d'un aliment déclenche chez elle le besoin, la nécessité de le manger immédiatement et en totalité, ce qui entraîne aussitôt un remords intense.

Delay et al. (1959) *Annales Médico-psychologiques, revue psychiatrique*

Existing evidence for psychedelics for people with AN

- **Qualitative analyses** of experiences of ceremonial ayahuasca use among people with eating disorders in naturalistic settings.[1,2]
  - Themes included reduction or cessation of disordered eating behaviors and shifts in body image perception.
  - Eleven participants **(69%) reported some decrease in symptom severity** and half reported reductions in co-morbid anxiety, depression, or substance use.
  - One person reported brief symptom **exacerbation** shortly after ayahuasca use but this was followed by improvement.
  - Limitations of this study included **sparse information about participant diagnoses and treatment histories**.

[1] LaFrance et al., (2017) Journal of psychoactive drugs, 49(5), 427-435.
[2] Renelli (2018) (Doctoral dissertation, Laurentian University of Sudbury).

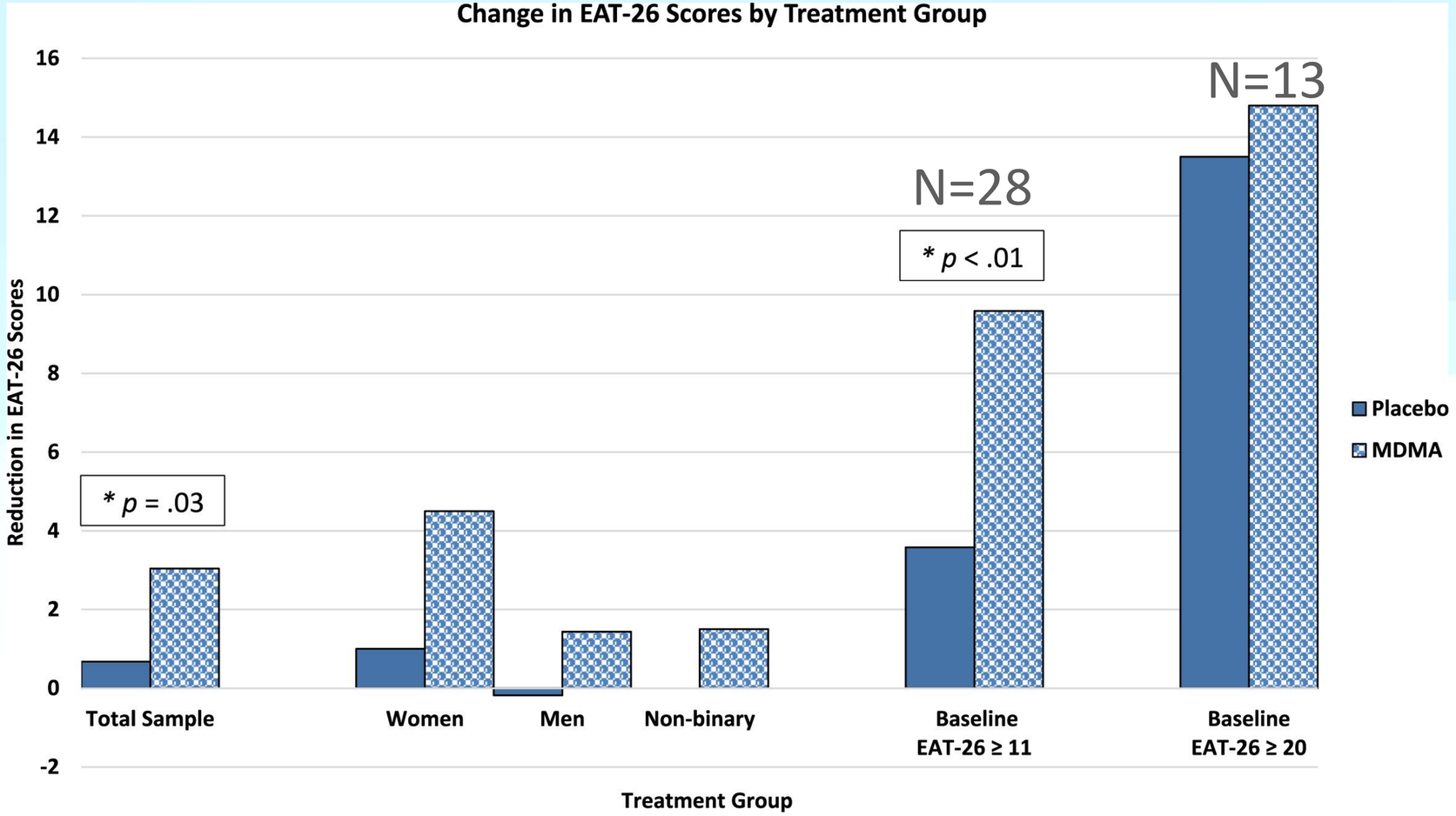
Existing evidence for psychedelics for people with AN

- Secondary analysis of large survey data suggesting ↓ depression and ↑ wellbeing after classic psychedelic use for people self identified as having an eating disorder[3]
    - Study **limitations** included that the sample reported lifetime history of an eating disorder, but neither current nor past specific diagnoses were assessed. Though parent survey was large, only 28 respondents had ED history

[3] Spriggs et al. (2021) Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity, 26(4), 1265-1270.

Existing evidence for psychedelics for people with AN

Secondary analysis of study on MDMA for PTSD (N-89): variable data



Brewerton et al (2022) Journal of Psychiatric Research, 149, 128-135.

Existing evidence for psychedelics for people with AN

- Peck et al. (2023) pilot (n=10, half the sample in partial remission) of single-dose psilocybin treatment in AN.
- Significant decreases in EDE shape, eating, and weight concern subscales. No changes in BMI.
- No serious AEs

Table 4 | Qualitative perceptions of treatment

3-month follow-up % agreement since the psilocybin dosing…	***n*=10**
1. Have you felt that the overall quality of your life has improved?	70%
2. Have you felt as though the importance you place on your physical appearance has decreased?	60%
3. Have you felt more optimistic regarding your life endeavors?	90%
4. Have you felt a shift in your personal identity or a sense of who you are?	70%
5. Have you felt a greater sense of spirituality?	60%
6. Do you feel that the psilocybin dosing was one of the top five most meaningful experiences of your life?	80%
7. Was one dosing session enough? (% disagreement)	90% (No)

Pilot study design considerations

- **Primary outcomes**
  - Safety (CCSRS, AE's)
  - Depressive and anxiety symptoms (BDI-II, HADS, STAI)
  - Quality of Life (EDQLS)

- **Secondary & exploratory outcomes**
  - Eating disorder severity as measured by EDE-Q
  - BMI at 3 months post final dosing session
  - Motivation to change (ANSOCQ)
  - Food preferences (FPQ, food choice task)

Pilot study design considerations

- Careful screening of prospective participants
  - High rates of medical (esp. cardiac) and psychiatric comorbidity
- Selection and structure of adjunctive therapy
  - Motivational enhancement therapy (vs. CBT, ACT, etc.)
- Selection of doses
  - Anecdotal reports of decreased sensitivity to classic psychedelics in this population led us to opt for fixed doses (rather than weight based)

Inclusion criteria

- 18 to 65 years old
- Meet DSM-5 criteria for AN, and have a history of AN for at least 3 years prior to screening
- Have a screening BMI ≥16 and ≤19 kg/m^2 and report being unable to maintain a BMI >19 kg/m^2 for more than 12 consecutive months during the past 3 years*
- Have at least one prior attempt at treatment
- If on an antidepressant, must be able to taper off safely prior to receiving study drug

Exclusion criteria

- Chronic purging behaviors
- Clinically significant hepatic impairment
- History of psychosis or bipolar spectrum disorder
- 1st degree relative with psychotic illness or bipolar disorder

Initial study design

- Targeting 18 completers
- Participants paired with two facilitators
- Medication taper, if applicable, occurred before baseline

Week 1	Baseline assessments
Weeks 2-5	Preparation sessions
Week 6	Psilocybin session 1 + next-day follow-up
Week 7	1-week integration session
Week 8	Psilocybin session 2 + next-day follow-up
Weeks 9-11	Weekly integration sessions
Week 12	1-month follow-up
Week 16	2-month follow-up
Week 20	3-month follow-up
Week 32	6-month follow-up

Participant demographics (n=20)

		% (N)
		Mean ± SD
Age at screening		32.9 ± 14.3
Sex (female)		95% (19)
Race/ethnicity		
Caucasian		100% (20)
non-Hispanic		100% (20)
BMI at baseline (kg/m^2)		18.2 ± 1.2
Education level		
Some college		15% (3)
4 year degree		35% (7)
Masters		15% (7)
Doctorate/professional degree		35% (3)
Marital status		
Single		55% (11)
Married		45% (9)
Primary ED diagnosis		
AN-R		65%(13)
AN-R, partial remission		20% (4)
AN-BP		10% (2)
AN-BP, partial remission		5% (1)

Co-occurring disorders		
MDD with current depressive episode		35% (7)
Current GAD		25% (5)
Current OCD		10% (2)
Social anxiety disorder		30% (6)
Substance use disorder (mild)		5% (1)
OCPD		20% (4)
Avoidant PD		5% (1)
Persistent Depressive Disorder		5% (1)
Panic disorder		5% (1)
PTSD or other trauma-related dis.		10% (2)
ADHD		5% (1)
Years since AN diagnosis		14.7 ± 10.7
Duration of illness >7 years and BMI ≤ 18 kg/m^2		7 (35%)
On medication at screening		40% (8)

Experience with first several participants

- 2 of 3 initial volunteers exhibited lower than expected subjective effects during at least one session

Volunteer	Session #	Dose (mg psilocybin)	Weight (kg)	Dose by weight (mg/kg)	MEQ score	CEQ score
1401	**1**	**20**	**48.6**	**0.41**	**5.3**	**2.4**
1401	**2**	**25**	**48.6**	**0.51**	**9.3**	**1.65**
1403	**1**	**20**	**41.6**	**0.48**	**6.7**	**0.65**
1403	2	25	41.6	0.60	57.3	2.85
1405	1	20	44.9	0.45	48.0	1.15
1405	2	25	44.9	0.56	31.3	0.3

Experience with first several participants

Volunteer	Session #	Dose (mg psilocybin)	Weight (kg)	Dose by weight (mg/kg)	Experience of unity	Spiritual experience	Insightfulness	Disembodiment	Impaired control and cognition	Anxiety	Complex imagery	Elementary imagery	Audio-visual synesthesia	Changed meaning of percepts
1401	**1**	**20**	**48.6**	**0.41**	**0.2**	**0**	**0**	**5**	**4.4**	**1.8**	**3**	**0**	**7.7**	**0**
1401	**2**	**25**	**48.6**	**0.51**	**0**	**0**	**0**	**5**	**9**	**2.5**	**4**	**10**	**7.3**	**0**
1403	**1**	**20**	**41.6**	**0.48**	**0**	**0**	**0**	**0**	**0**	**0**	**0.7**	**0**	**0**	**1**
1403	2	25	41.6	0.60	16.2	4.3	0	37.3	15.1	37.8	30.7	6.3	3.7	9.7
1405	1	20	44.9	0.45	27	31.3	39.3	47.3	72.9	31.8	95.7	93.3	69.3	40
1405	2	25	44.9	0.56	15.4	8.3	9	38.3	29.7	8	41	23	30	9

No clear relationship between acute effects and BMI, recent medication use, symptom severity

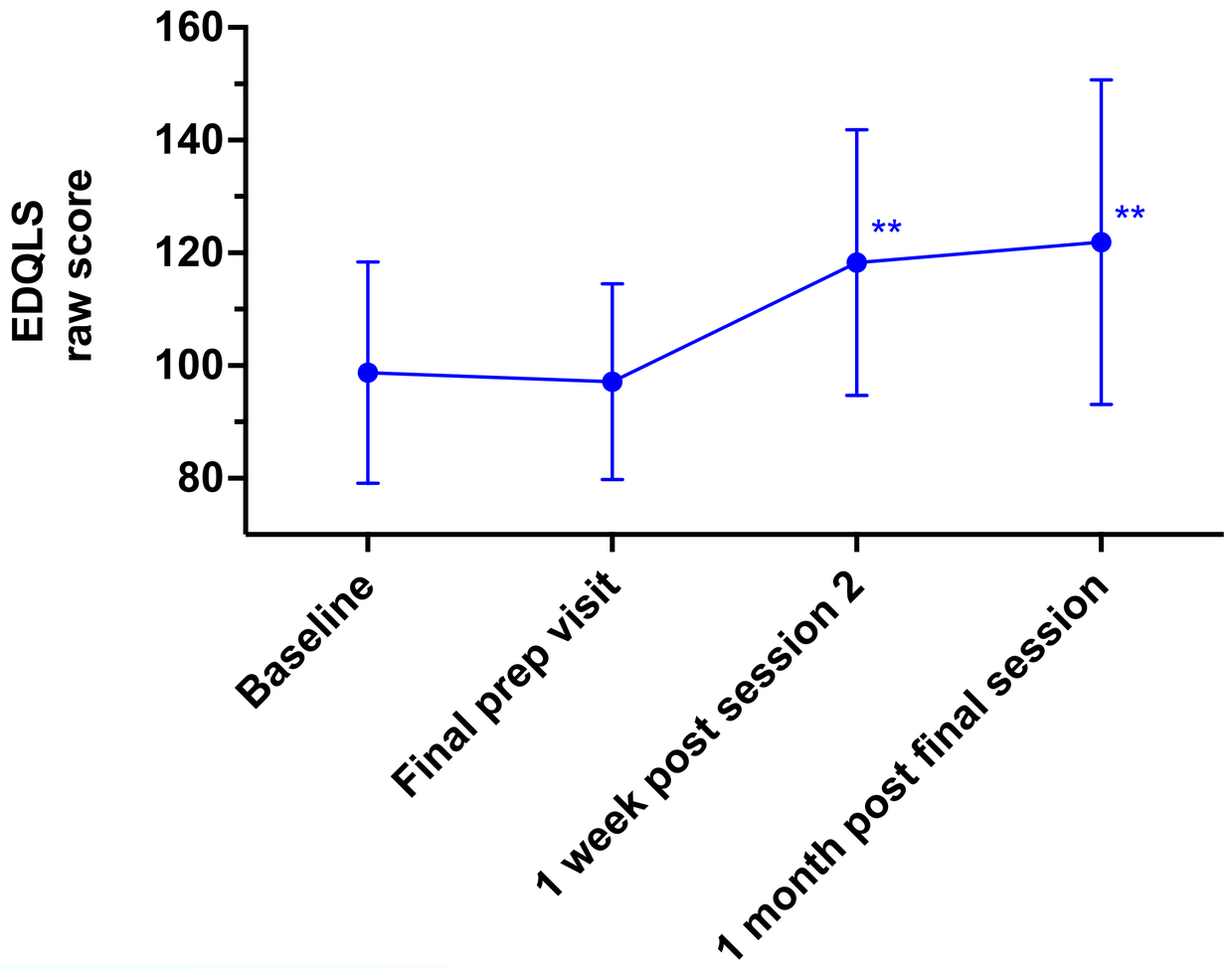
Changes in study design

- Reduced effects in early volunteers led to a change in study design
  - Up to **4** psilocybin sessions (up from 2)
  - Max dose of **30 mg**
  - Flexible window of 2-10 weeks between sessions 2, 3, and 4
    - If >2 weeks between sessions, additional check-ins with study facilitators every 1-2 weeks
- Protocol changes due to COVID-19
  - Increased flexibility for conducting follow-up visits remotely
    - Loss of data for tasks and BMI
  - PPE for in-person visits
  - Limits on out-of-state participants

Safety outcomes and retention

- No significant differences in mean CSSRS suicidal ideation scores between baseline and post-drug timepoints
  - One participant experienced worsening of SI compared to baseline (from passive thoughts of death at baseline to thoughts of suicide with no plan or intent)
- Adverse events: Similar rates of common AE's compared to previous studies: headache, nausea, dizziness. Higher rates of endorsement of items on the CEQ
  - 1 SAE – symptomatic bradycardia with hospital observation 1 week after first dose, unclear relationship to study drug
  - 1 UPIRSO – syncope during psilocybin session
- 2 participants dropped out after completing psilocybin sessions; 1 participant missed several long-term follow-up timepoints but returned for 6-month follow-up; 1 participant declined a second session but agreed to come for follow-up.

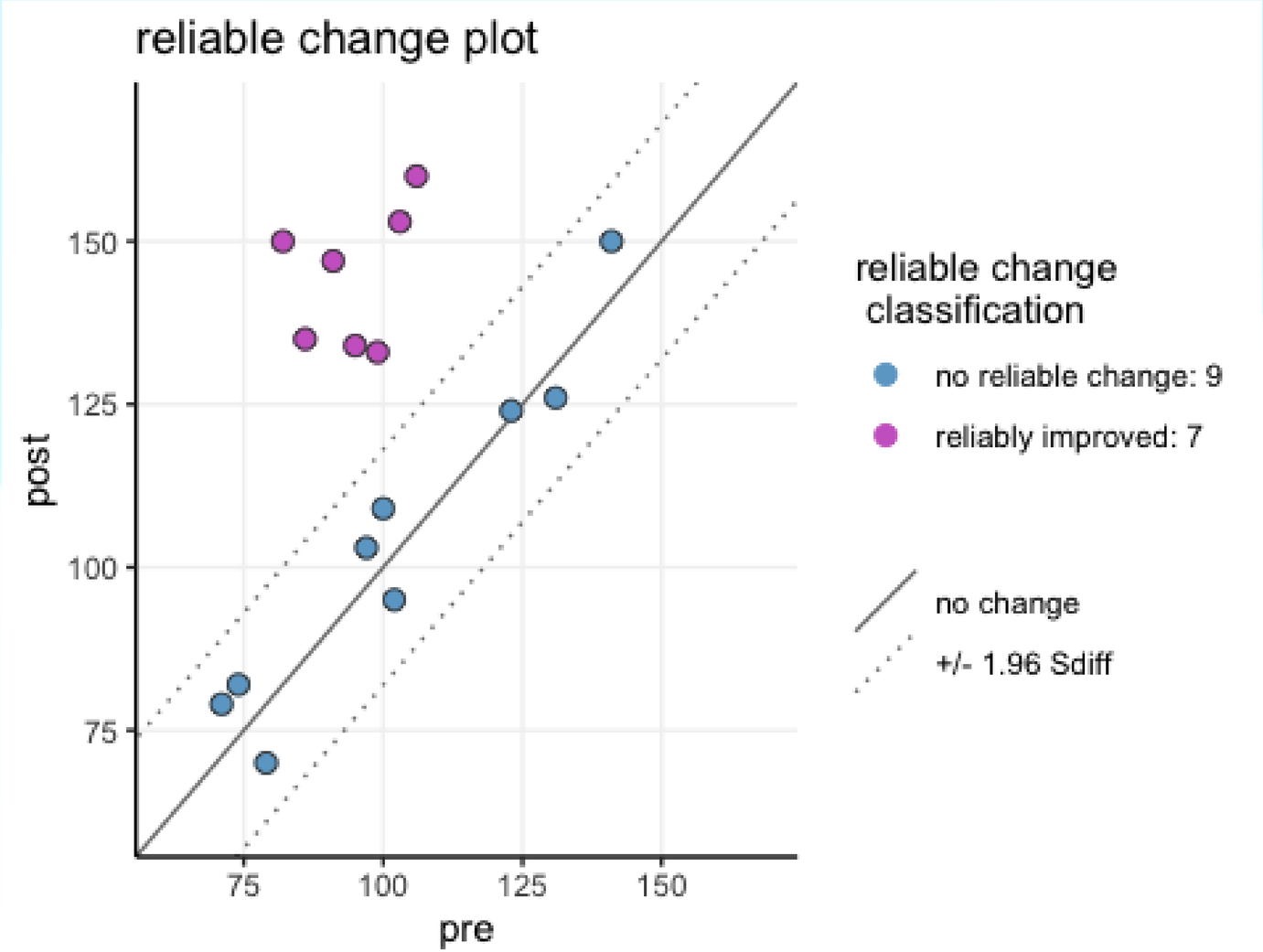
Quality of Life (EDQLS)



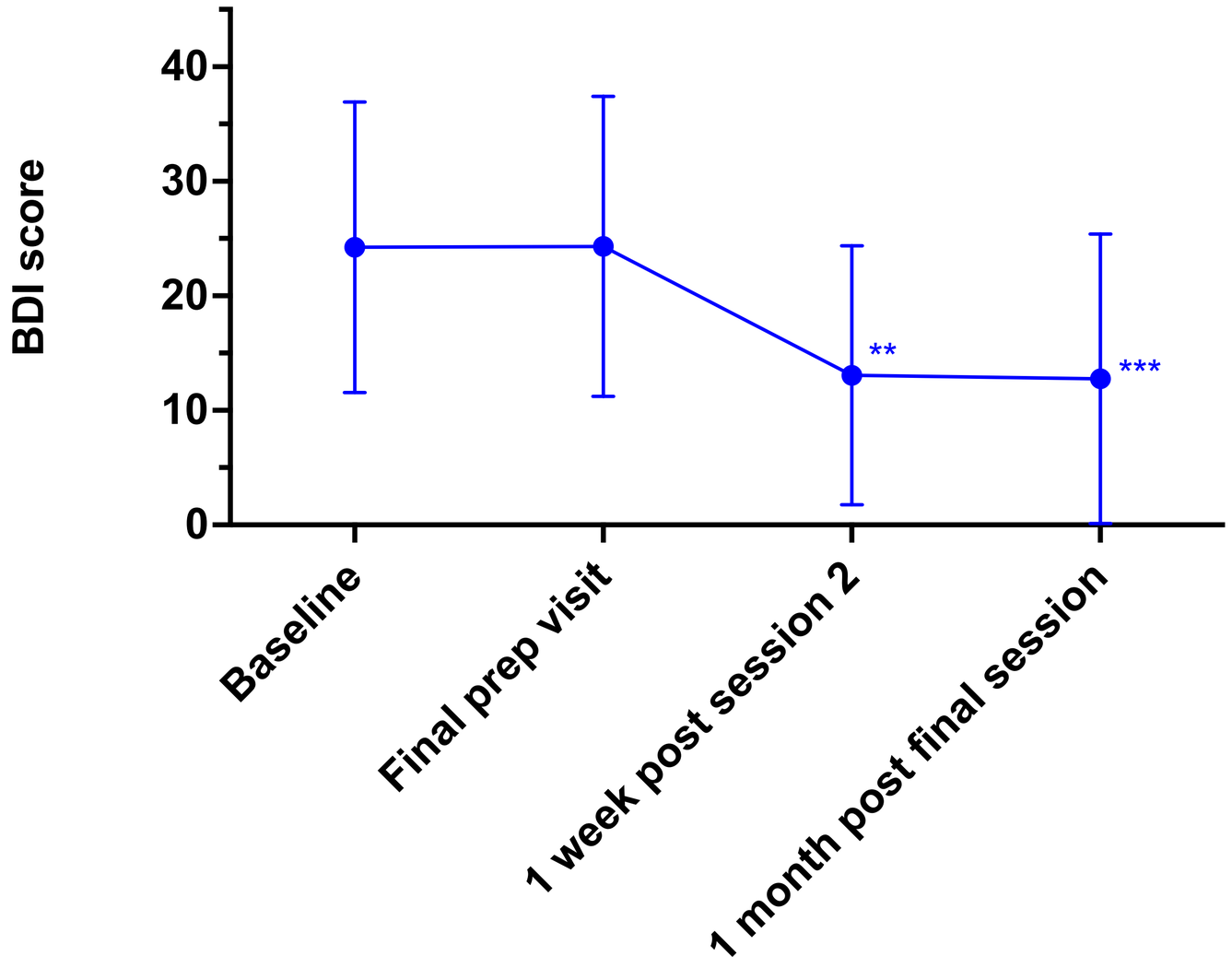
N=16 (completed at least 2 sessions and 1 month follow-up)

Cohen *d* (95% CI) effect size from baseline was 0.83 (0.15–1.50) at 1 week post session 2, and 0.91 (0.29–1.53) at 1 month post final session. Asterisks indicate significant difference from baseline using Wilcoxon signed rank test (** = $p<0.01$).

Quality of Life (EDQLS)



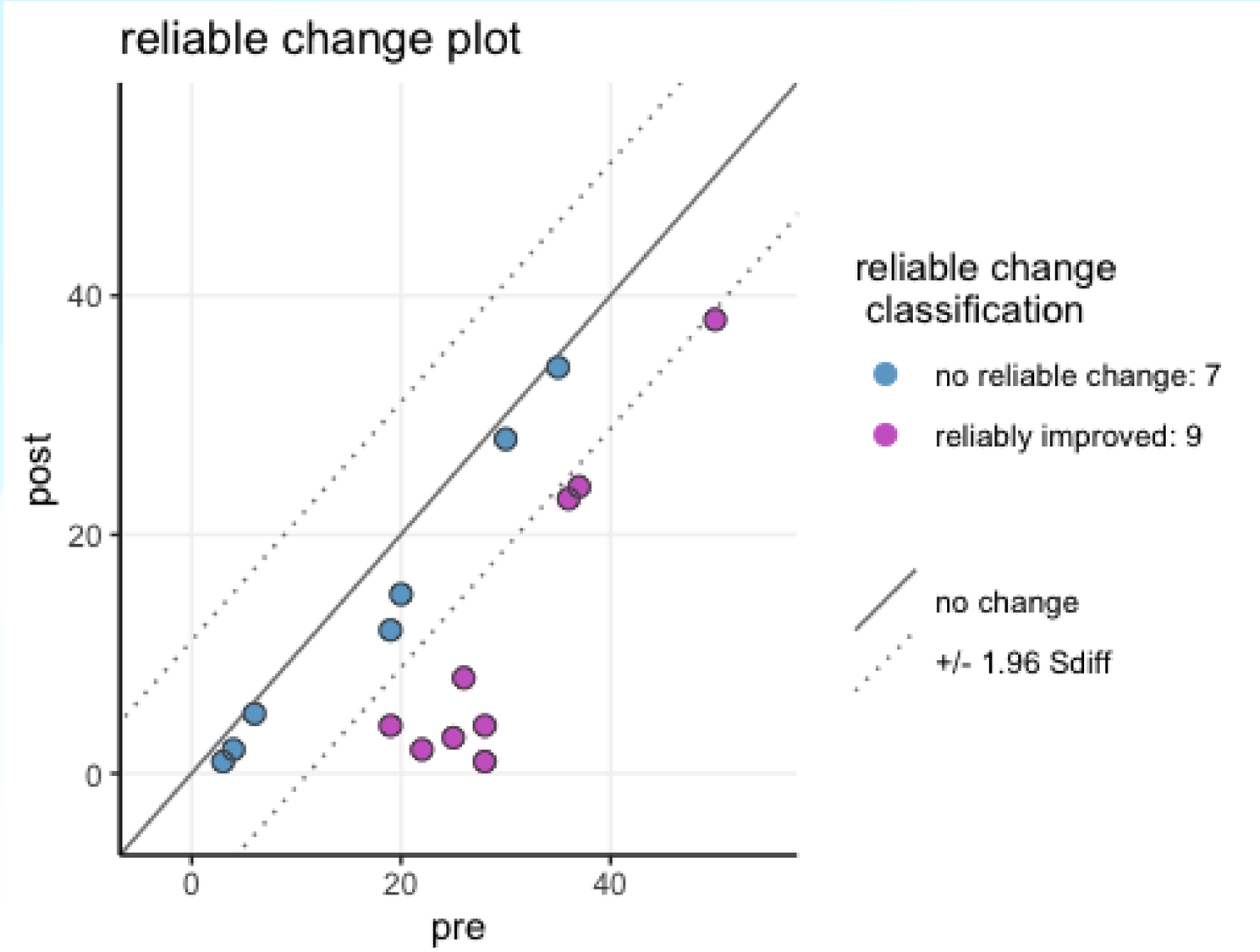
Mood (Beck Depression Inventory)



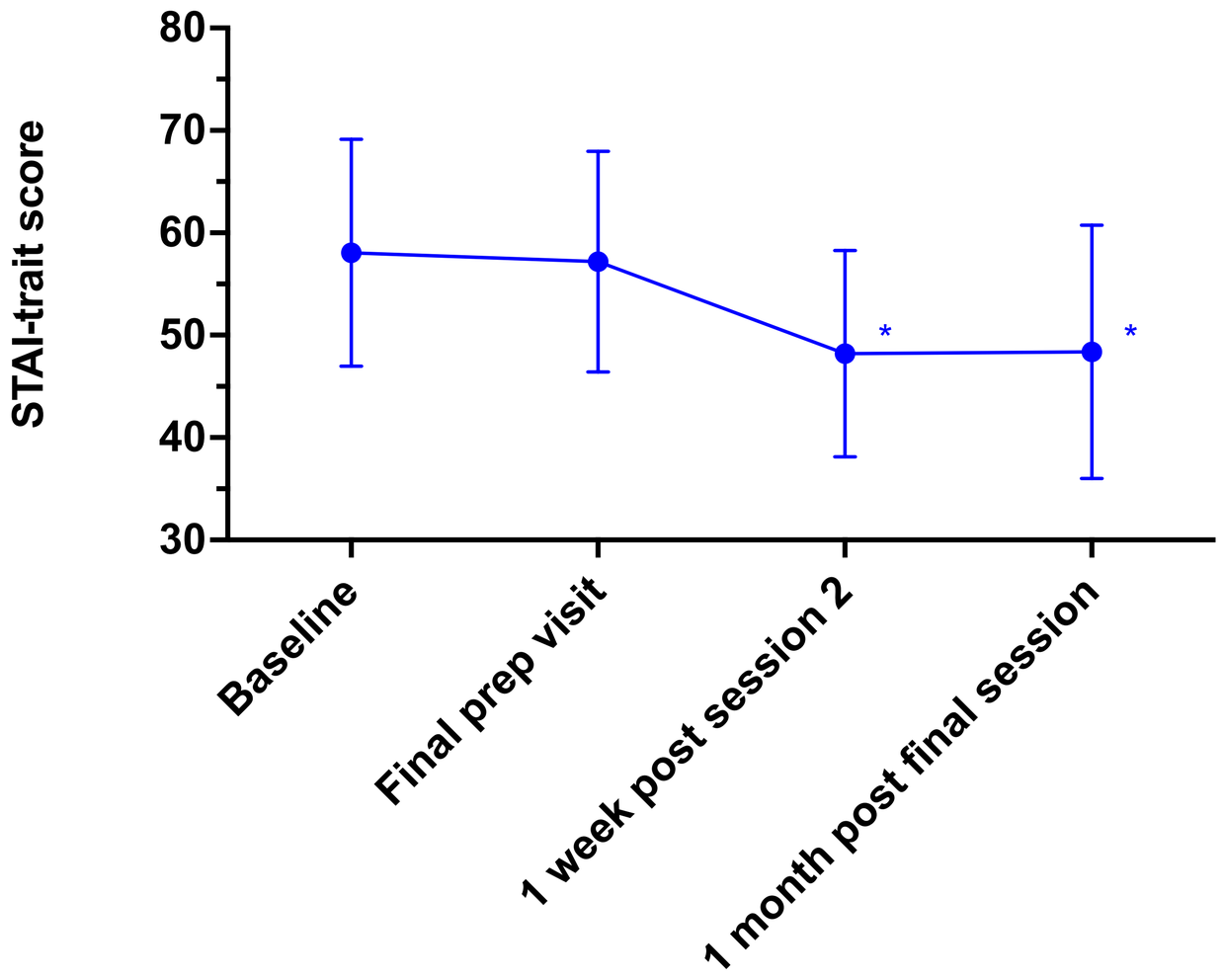
N=16

Cohen d (95% CI) effect size from baseline was 0.85 (0.30–1.40) at 1 week post session 2, and 0.91 (0.48–1.33) at 1 month post final session. Asterisks indicate significant difference from baseline using Wilcoxon signed rank test (** $p < 0.01$, *** $p < 0.001$).

Mood (Beck Depression Inventory)



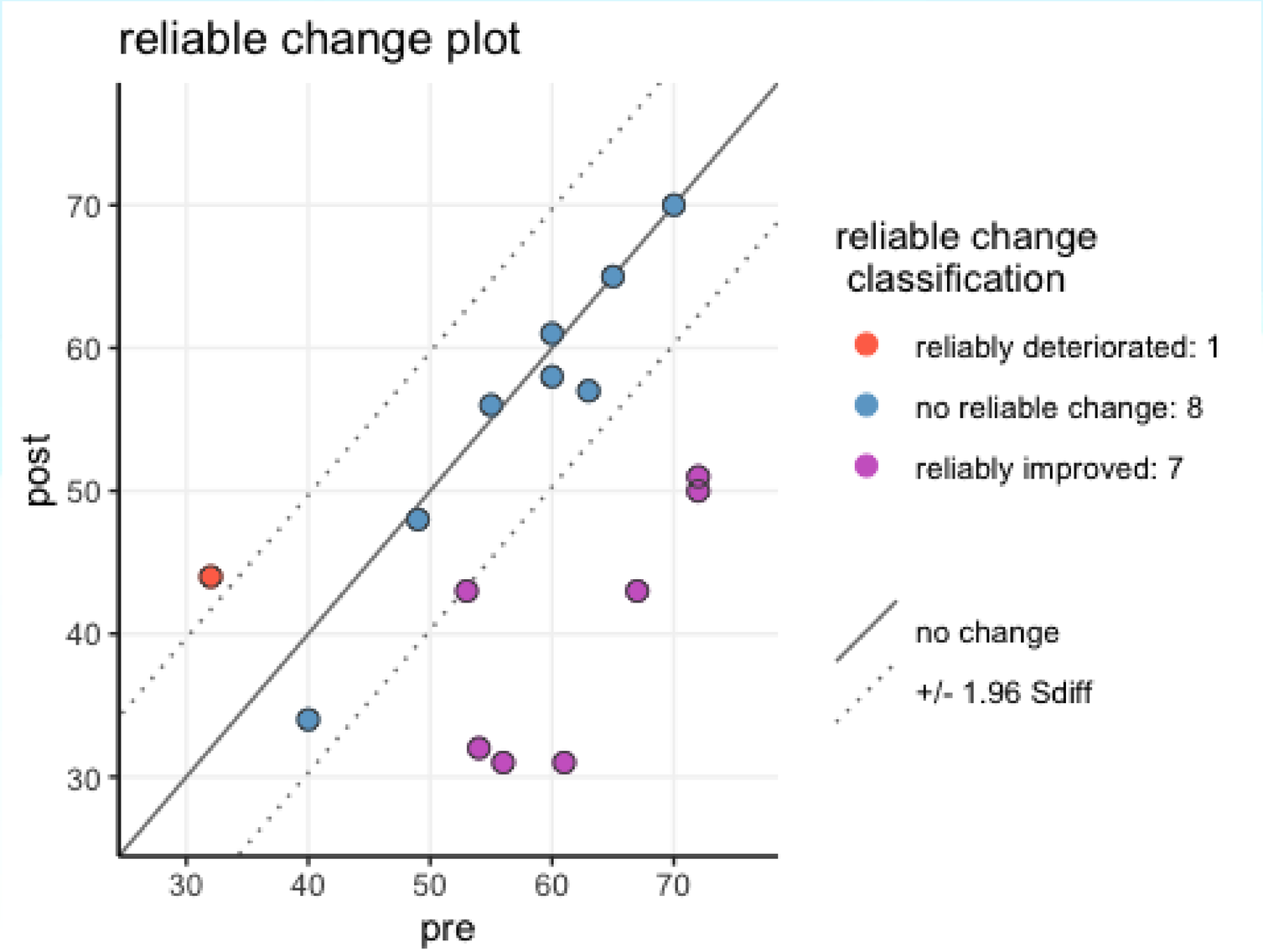
STAI Trait



N=16

Cohen d (95% CI) effect size from baseline was 0.86 (0.21–1.50) at 1 week post session 2, and 0.82 (0.20–1.45) at 1 month post final session. Asterisks indicate significant difference from baseline using Wilcoxon signed rank test (* p <0.05).

STAI Trait


reliable change plot
post
pre
30
40
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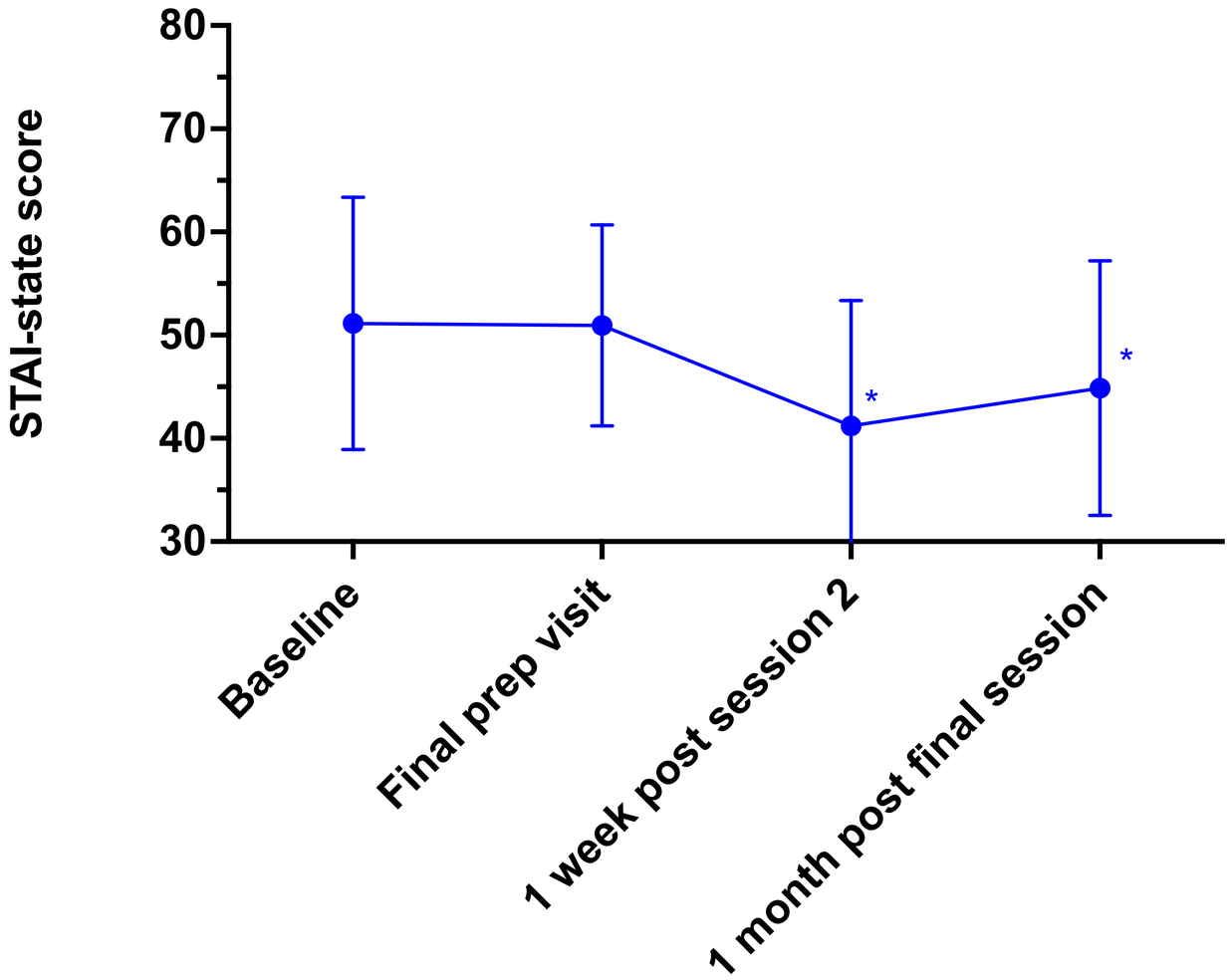
reliable change classification
reliably deteriorated: 1
no reliable change: 8
reliably improved: 7
no change
+/- 1.96 Sdiff

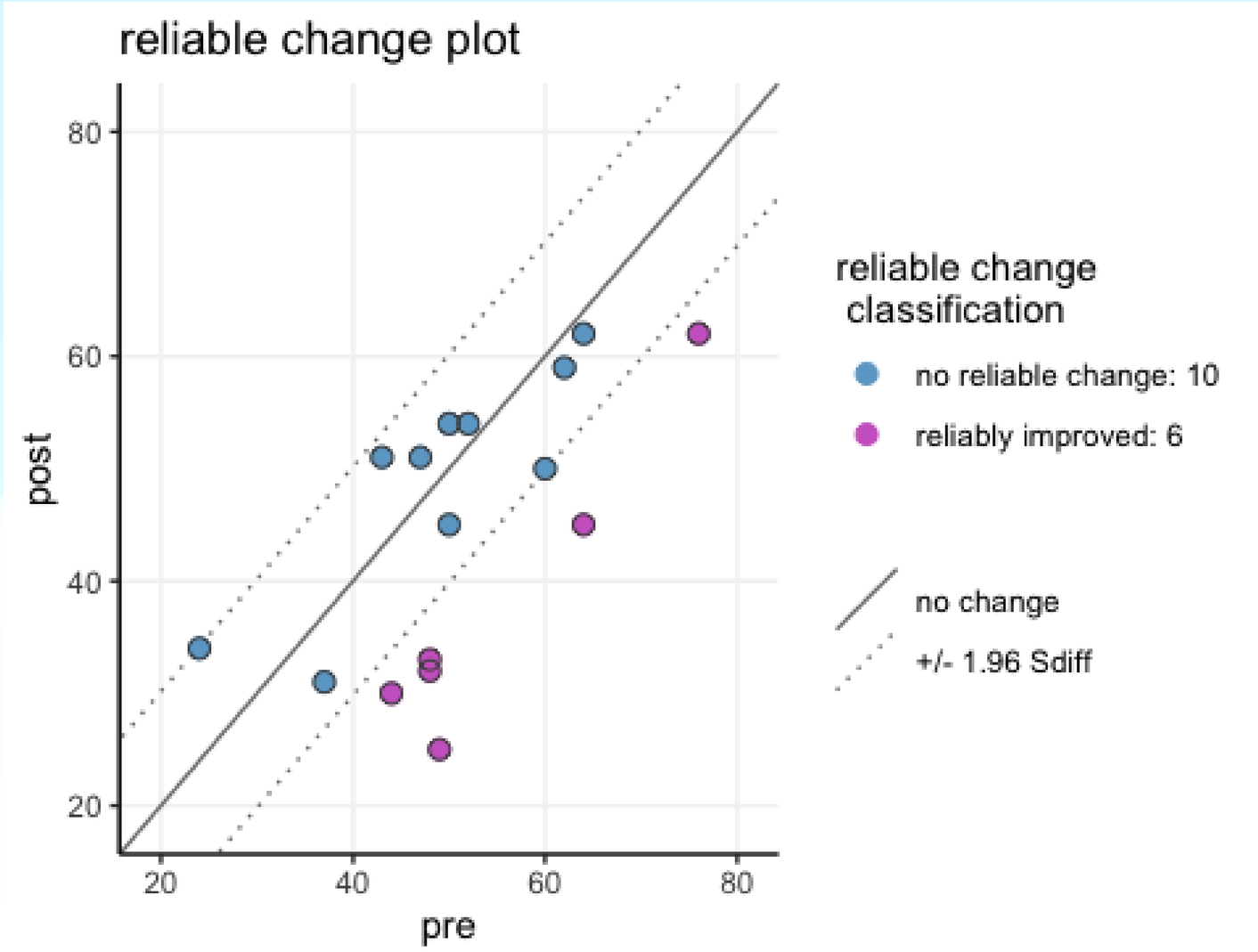
STAI State



N=16

Cohen d (95% CI) effect size from baseline was 0.76 (0.19–1.33) at 1 week post session 2, and 0.51 (0.06–0.96) at 1 month post final session. Asterisks indicate significant difference from baseline using Wilcoxon signed rank test (* p <0.05).

STAI State


reliable change plot
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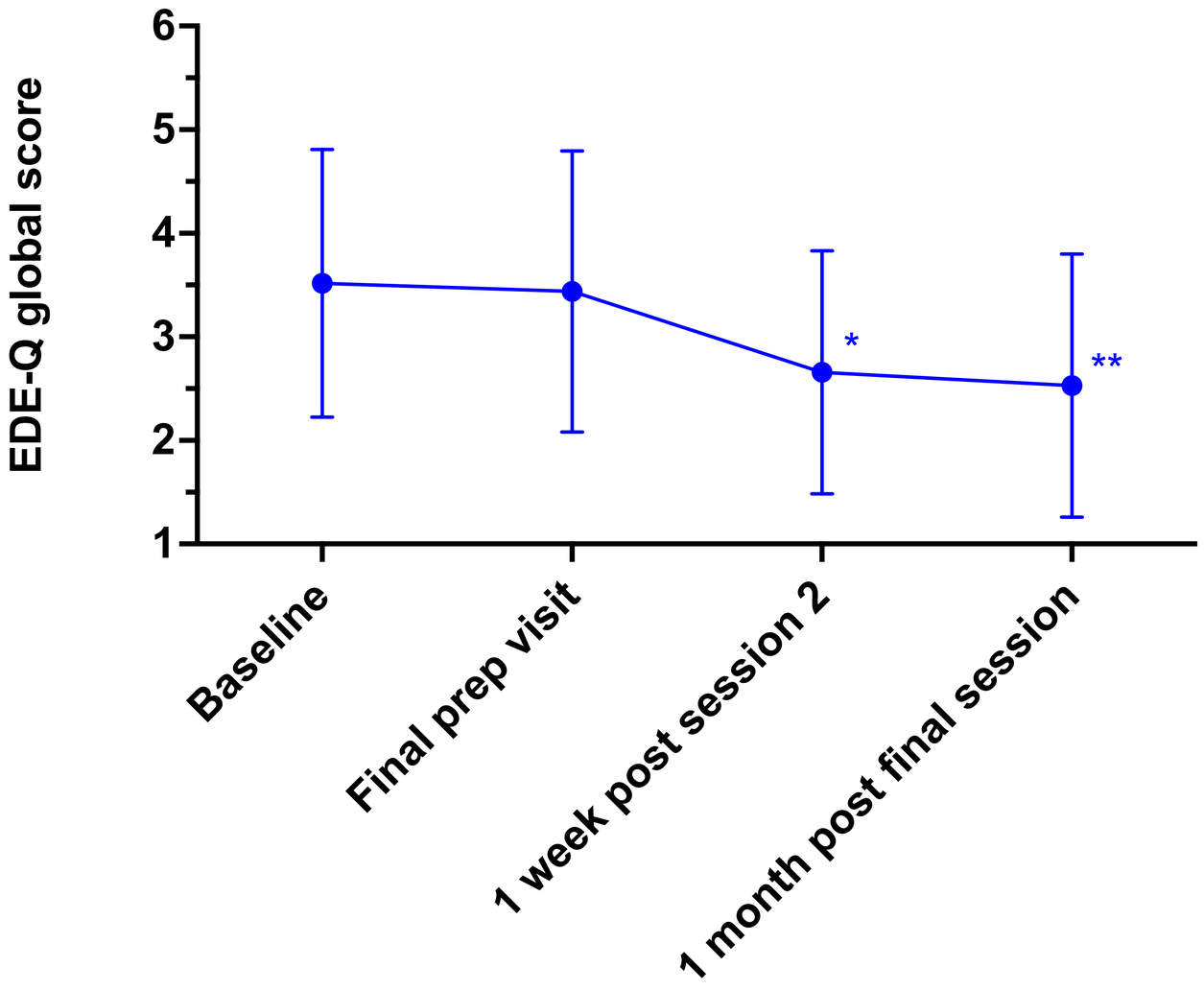
no change
+/- 1.96 Sdiff

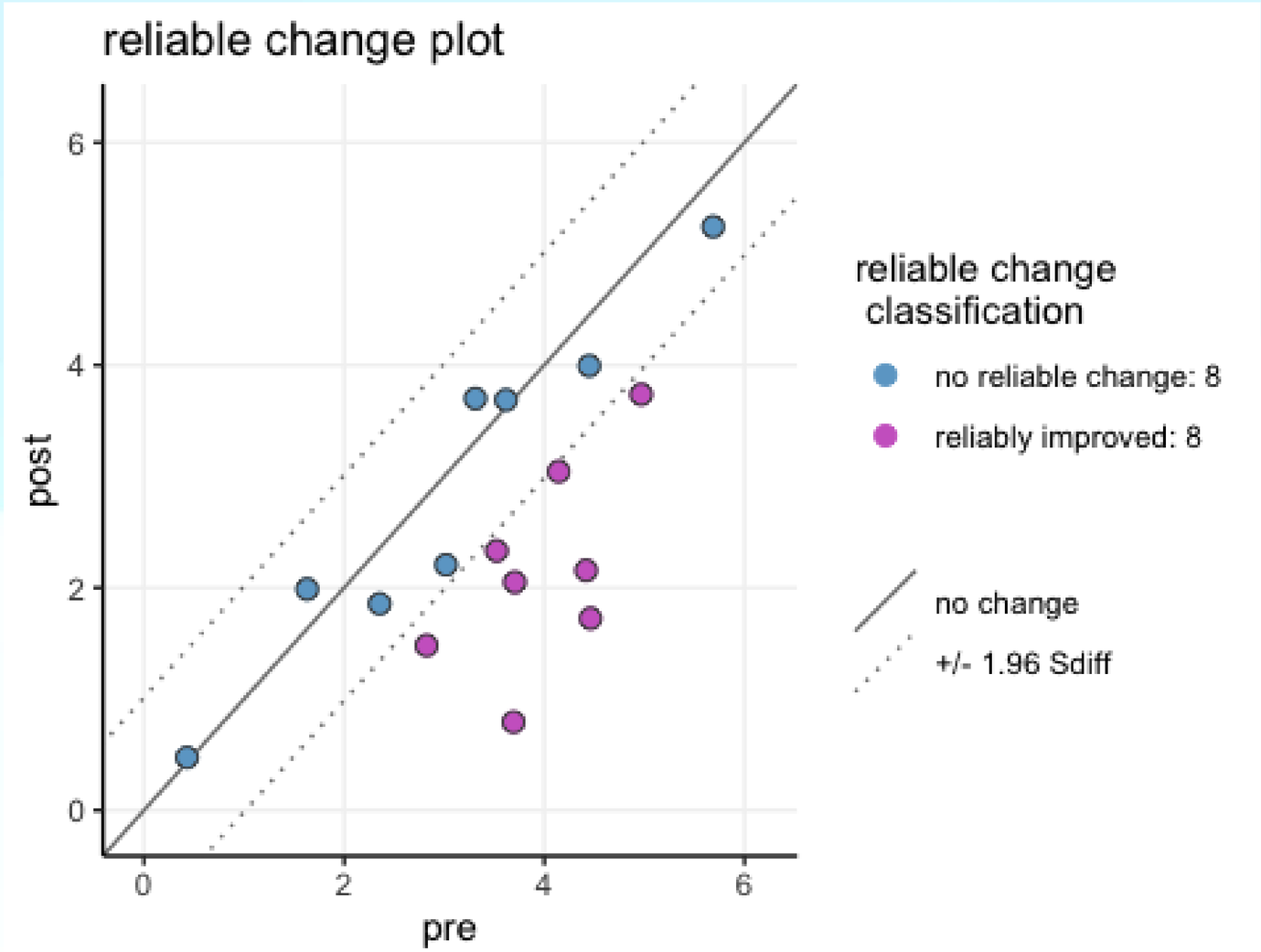
Eating disorder symptom severity (EDE-Q global score)



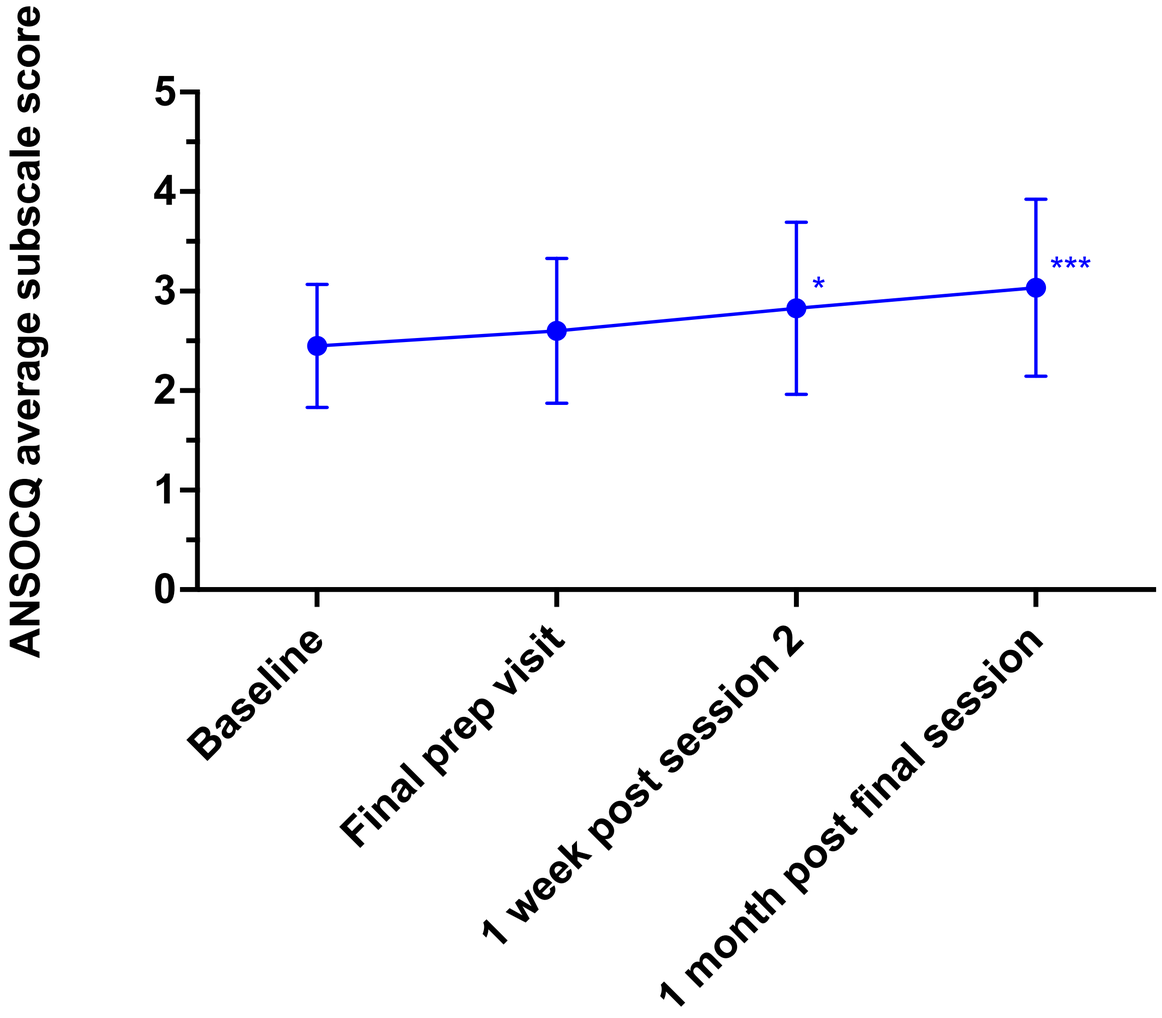
N=16

Cohen d (95% CI) effect size from baseline was 0.60 (0.08–1.12) at 1 week post session 2, and 0.77 (0.30–1.23) at 1 month post final session. Asterisks indicate significant difference from baseline using Wilcoxon signed rank test (* $p < 0.05$, ** $p < 0.01$).

Eating disorder symptom severity (EDE-Q global score)



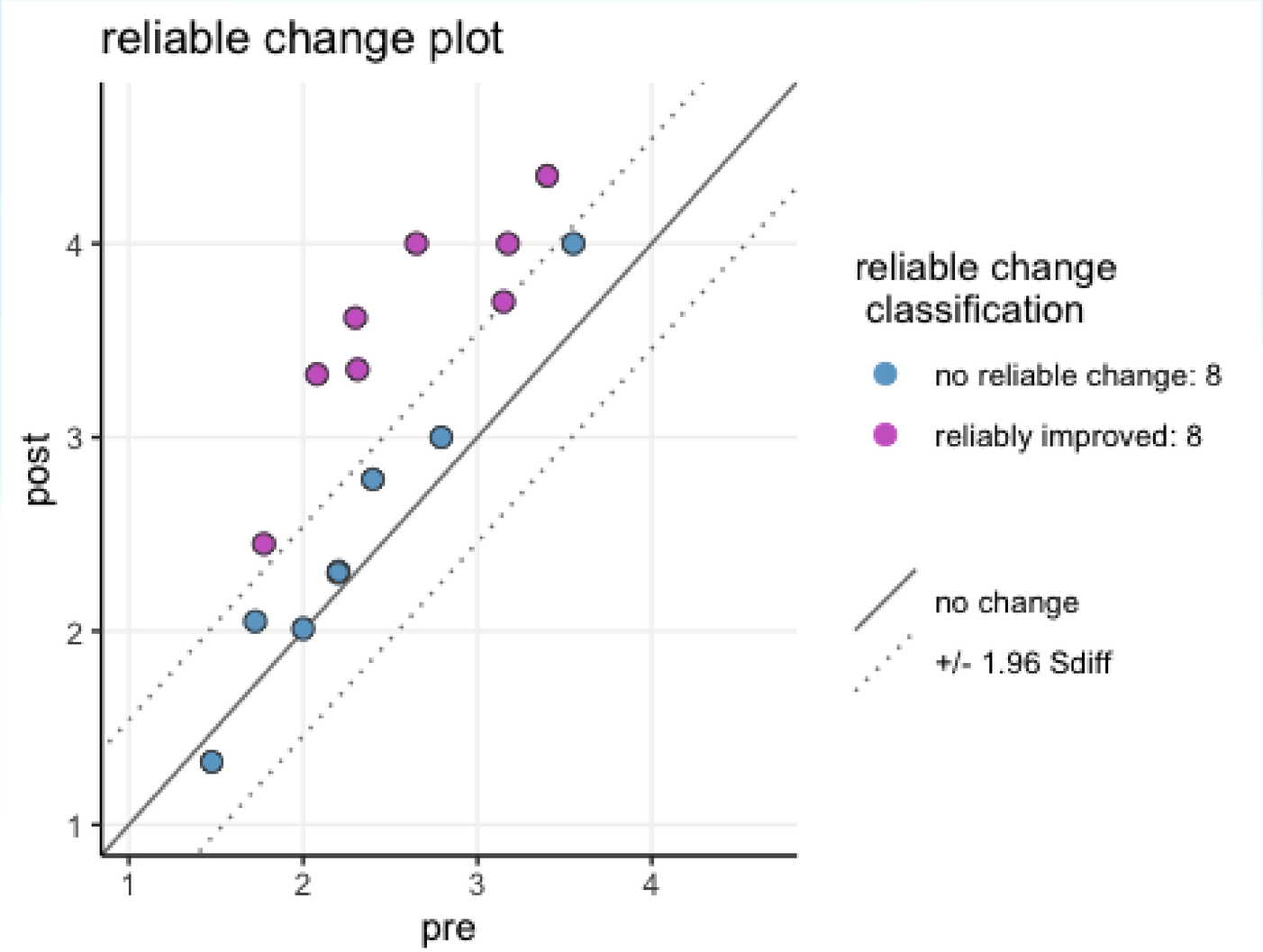
Motivation to change (ANSOCQ total score)



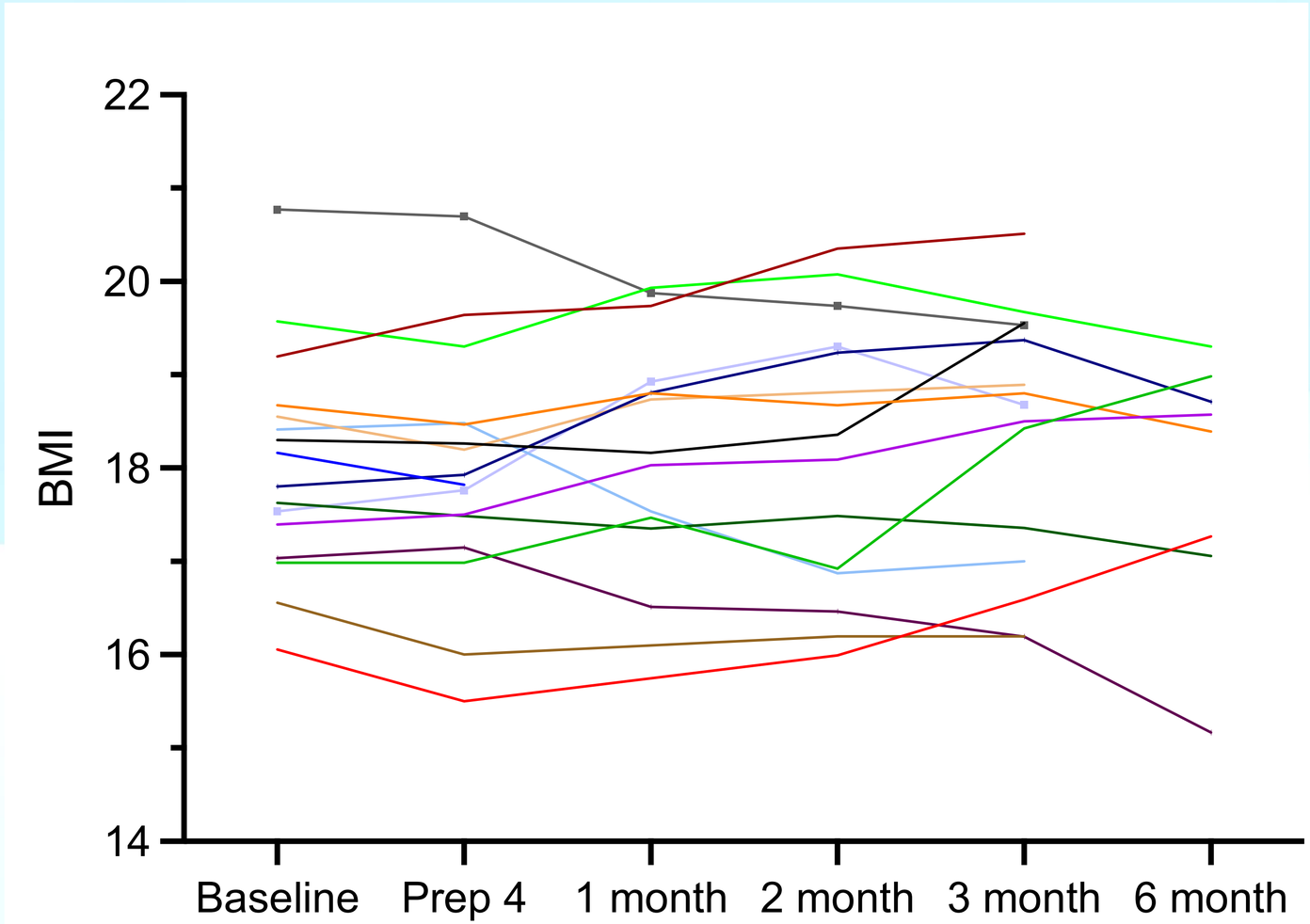
N=16

Cohen d (95% CI) effect size from baseline was 0.43 (0.11–76) at 1 week post session 2, and 0.66 (0.35–0.96) at 1 month post final session. Asterisks indicate significant difference from baseline using Wilcoxon signed rank test (* p <0.05, *** p <0.001).

Motivation to change (ANSOCQ total score)

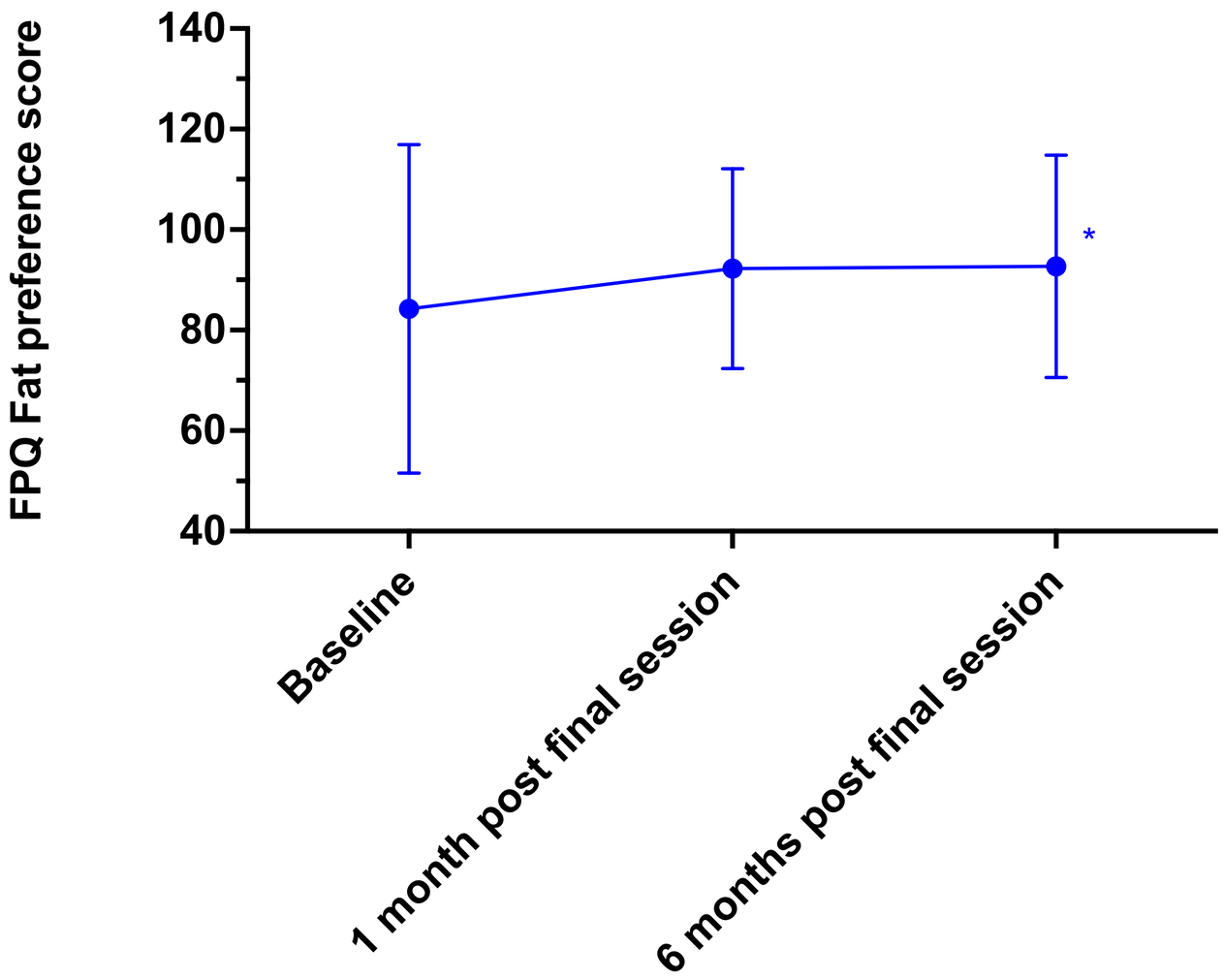


BMI



- No significant change between baseline and 3 month follow up

FPQ fat preference score



N=16

Cohen d (95% CI) effect size from baseline was 0.27 (0.07–0.60) at 6 months post final session. Asterisk indicates significant difference from baseline using Wilcoxon signed rank test (* p <0.05).

Lower subjective effect scores in AN vs MDD samples

Dose	N	Mean MEQ (% of max)	Mean CEQ (% of max)
20 mg	16	44.8	34.2
25 mg	15	44.0	28.2
30 mg	10	52.3	42.2

Dose	Mean MEQ (% of max)	Mean CEQ (% of max)
20 mg/70kg	61.6	36.8
30 mg/70kg	68.2	34.3

Davis et al. (2021) *JAMA Psychiatry*

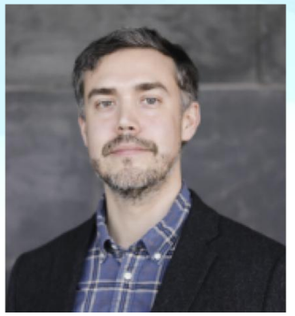
In participants' own words

- "In the past my routine with eating and exercise has just been… super rigid, and if I ever like deviate from it, its been so much of a big deal… **The eating disorder voices in my head** that are normally so… imperious have seemed to be **less loud**, or… less… **overpowering**."
- "I am **more aware of how underweight I was**. I often would just downplay, like oh that's fine, I'm really not that underweight, but now… even though … I've gained some weight, and even despite that, I feel like even more that I need to … gain more weight. Maybe it relates to being...having a little **more self-compassion**, and … trusting my body…just kind of like **befriending my body**, where I've like been mean to it for so many years"
- *How is your quality of life now?*
  - "…It's better than it's been in probably like 20 years, um and I'm not very old, so that's a long time for me. And it's like I also have a lot of **hope for the future**, and that's a good thing as well."

Open questions

- What are the ideal preparatory/integration conditions?
- What type/magnitude of support is ideal?
- When is the optimal time in the course of the illness to administer treatment?
- Who are the ideal candidates?
- What can we do to optimize patients before treatment to maximize potential benefits?

Acknowledgments



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