



**BBRF MEET THE SCIENTIST WEBINAR
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Hormones, the Brain, and Female Suicide Risk



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Disclosures and a thank-you

- No financial conflicts. No pharmaceutical funding.
- Support: NIMH, and a 2018 BBRF Young Investigator Grant (#27304) that paid for the blood assays in CLEAR-1.
- Volunteer: IAPMD clinical advisory board.
- Some treatments I'll mention are **off-label**. This is education, not individual medical advice. I'm a licensed clinical psychologist, **not a physician**, so I can't speak to anyone's specific symptoms.
- **Nothing here means hormones should be given to treat cyclical suicidality.** Safety concerns with long-term premenopausal use, and some people have adverse mood effects we can't yet predict.

We'll be talking about suicide. If you need support at any point: call or text 988 (US).



HOW IT STARTED

Before I studied cycles, I treated instability.

I loved working with patients who were blamed for their own symptoms because they experienced unpredictable emotions and impulsivity (e.g., borderline personality disorder).

What struck me was how seemingly unpredictable their symptoms could be.

Relationships · work · substances · self-harm · suicidality · trust in therapy

Why does this get worse **when** it does?



DBT, circa 2012. The DBT workbook on the table.



Four questions

1

Does suicide risk really follow the menstrual cycle?

Hospital records, PMDD, and what we found when we followed people day by day.

2

Why would normal hormones cause symptoms?

Hormone levels are normal. The brain's response to normal change is the problem.

3

Is hormone sensitivity one thing?

Two timings, two symptom profiles, and a working model: sensitivity to the surge vs. sensitivity to the fall.

4

Can we find the trigger, and for whom?

Three double-blind trials: what they prevented, what they made worse, and the first clues toward matching treatment to the person.

1

PART 1

Does suicide risk follow the menstrual cycle?



Females carry most of the burden of suicidal thoughts and attempts

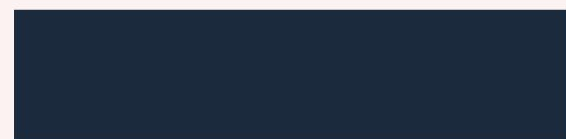
3x

more likely than males to have suicidal thoughts and to attempt suicide

Assigned female at birth



Assigned male at birth



three times the rate

Relative rate, suicidal thoughts and attempts

#1

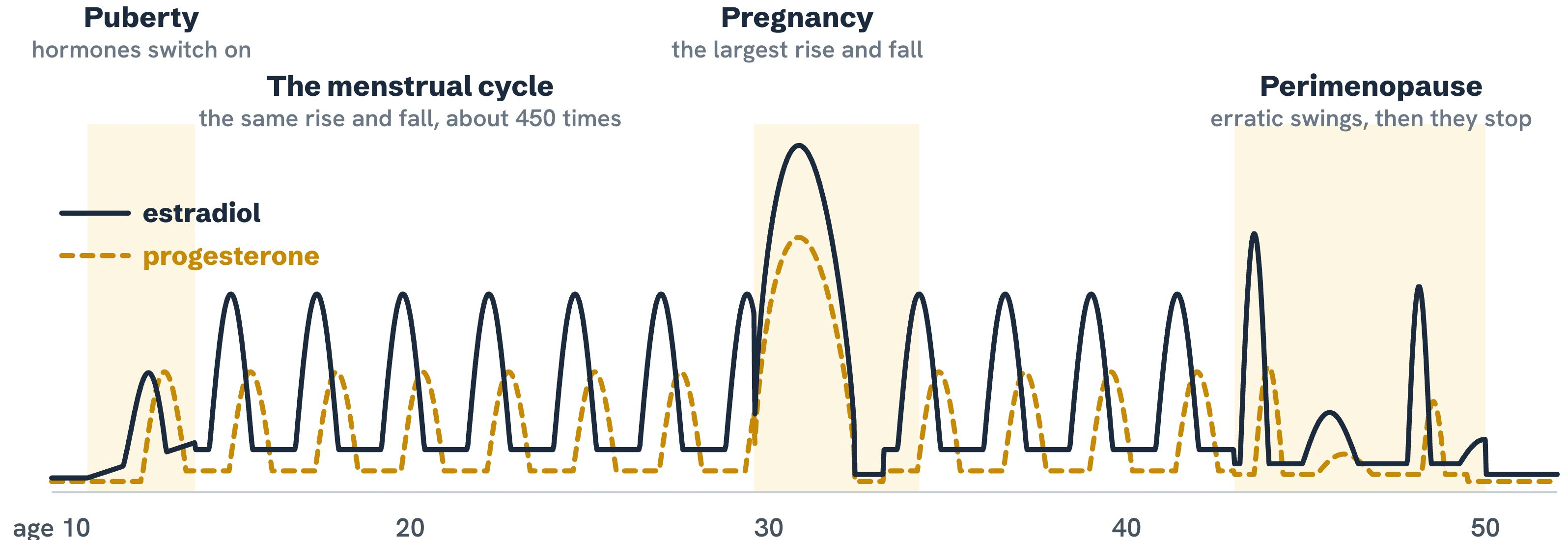
cause of hospitalization during the reproductive years: suicidality

4th

leading cause of death, ages 15 to 45, in the US

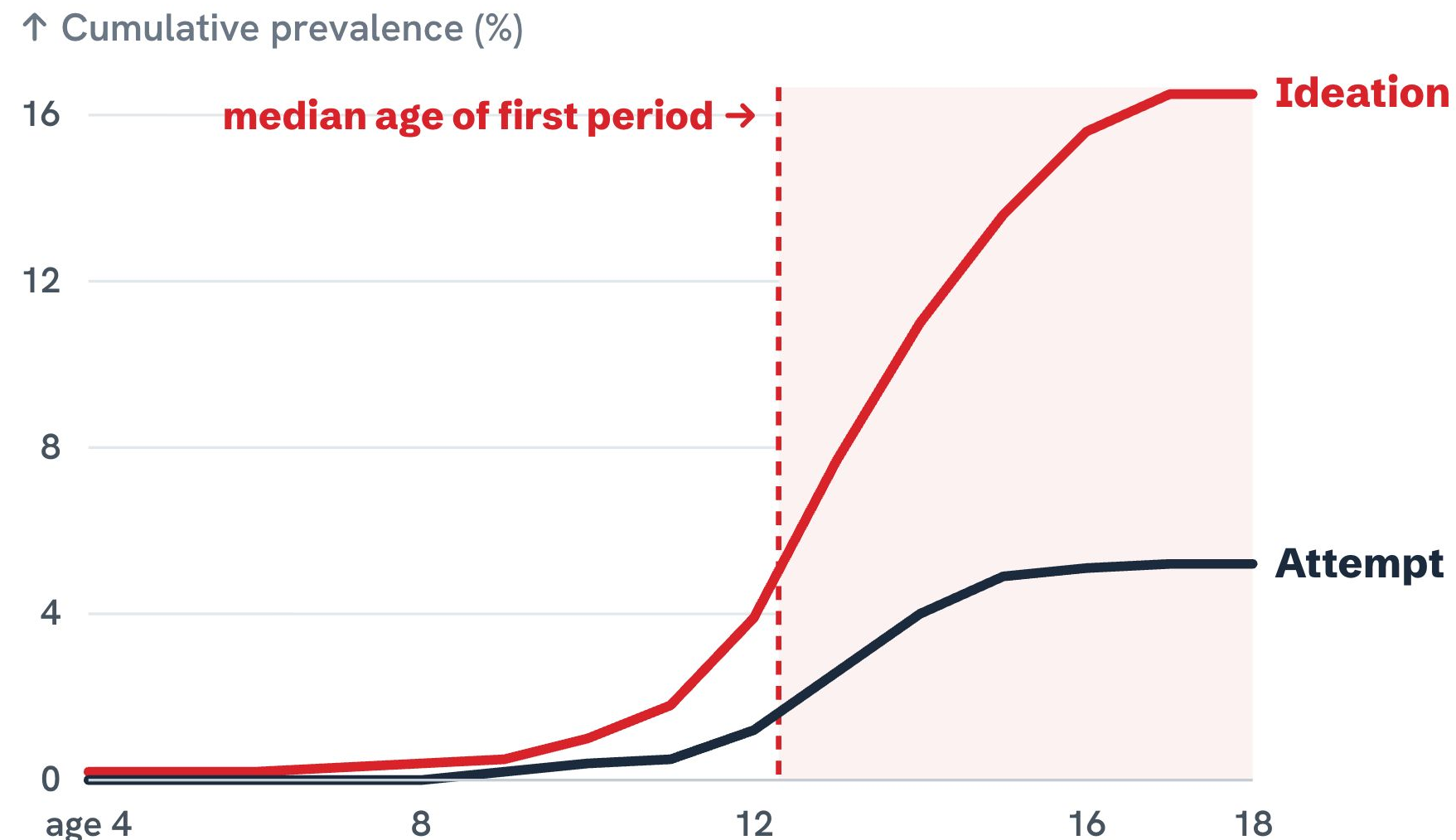


Mental health problems cluster at hormone changes





Suicidal thoughts and behaviors climb steeply after puberty, beginning around the first period



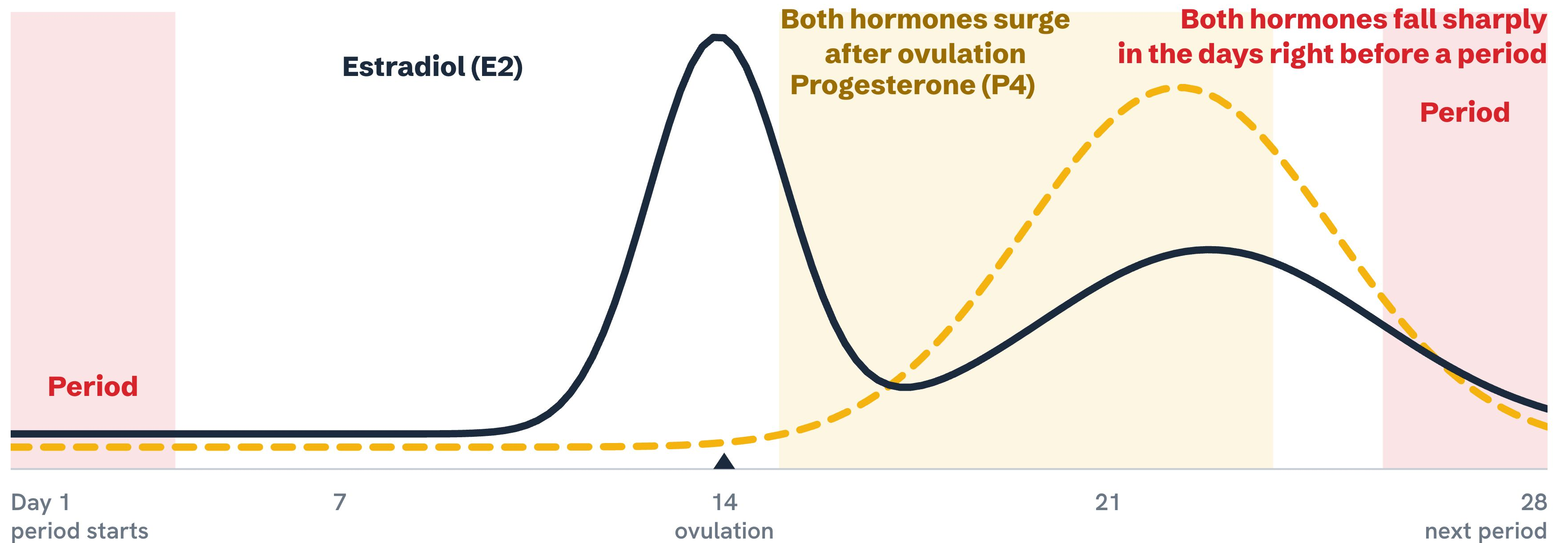
Mood disorders. Minimal sex difference in childhood; about 2:1 female by mid-adolescence.

ADHD and autism. Distress and impairment rise at puberty in girls.

Suicidality. A sharp post-pubertal increase that coincides in time with the onset of the cycle.



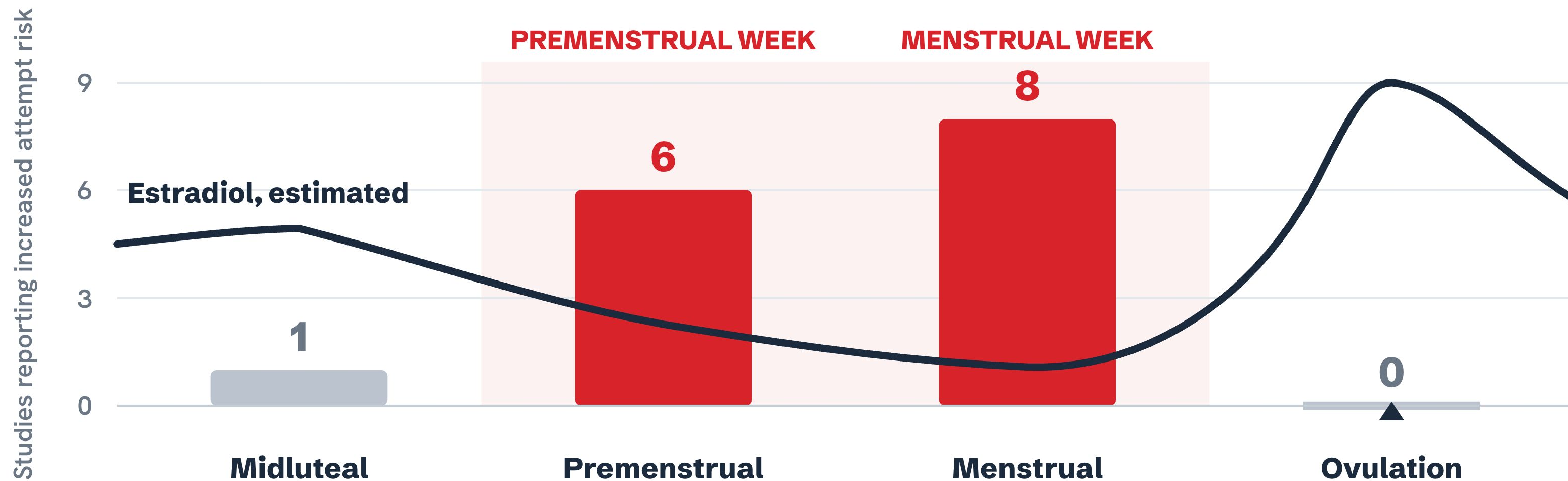
The Menstrual Cycle - Two Critical Hormone Triggers



E2 = estradiol (the main estrogen). P4 = progesterone. Idealized 28-day cycle.



Hospitalizations and emergency visits for suicide attempts cluster in the two weeks around menstruation

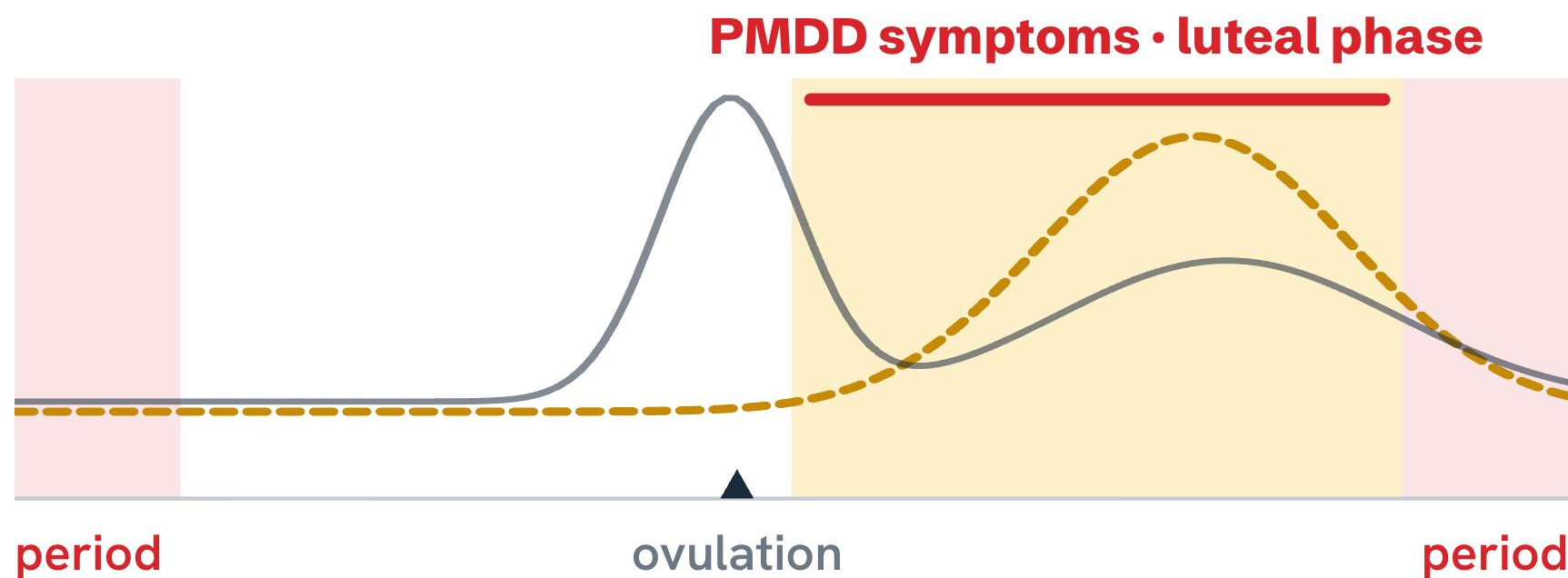


15+ studies over 50 years, across countries. Risk is highest in the days around the onset of bleeding.



PMDD is the only formal menstrual-cycle mood diagnosis

About 5.5% of cycling people. Symptoms start after ovulation and clear once the period begins.



DIAGNOSIS (DSM-5)

5+ symptoms (at least one emotional), present the week before menses, gone the week after:

- mood swings
- irritability, anger, or conflict
- depressed mood
- anxiety
- decreased interest
- difficulty concentrating
- lethargy or fatigue
- change in appetite
- sleeping too much or too little
- feeling overwhelmed or out of control
- physical swelling, pain, or bloating

Exclusion: not “merely an exacerbation” of another disorder. Since comorbidity is common, this rules out most patients with cyclical worsening.



PMDD is the best-established hormone-sensitive disorder, and suicide risk in PMDD is high

599 patients with PMDD diagnosed by a medical provider using daily ratings

72%

lifetime suicidal thoughts

34%

lifetime suicide attempt

51%

lifetime self-injury

Rates were similar with or without another psychiatric diagnosis. Severe PMDD by itself carries suicide risk.

Suicidality is not in the diagnostic criteria, and for years it was assumed to be rare because symptoms remit every month. It is not rare. PMDD is not a mild PMS story.



In a national registry, premenstrual disorders carried nearly twice the rate of death by suicide

1.92x

the rate of death by suicide among people with a diagnosed premenstrual disorder, compared with matched people without one

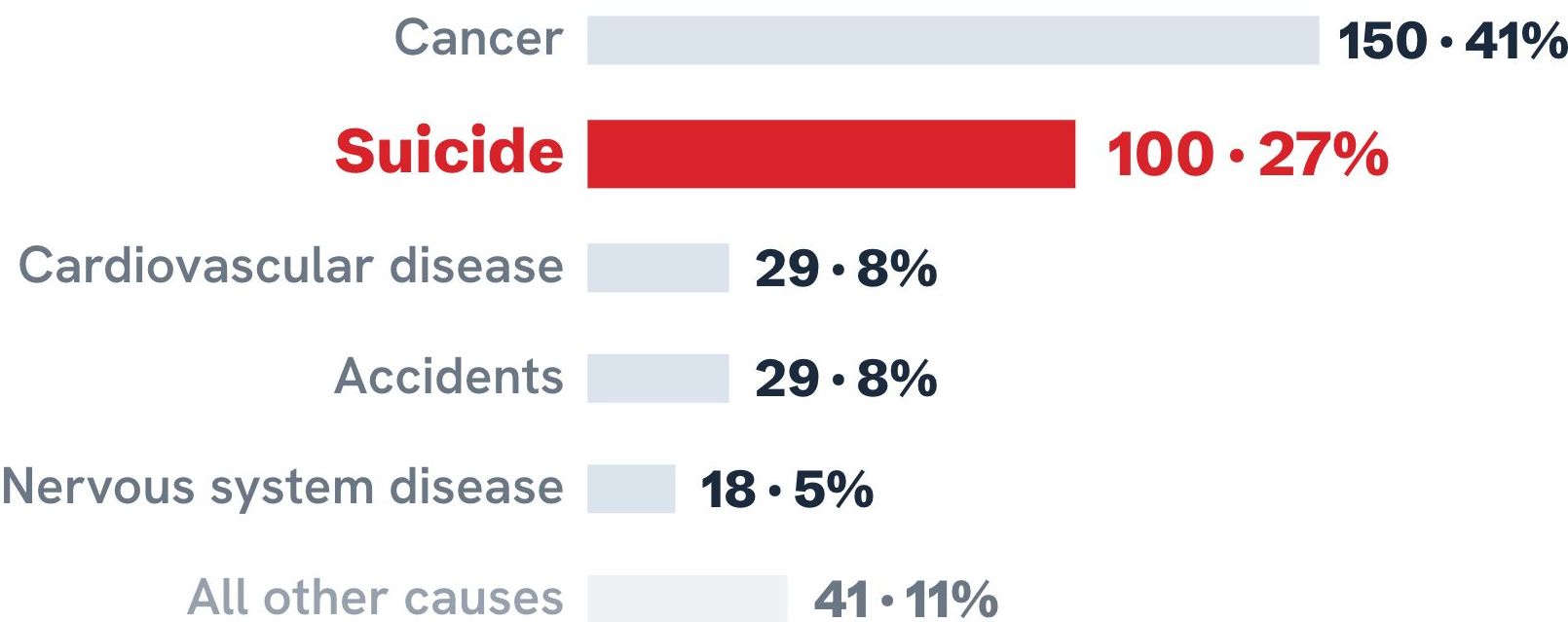
2.30 suicide deaths per year per 10,000 people with a premenstrual disorder

1.06 matched people without one

406,488 people followed in Swedish national registers, up to 18 years

Suicide accounted for 27% of all deaths in this group.

367 deaths among people with premenstrual disorders



Overall mortality was not elevated. The excess was specific to suicide. Among those diagnosed before age 25, roughly **one death in three** was a suicide.



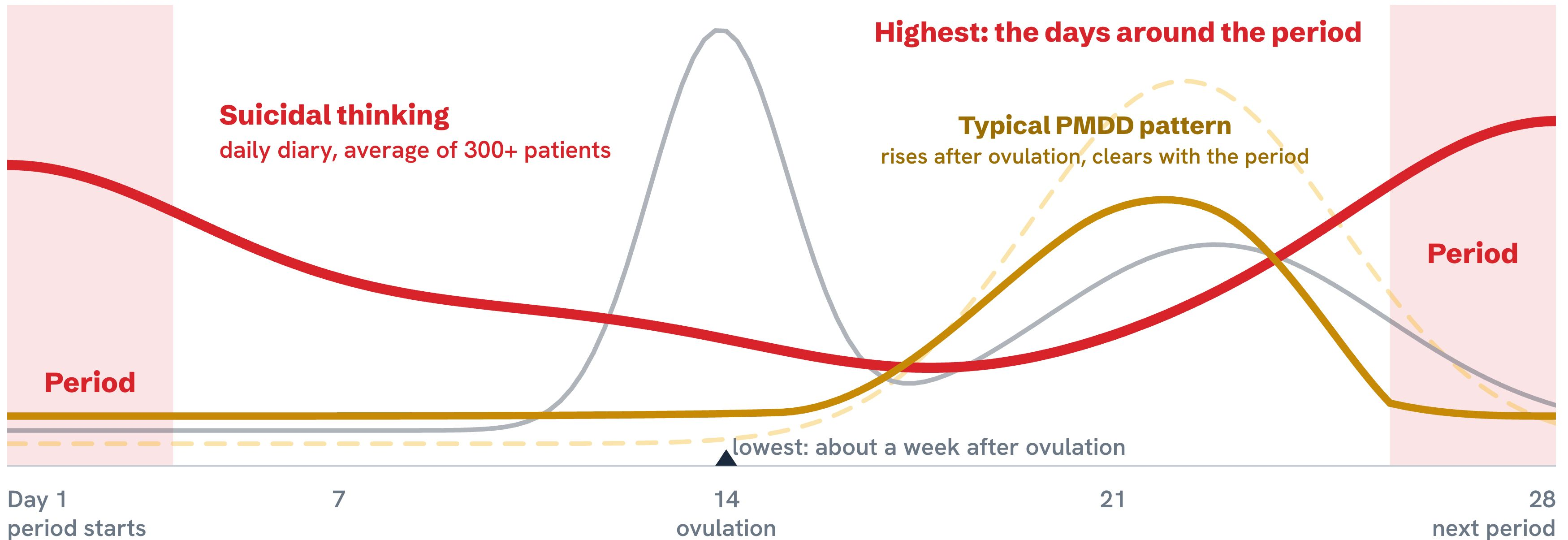
Cyclical worsening shows up across many conditions, in some people with each

Major depression	about 60% show premenstrual worsening	Bipolar disorder	both depression and mania
Bulimia nervosa	restriction, binging, purging	Anxiety and fear disorders	re-experiencing, avoidance, fear learning
Borderline personality	anger, shame, rejection sensitivity, aggression	ADHD	inattention, hyperactivity, impulsivity
Risky substance use	alcohol and cannabis use	Suicidal thoughts and behaviors	the focus of this talk

Not present in everyone with a given condition, but people with chronic mental health conditions are at higher risk of cyclical symptom change. None of them can currently receive a cycle-related diagnosis.



Following people day by day: a second pattern, peaking around menstruation



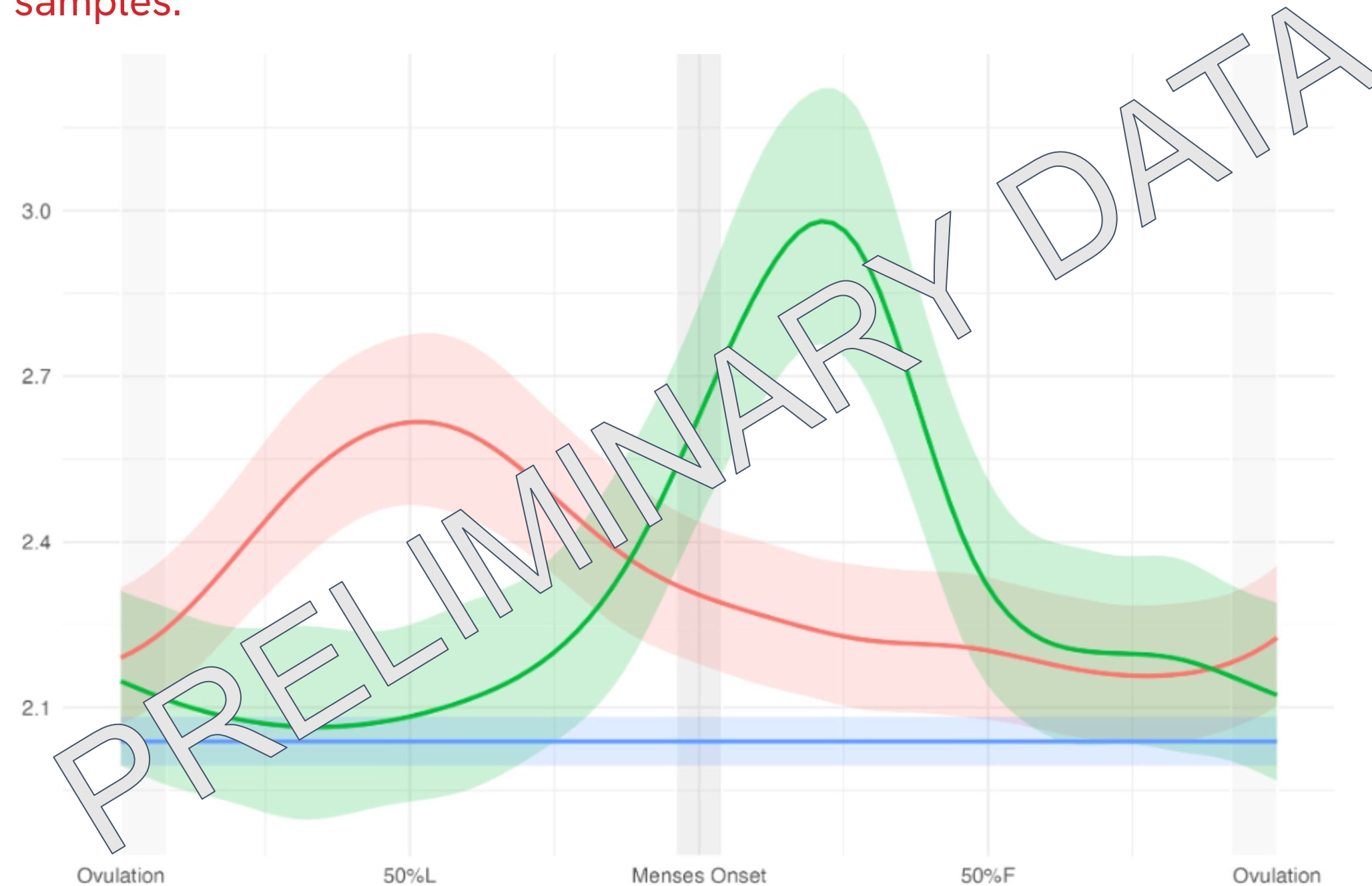
LED BY
Jackie Ross, PhD

Owens et al., 2023, J Psychopathology & Clinical Science (N = 38); Ross et al., 2024, American Journal of Psychiatry (N = 119); CLEAR trial baselines.
Average pattern, schematic.



Common patterns of suicide risk across the menstrual cycle

The same three-group structure replicates across 139 patients with suicidal thoughts, 124 with BPD, and adolescent samples.



Luteal pattern

Builds over about 1.5 weeks before menses; irritability, anxiety, suicidal thoughts and behaviors. The PMDD timing.

Perimenstrual pattern

Peaks in mid-to-late menses and settles only by ovulation; depression, hopelessness, suicidal thoughts and behaviors.

No cycle effect, about half

Symptoms are real and often moderate, but the cycle isn't driving them.

When symptoms occur, not which sensitivity a person has.



COLLABORATOR
Jessica Peters



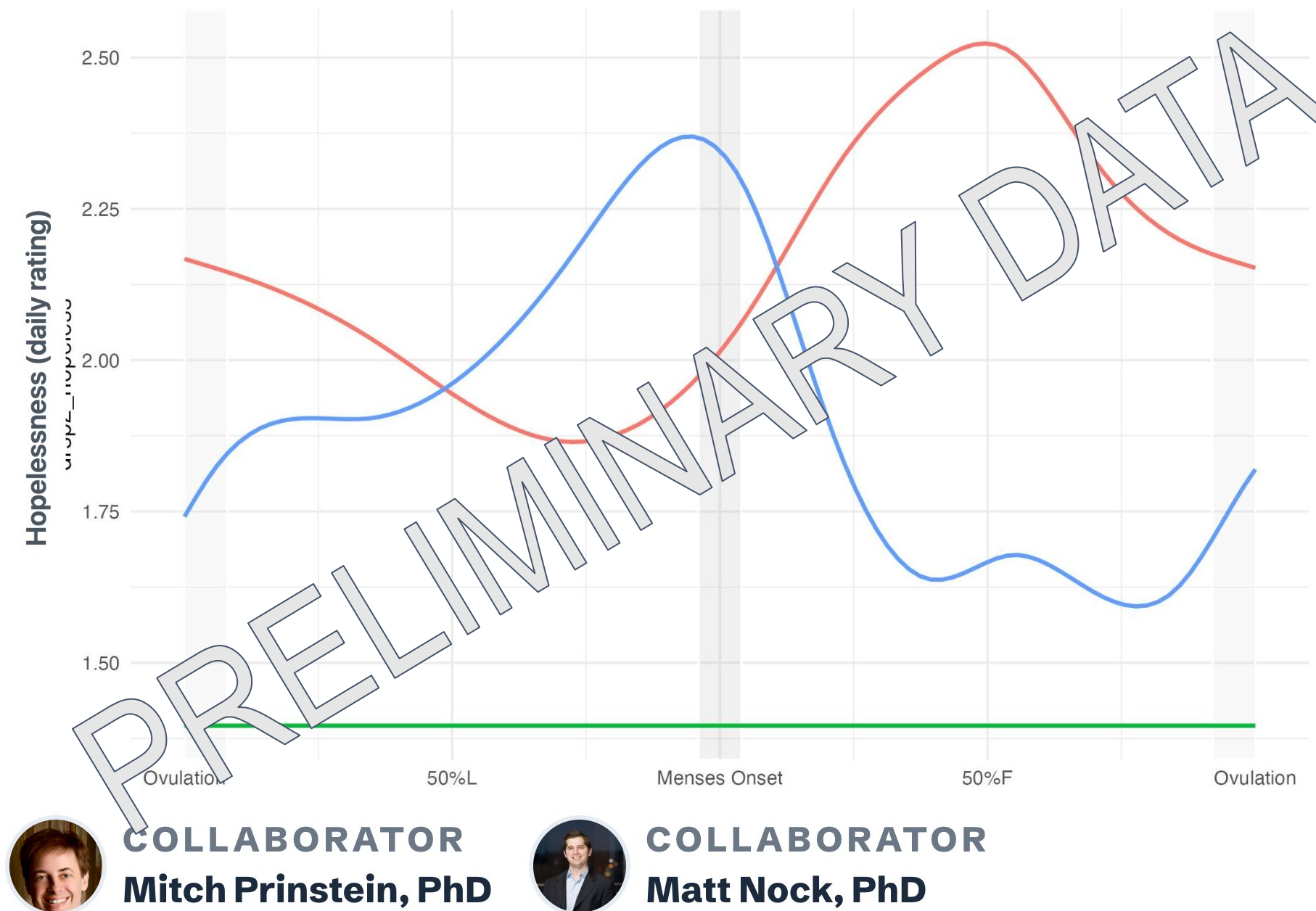
SUICIDE RISK AND THE MENSTRUAL CYCLE

Teenagers show the same three patterns, and the cyclical ones have more severe suicidality

94 teens with suicidal thoughts, about half with a prior attempt, followed daily soon after their first period.

Same subgroups as in adults: luteal, perimenstrual, and no cycle effect.

Girls with a cyclical pattern had more severe suicidality.



LEAD AUTHOR
Ashley Ross



COLLABORATOR
Elizabeth Andersen, PhD

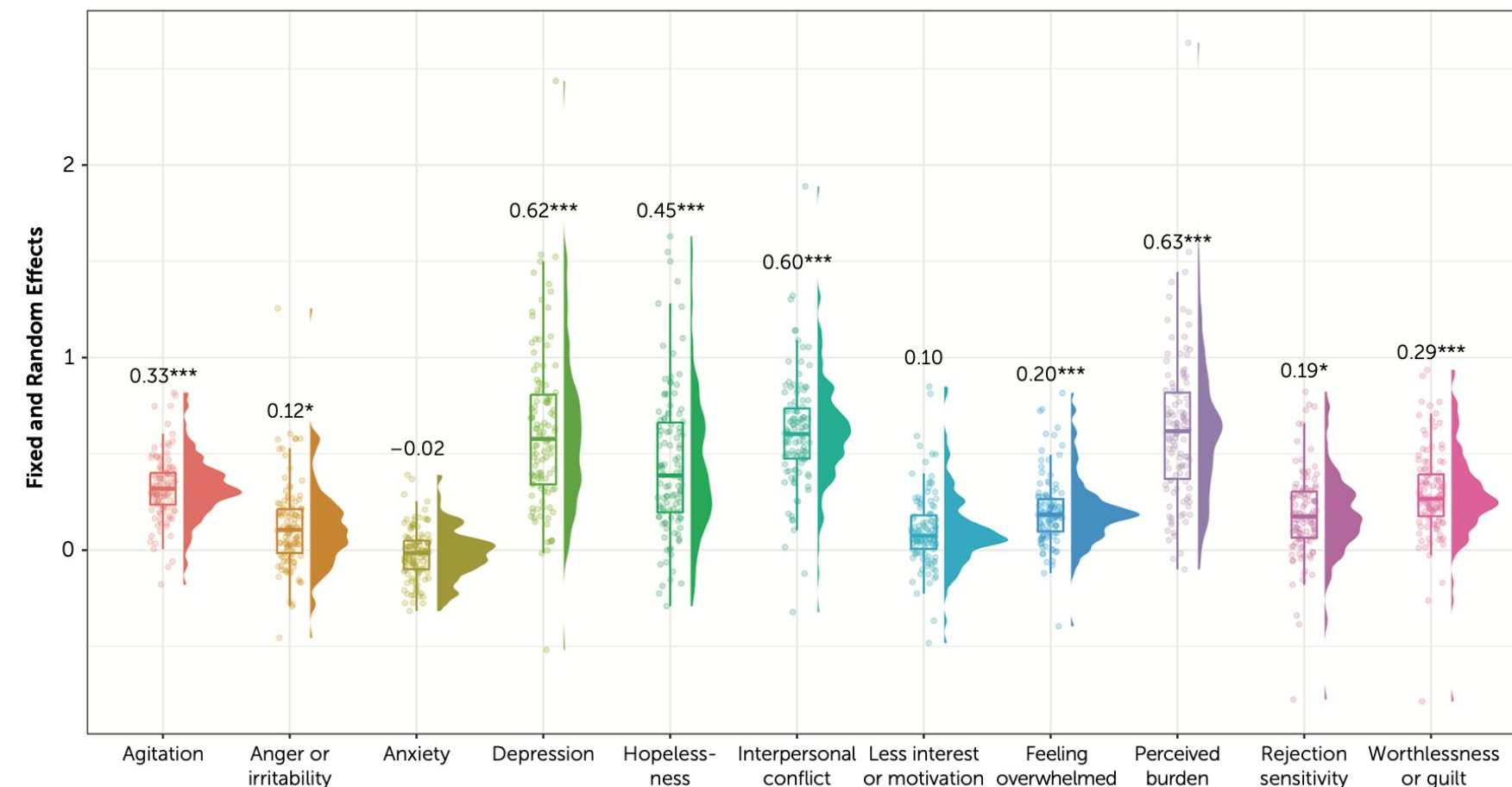


COLLABORATOR
Susan Girdler, PhD



The psychological route to suicidal thinking differed from person to person

FIGURE 1. Graphical depiction of fixed and random effect estimates from multilevel models predicting suicidal ideation from each psychiatric symptom^a



In every analysis, the link between a symptom and suicidal thinking varied from person to person. For one patient hopelessness tracks the risk; for another, feeling like a burden; for a third, the daily link is weak.

Differences were largest after ovulation through menses, the window where the hormone changes are.

Suicidal planning was the exception. Where it worsened perimenstrually, it did so consistently across people.

The psychological mechanism is not one mechanism, which is the same argument for matching treatment to the person.



LED BY
Jackie Ross, PhD

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PART 2

**Why would normal hormone changes
cause psychiatric symptoms?**

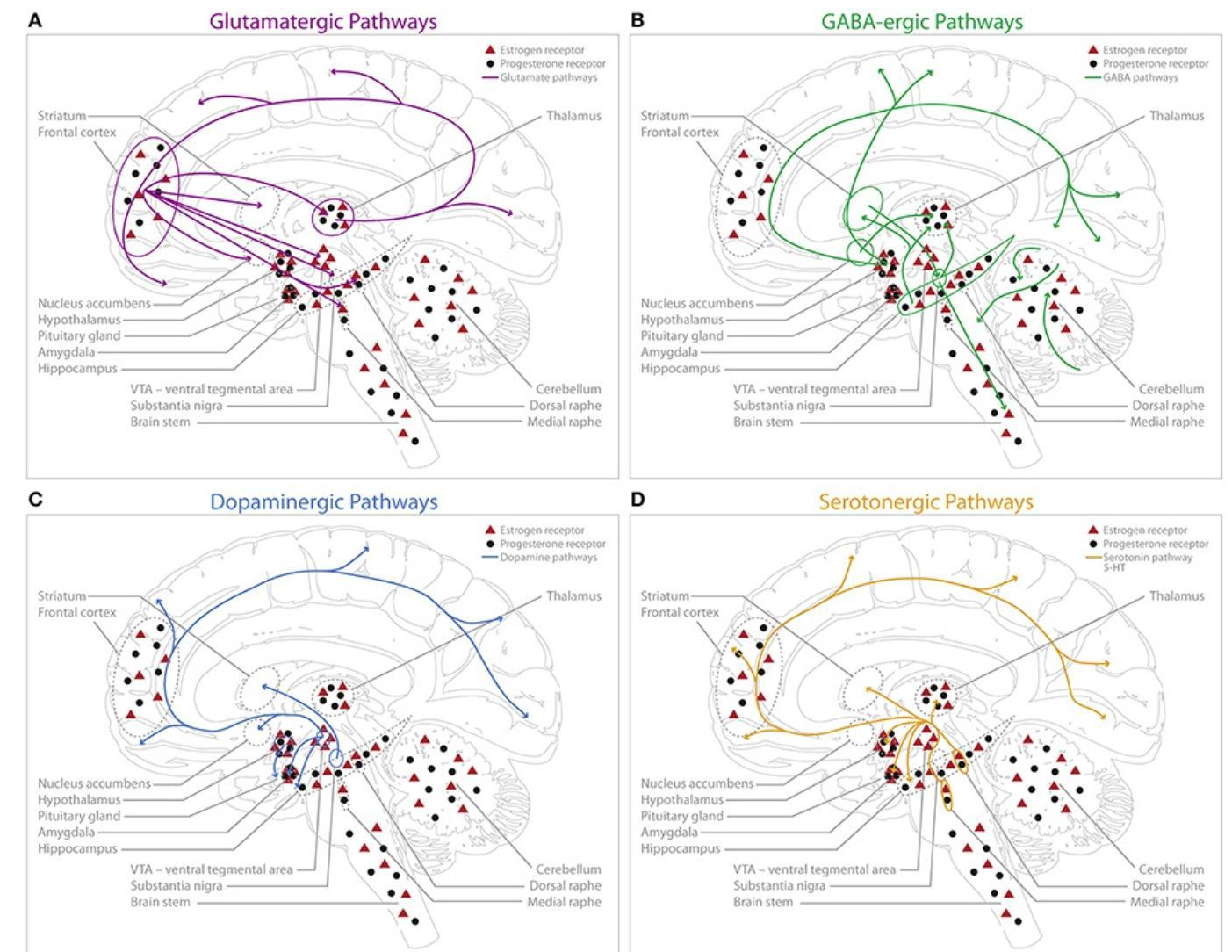
HORMONE SENSITIVITY

Estradiol and progesterone are powerful brain chemicals... but the brain's ability to adapt is also powerful

Both E2 and P4 have strong effects on brain structure, connectivity, and function.

Receptors for these hormones are dense in the circuits that run threat, reward, stress, memory, and thinking (glutamate, GABA, dopamine, serotonin).

So a normal monthly change in hormones is also a normal monthly change in brain chemistry.

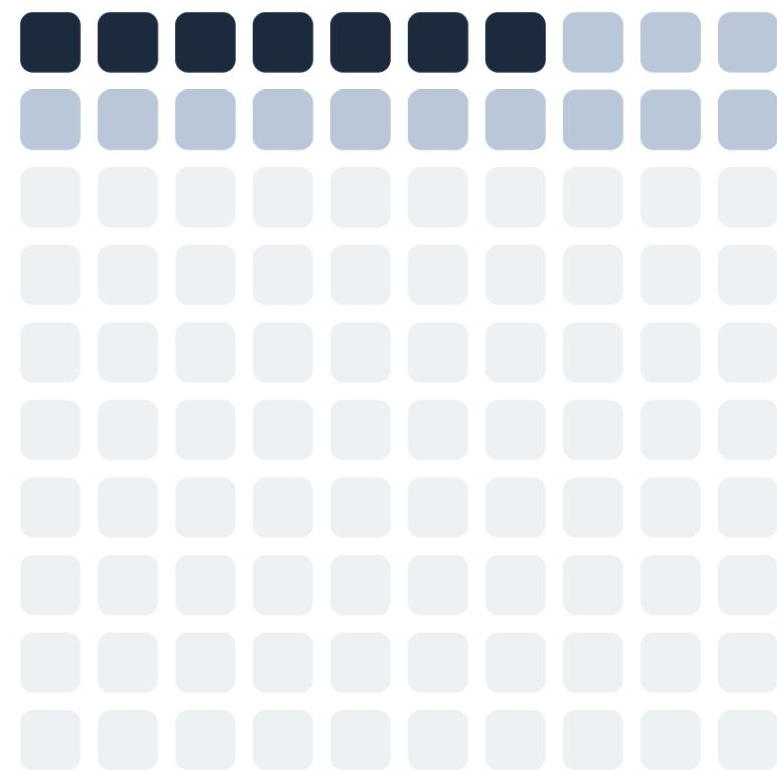


HORMONE SENSITIVITY

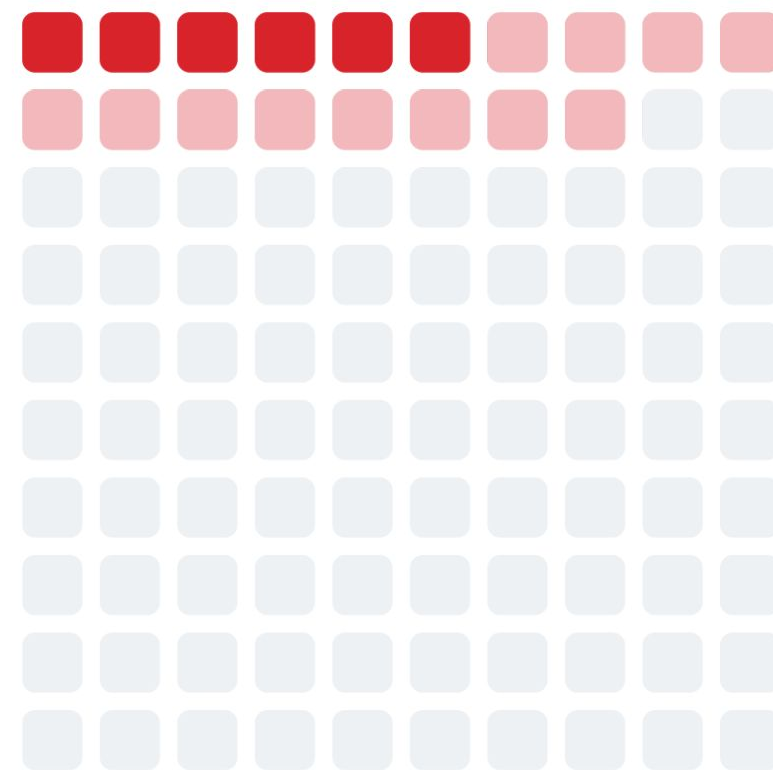


**Everyone gets the same hormone changes,
but only a minority get sick from them**

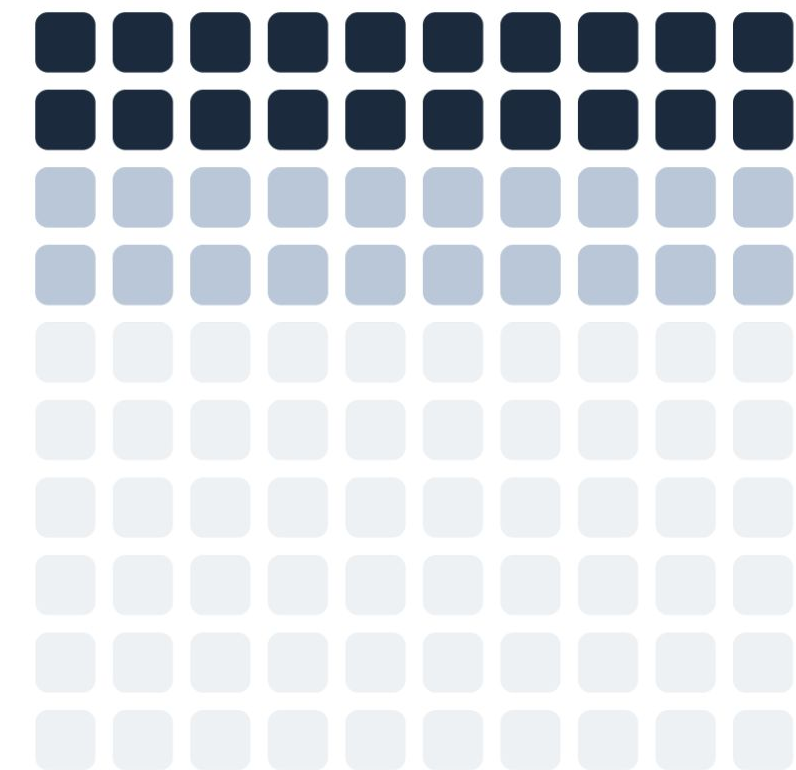
**Perinatal
7-20%**



**Premenstrual
6-18%**



**Perimenopausal
20-40%**



**Universal hormone changes, symptoms in a minority:
the hormones alone cannot be the explanation.**



It is not a hormone imbalance: hormone levels are normal

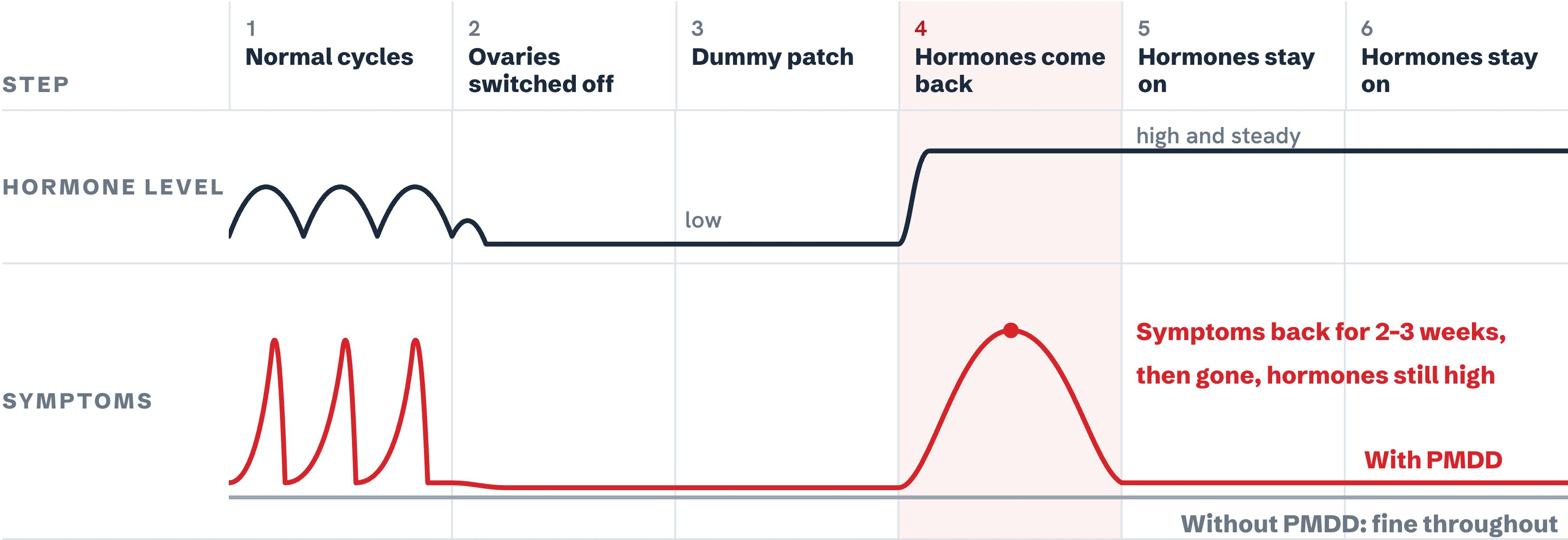
In PMDD, the menstrual cycle and the hormones are normal: **normal amounts, normal balance, normal patterns, normal metabolism.**

Experiments comparing patients with healthy controls show the difference is in the **brain's sensitivity** to a normal hormonal event.

Patients often find this disappointing. An “imbalance” feels more fixable and less stigmatized than “it’s my brain.” But it is the more useful truth: it tells us what to target.



The classic experiment: normal hormones, abnormal response



The hormone levels are normal. The brain’s response to the change is different.



INVESTIGATOR
Peter Schmidt, NIMH

Schmidt et al., NIMH: NEJM 1998 (10 with PMDD, 15 without); Am J Psychiatry 2017 (12 with PMDD). Schematic.

3

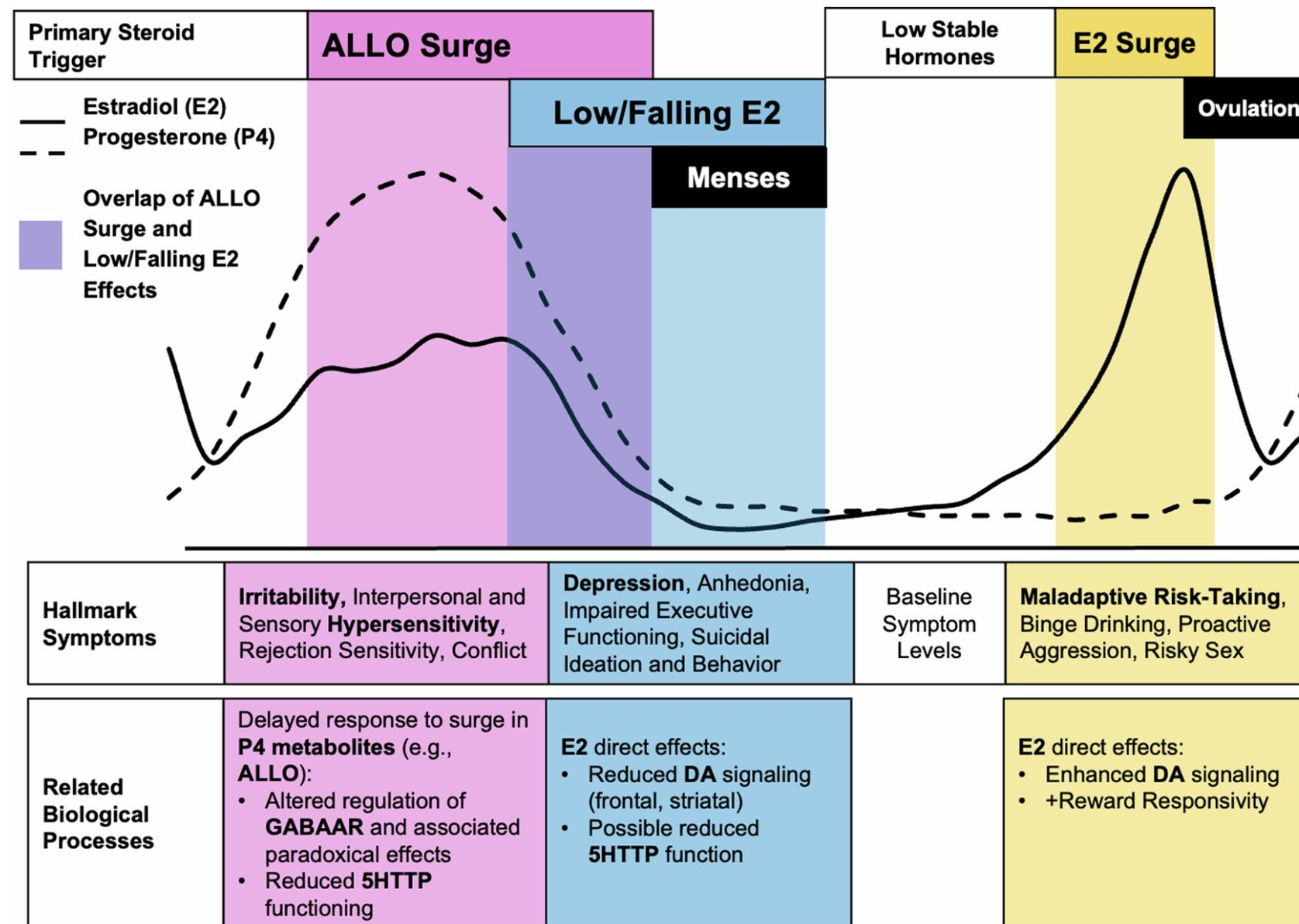
PART 3

**Are there different kinds
of hormone sensitivity?**



DIFFERENT SENSITIVITIES

A working framework: three sensitivities, three windows, three symptom profiles



Sensitivity to the progesterone (ALLO) surge after ovulation

agitated negative feelings: irritability, anxiety, feeling overwhelmed

Sensitivity to the estradiol fall around the period

low, flat negative feelings and foggy thinking: depression, hopelessness, brain fog

Sensitivity to the estradiol surge at ovulation

heightened reward-seeking: impulsivity, substance use

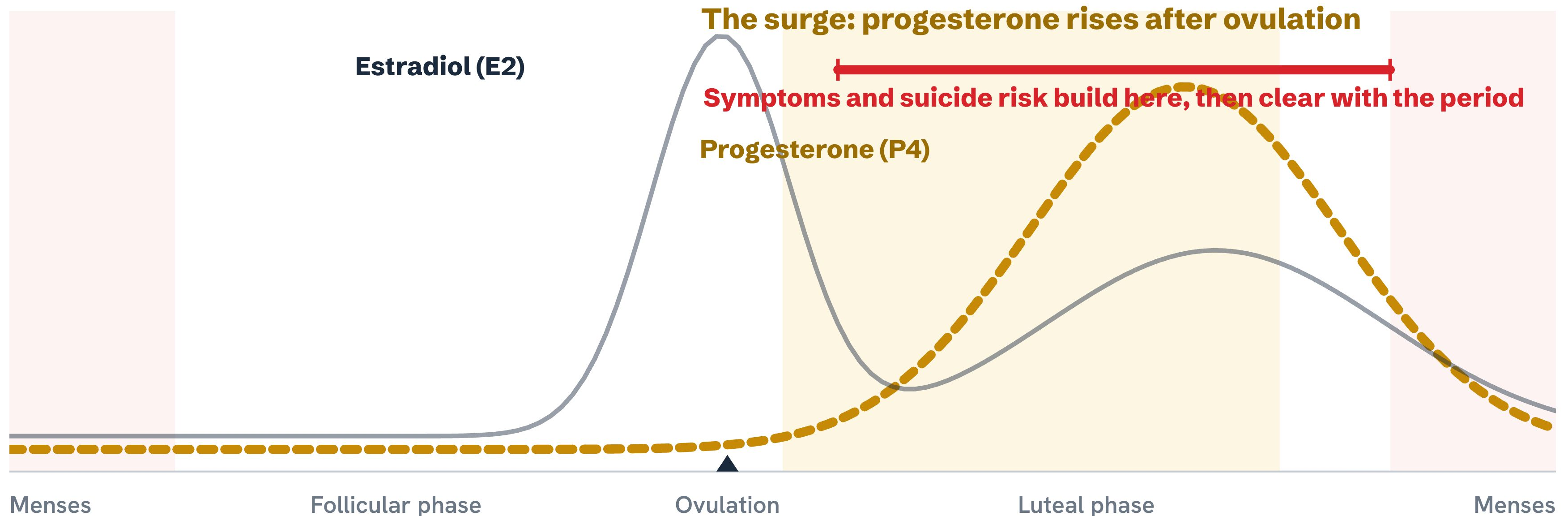
Not mutually exclusive; one person can have more than one.



COLLABORATOR
Jess Peters, PhD



Sensitivity #1: the progesterone surge after ovulation (the PMDD timing)

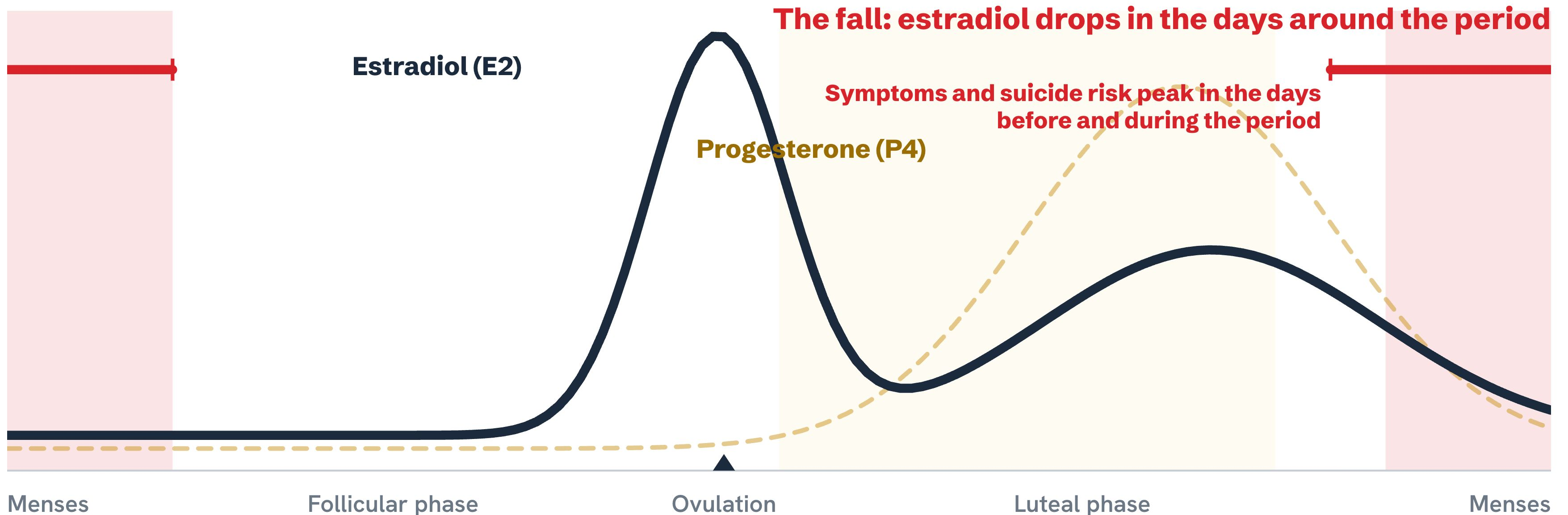


Mechanism. Progesterone → ALLO, which acts on GABA, the brain's "brake pedal."

Often: irritability, anxiety, feeling overwhelmed.



Sensitivity #2: the estradiol fall around the period (the perimenstrual timing)



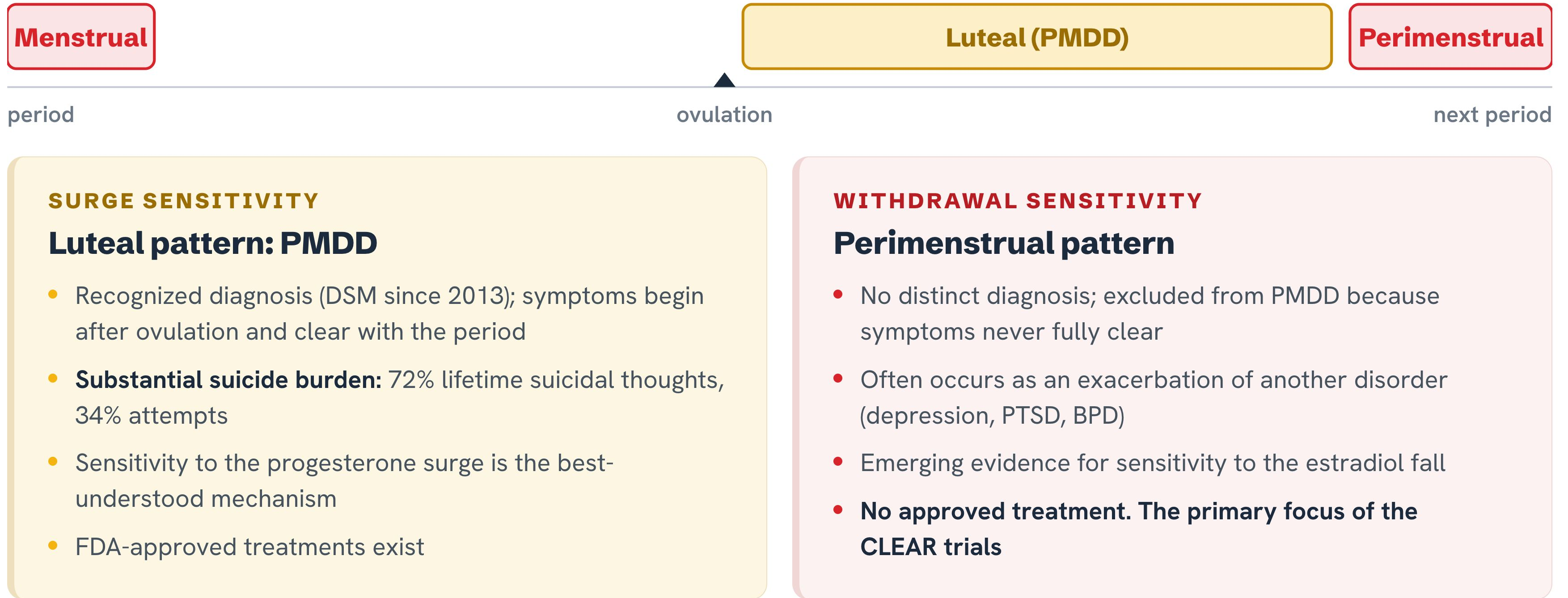
Mechanism. Estradiol fall → less dopamine, serotonin, and growth-factor support.

Often: depression, hopelessness, brain fog.

DIFFERENT SENSITIVITIES



Both patterns can carry suicide risk, but only one currently has a diagnostic home



4

PART 4

Can experiments identify the trigger, and eventually help us match treatment to the person?



CLEAR-1: if the hormone fall causes the spike, preventing the fall should prevent the spike

SAMPLE

30

outpatients with suicidal thoughts in the past month, **73% of whom had made an attempt**. Recruited with no mention of the cycle; none met criteria for PMDD.

DESIGN

Double-blind, placebo-controlled crossover

Two weeks of real hormones (patch + pills) vs. identical placebo, in random order, with a washout cycle between.

half the patients

Real hormones

washout

Placebo

the other half

Placebo

washout

Real hormones

patient and rater blind · estradiol patch 0.1 mg/day + oral proges

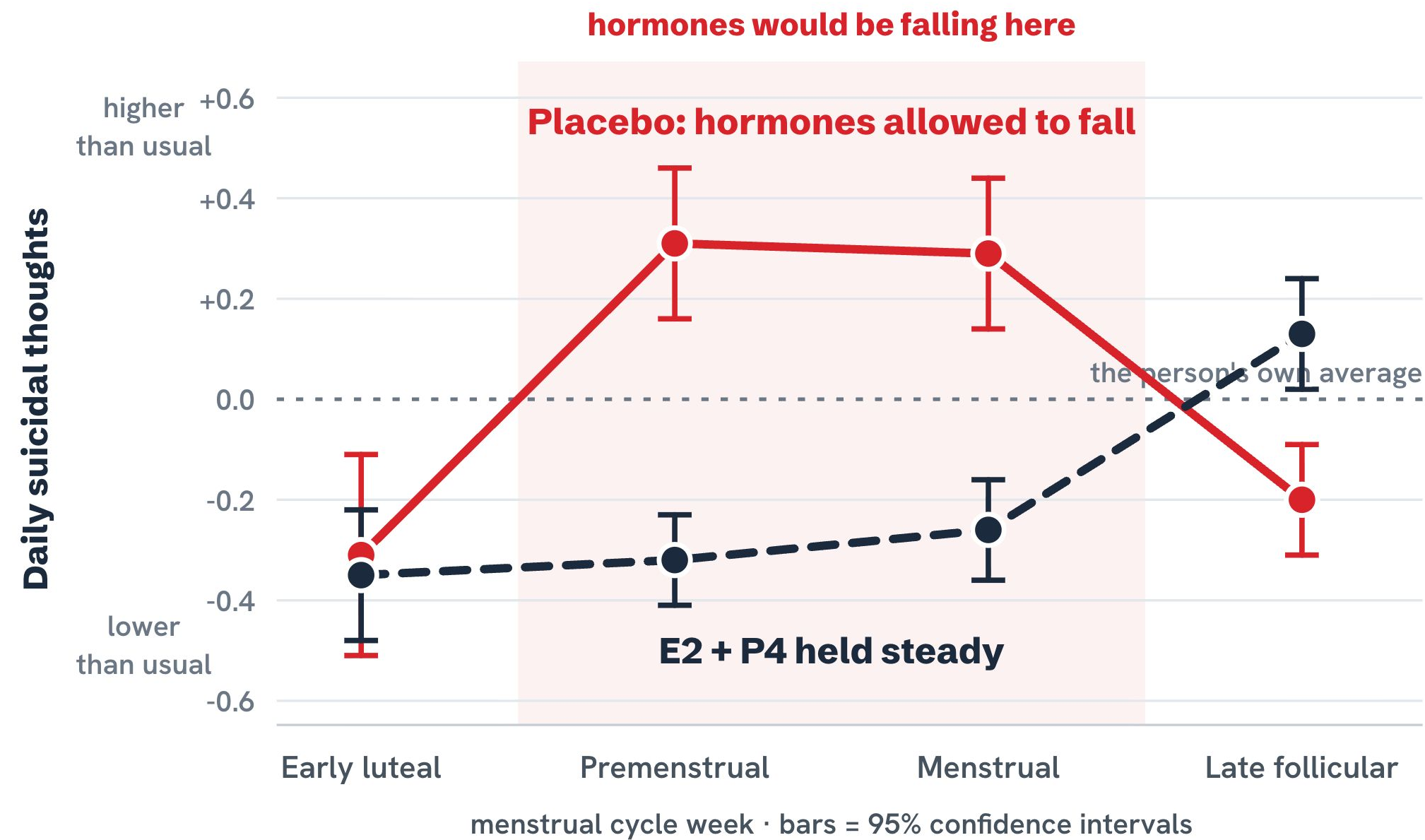
DAILY SURVEY

Every day, for months

Mood and suicidal thoughts rated daily, so the timing of any change is measured rather than recalled.



CLEAR-1: hold hormones steady, and the perimenstrual spike does not happen



Values from Eisenlohr-Moul et al., 2022, Translational Psychiatry, Fig. 4 (N = 28 analyzed; double-blind placebo-controlled crossover), redrawn.



CLEAR-2: which hormone matters?

CONDITION A

Estradiol only

real E2 patch + placebo pills

CONDITION B

Progesterone only

placebo patch + real P4 pills

CONDITION C

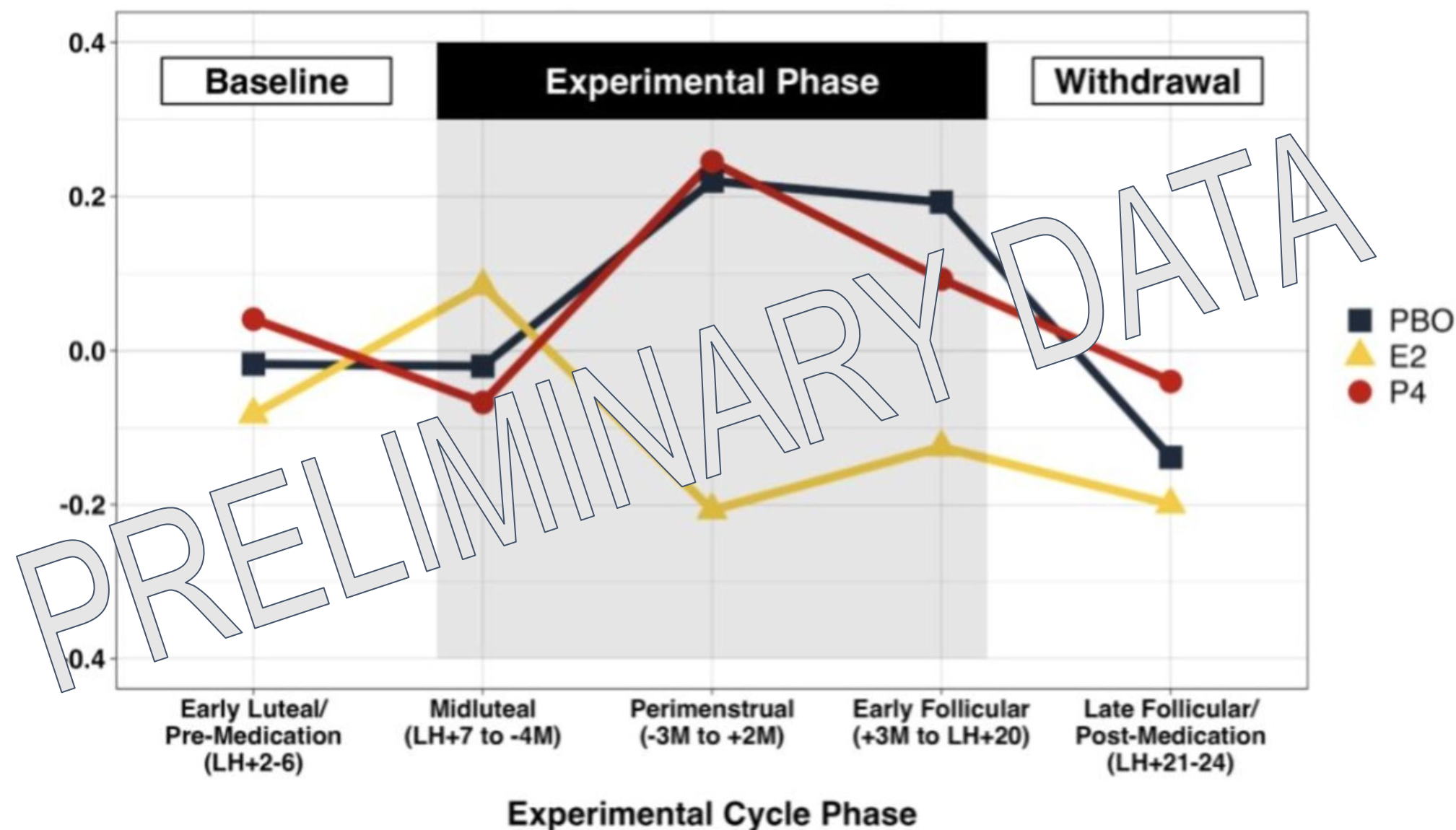
Placebo

placebo patch + placebo pills

- 44 patients randomized, same population as CLEAR-1. Each completed all three conditions in random order, double-blind, with washout cycles between.
- Blood drawn three times per condition to measure estradiol, progesterone, and ALLO, the calming steroid the body makes from progesterone.
- **Our expectation going in: progesterone withdrawal, via ALLO, might explain this perimenstrual spike. It didn't.**

THE CLEAR TRIALS

In this timing pattern, estradiol prevented the spike, and progesterone did not



Placebo: suicidal thinking rises in the perimenstrual window, as hormones fall.

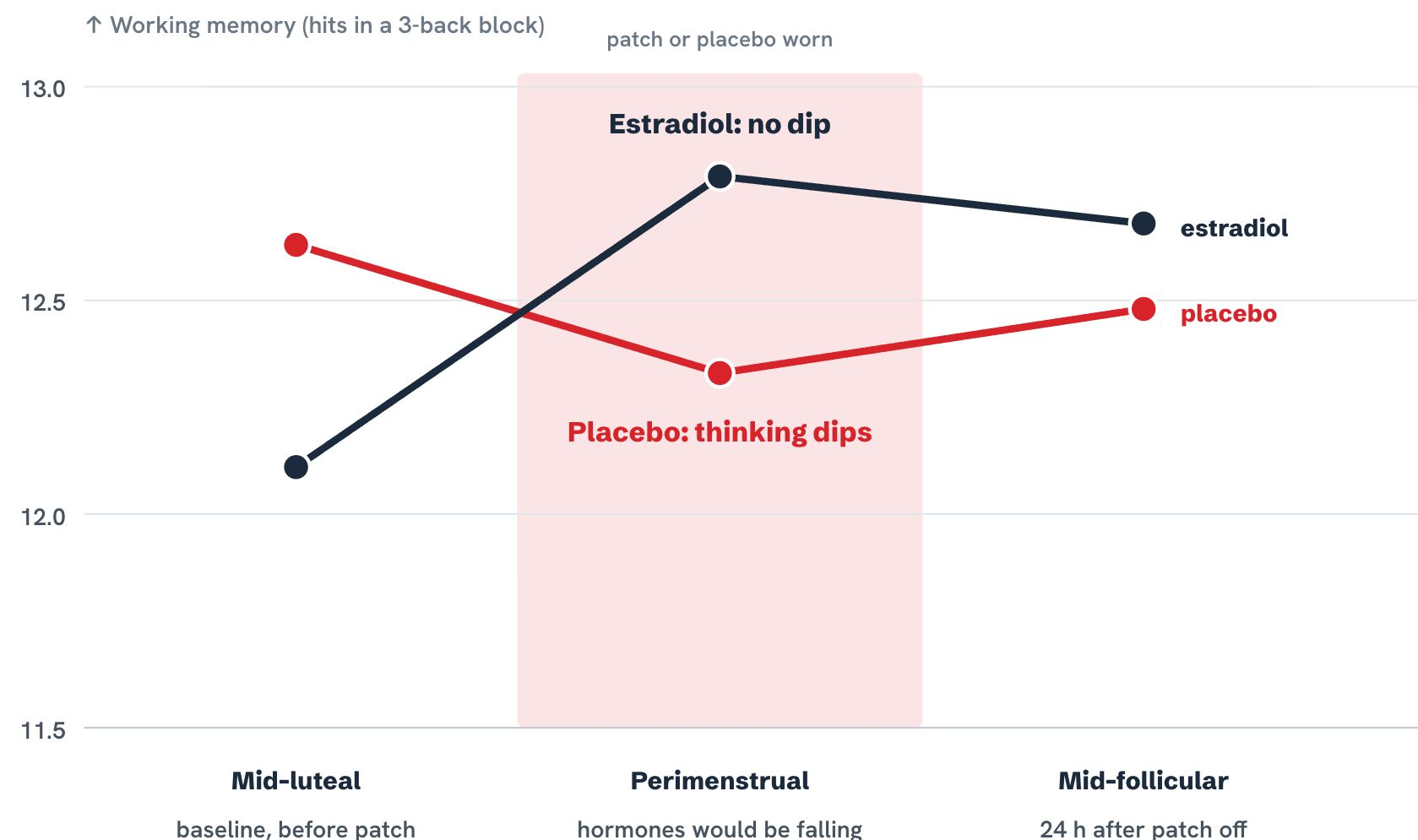
Estradiol alone: the rise is gone; thinking stays below each person's own average through the window.

Progesterone alone: looks like placebo. No protection, and a small number got worse.

Values are relative to each person's own average. The shaded block is the two weeks on study medication; the last phase is after the patch came off.



Estradiol changed cognition along with suicidal thinking



When suicidal thinking worsened, working memory worsened too. Estradiol prevented both changes.

Working memory depends partly on dopamine-regulated prefrontal systems.



LED BY
Katja Schmalenberger, PhD



Three trials, one conclusion, one caution

TRIAL	N	COMPARED	SUICIDAL THINKING	STATUS
CLEAR-1	30	E2 + P4 vs placebo	Prevented the perimenstrual spike	Published 2022
CLEAR-2	44	E2 vs P4 vs placebo	E2 prevented it; P4 worsened it for some	Under review
CLEAR-3	90	E2 + P4 vs placebo	Prevented the perimenstrual spike	In preparation

CONCLUSION

In patients with the perimenstrual pattern, **estradiol withdrawal can act as a causal trigger for the monthly spike, and preventing it prevents the spike.** In this timing pattern, progesterone and its metabolites did not explain it.

CAUTION

- Two-week mechanism experiments. **Not a sustainable treatment**, and nothing here is approved.
- **Not appropriate for luteal PMDD.** For some people with surge sensitivity, adding hormones can worsen symptoms.
- **The trigger is real; the treatment has to be matched to the person.**

PART 4 • CONTINUED

Can we eventually tell which sensitivity a person has?

Two early clues. These are research leads, not clinical tests.



Treatments today buffer the brain's sensitivity or remove the cycling hormones

FIRST LINE

SSRIs

Luteal-phase only or full cycle. Work within days in PMDD, unlike in depression. FDA-approved; about **60% benefit**.

SUPPRESS OVULATION

A specific birth-control pill (drospirenone + ethinyl estradiol)

Taken 24 days on, 4 off. FDA-approved for PMDD; smaller benefit, and mood reactions are common.

SEVERE CASES

Switch the ovaries off, add steady hormones back

A medication pauses the ovaries; steady estradiol and progesterone are added back. Symptoms return in the first add-back month, then settle. Effective in pooled trials; never taken to the FDA.

ALONGSIDE

Symptom-focused therapies

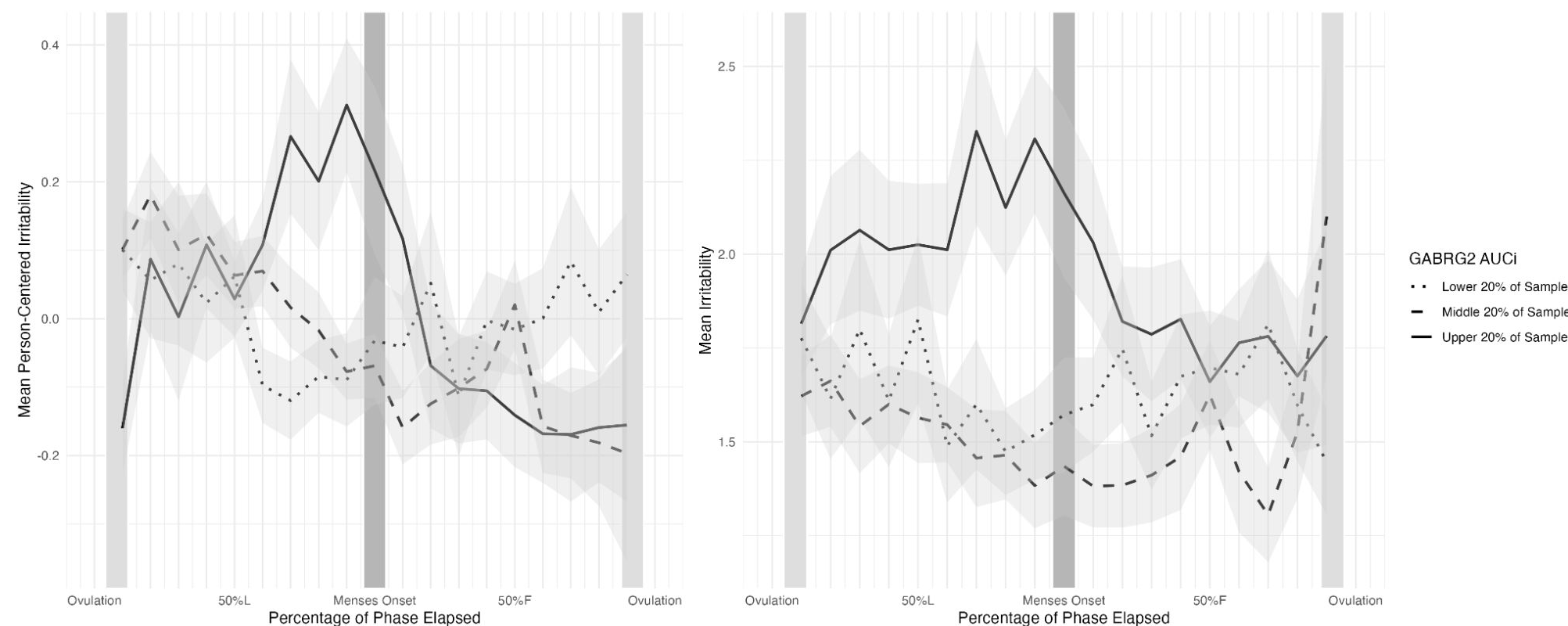
CBT, DBT, and targeted medication for specific symptoms.

All developed for PMDD. Nothing is approved for the menstrual pattern, and in secondary analyses many of these do not work for it.

WHO RESPONDS



Clue 1: a blood test that tracks the surge pattern (GABA receptor genes)



Daily irritability across the cycle, grouped by how much one GABA receptor gene (GABRG2) swings over the month in each patient's blood. Solid line = largest swings.

LUTEAL PATTERN

Bigger monthly swings in three GABA receptor genes (**GABRG2, GABRD, GABRA5**) → more **luteal** irritability, anxiety, and suicidal thoughts.

Not depression.

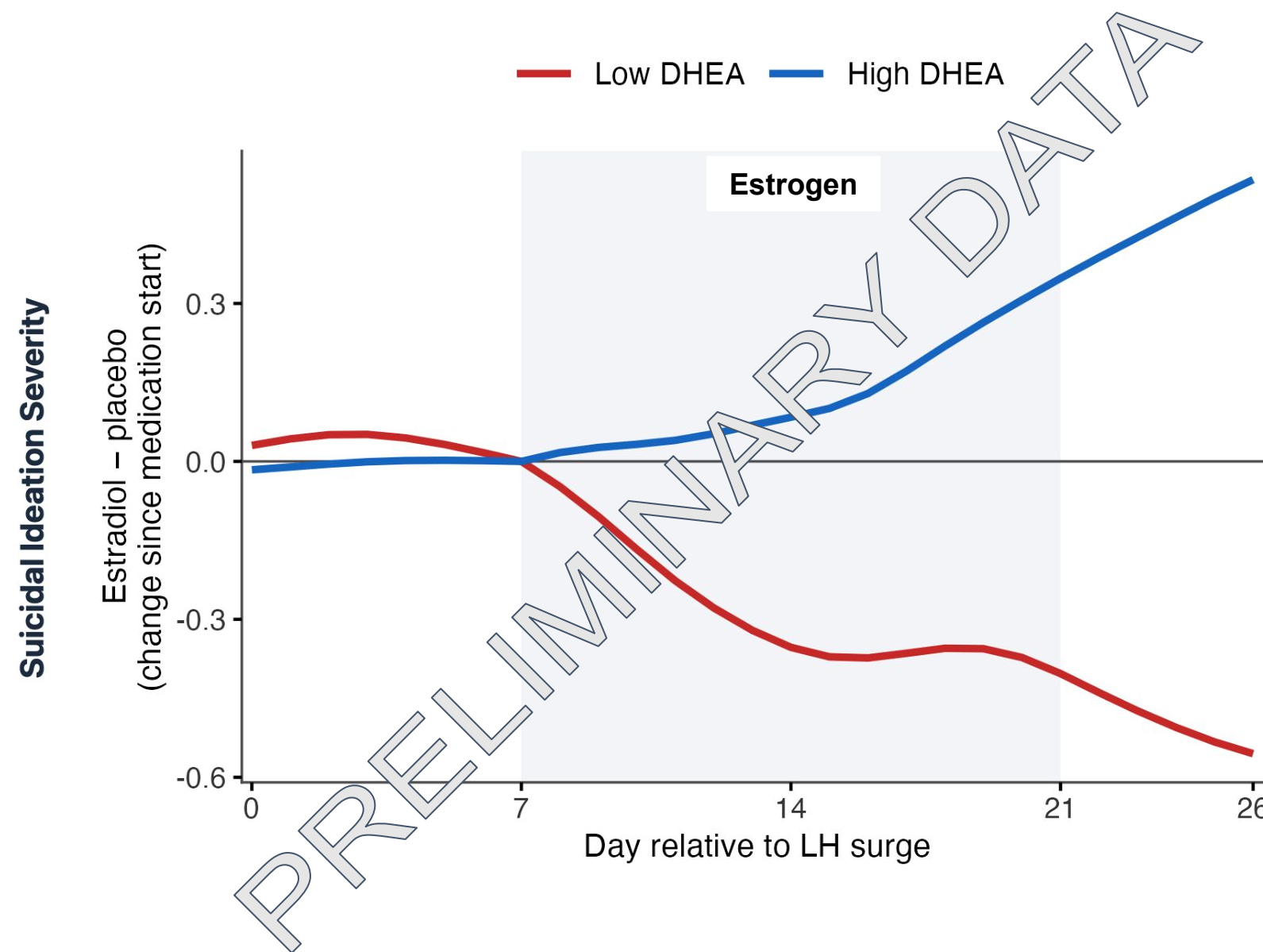
GABA receptors are the brake pedal ALLO acts on, so this points at the receptor remodeling we think underlies surge sensitivity.



LED BY
Jordan Barone, MD/PhD

WHO RESPONDS

Clue 2: lower baseline DHEA predicted more benefit from estradiol (preliminary)



WHAT WE SAW

In CLEAR-2, patients with lower DHEA before treatment got more benefit from the perimenstrual estradiol patch.

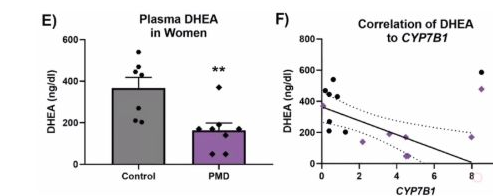
WHY IT MIGHT MATTER

DHEA is a steroid the body can convert toward estrogens. Less DHEA may mean less buffer against the fall.

WHY IT MATTERS FOR “WHO”

Measured before treatment, from a blood draw. That is what a usable predictor would look like.

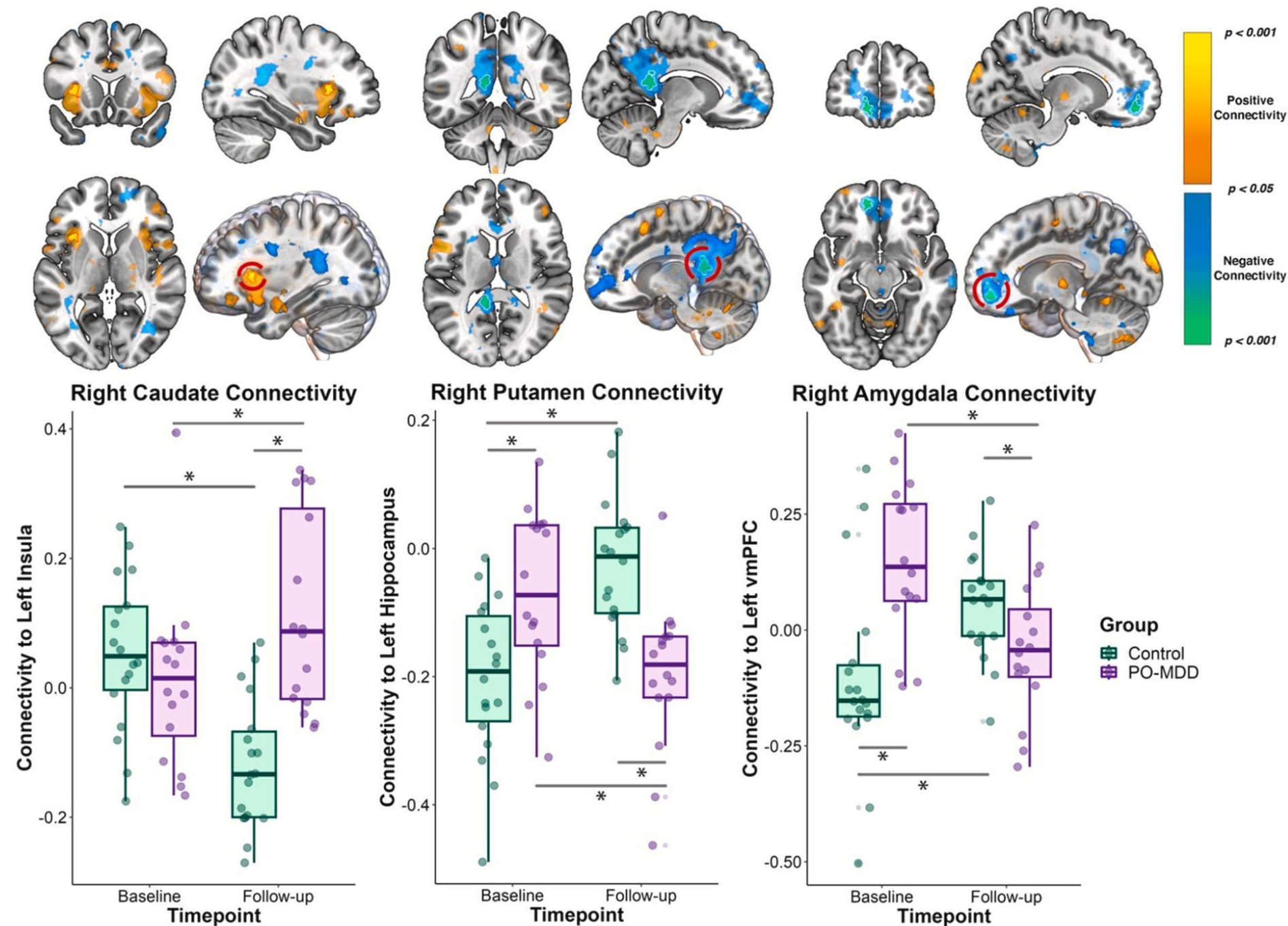
Context: DHEA is also lower in perimenopausal depression, another estradiol-withdrawal condition, and tracks a steroid-metabolism gene (CYP7B1). Rudzinkas et al., 2020, Mol Psychiatry.



WHAT'S NEXT



Understanding how estradiol changes how the brain's different regions talk to each other



Brain scans before and after an estradiol patch: 16 people with depression that began in perimenopause (purple) and 18 without (green).

Estradiol changed how strongly emotion and reward regions talked to each other, **in the depressed group only**: some connections strengthened, others weakened.



COLLABORATOR
Crystal Schiller

Hynd M, Gibson K, Walsh M, Phillips R, Prim J, Eisenlohr-Moul T, Walsh E, Dichter G, Schiller C. Estradiol modulates resting-state connectivity in perimenopausal depression. J Affect Disord. 2025 Feb 15;371:253-260. doi: 10.1016/j.jad.2024.11.068. Epub 2024 Nov 22. PMID: 39581384; PMCID: PMC12035911.

What changes in the brain when the suicidal state changes?

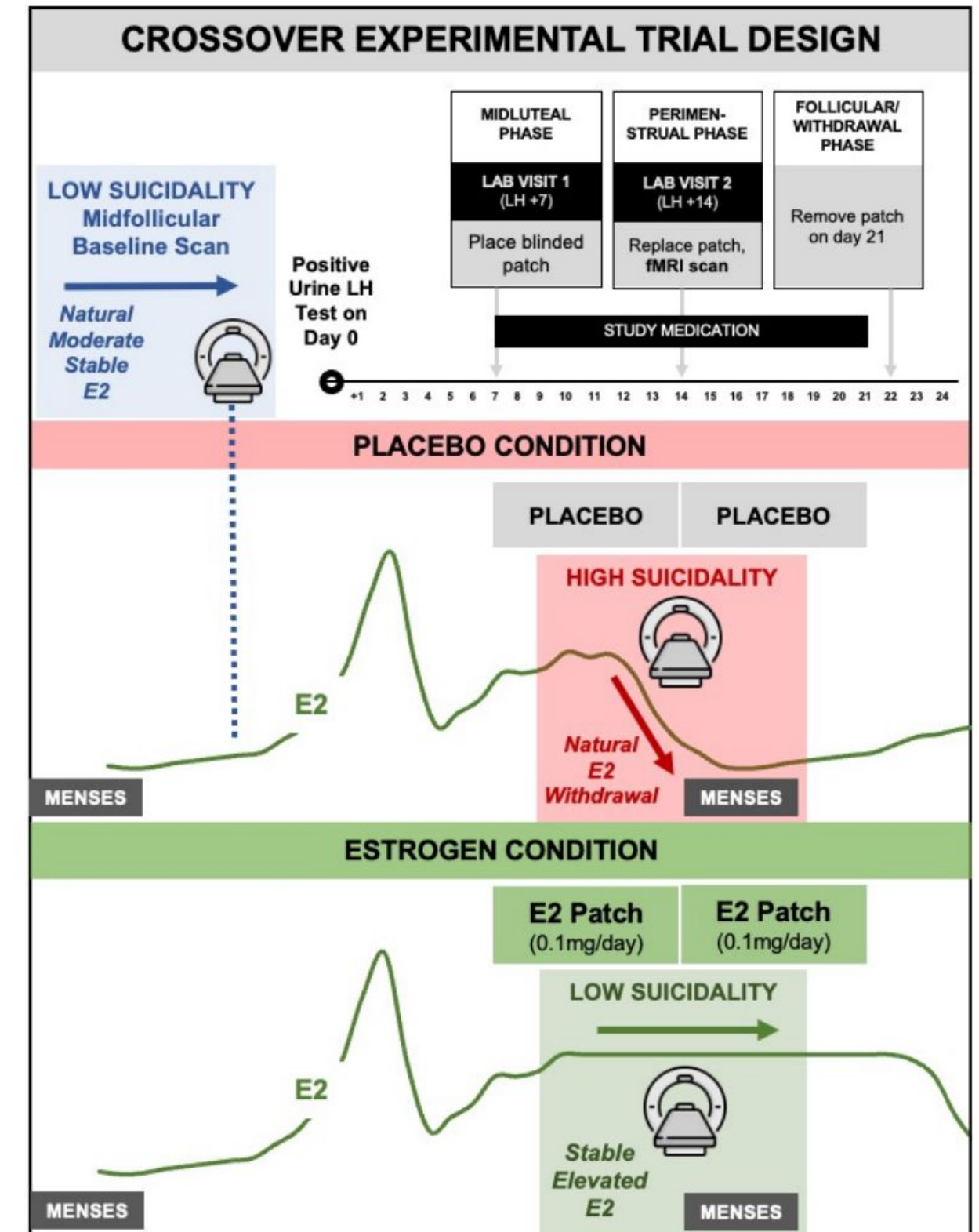
Estradiol patch alone vs. placebo, across the perimenstrual window, with brain imaging (resting-state fMRI).

The same person, scanned in three states:

- 1 Natural, lower risk:** early cycle, estradiol moderate and stable
- 2 Natural, higher risk:** perimenstrual estradiol fall, under placebo
- 3 Rescue:** same window, the fall prevented by the patch

Goal: Use a computational approach called group iterative multiple model estimation (GIMME) to compare brain changes in response to treatment, aiming to understand why some people benefit from estrogen while others do not.

Enrolling at the University of Chicago later this year. Ages 20–40, regular cycles, recent suicidal thoughts, in outpatient care.



WHAT YOU CAN DO

What you can do now



1

Track it

Two months of daily ratings, not memory. Free apps exist (e.g., MAC-PMSS). Recall alone gets the pattern wrong about 60% of the time.

2

Name the window

If suicidal thoughts reliably worsen in the luteal weeks or around the period, that is clinical information. Tell your prescriber and therapist, and bring the ratings.

3

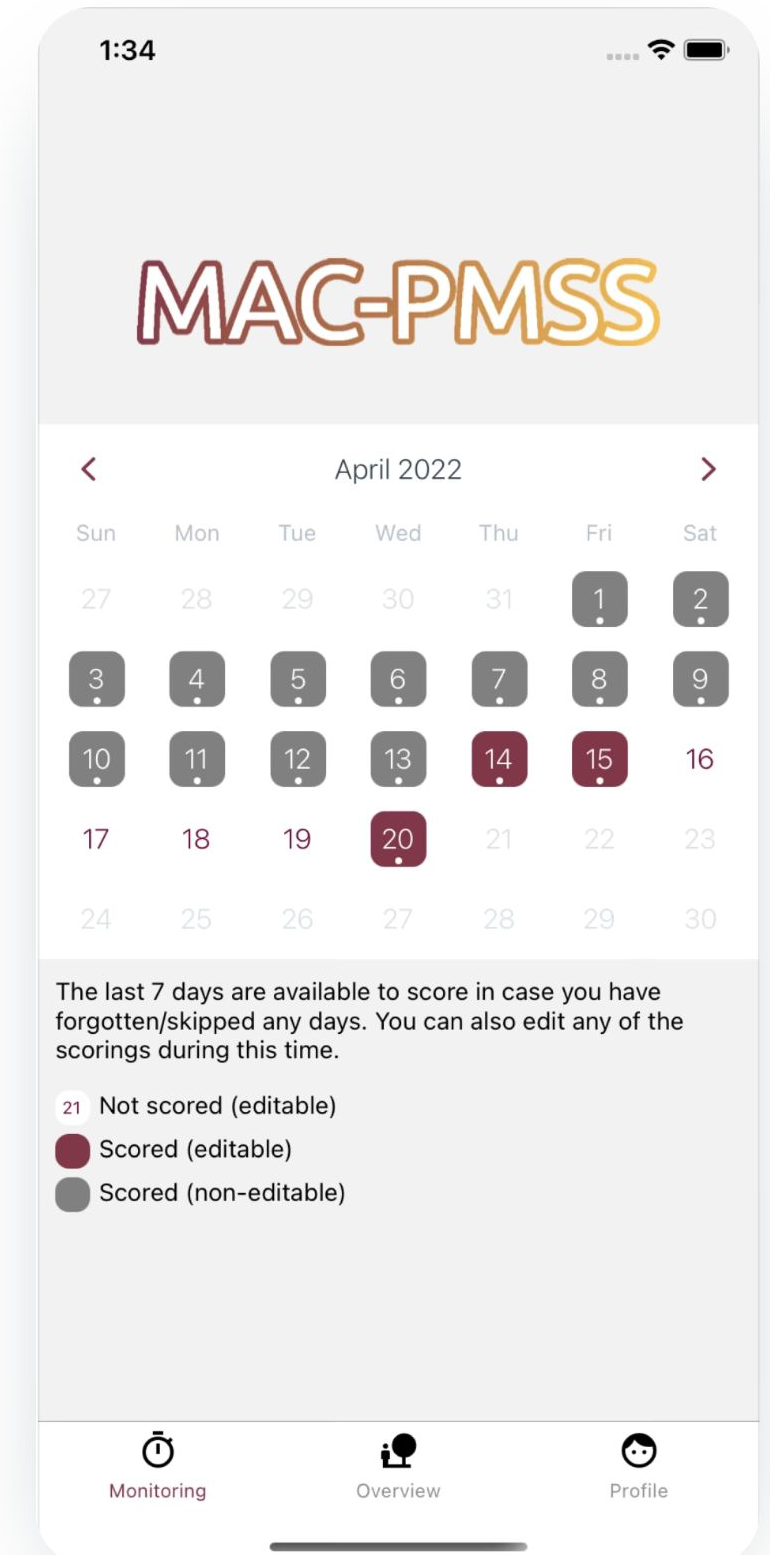
Time the safety plan

Extra check-ins, means safety, and support concentrated in your high-risk days. Predictable risk is preventable risk.

4

Know your pattern before changing hormones

SSRIs and continuous drospirenone have evidence for the luteal pattern. Hormonal changes can help or harm depending on the sensitivity involved. Track before and after.



Questions, and ways to get involved



IF YOU HAVE SYMPTOMS

Track two cycles and bring the ratings to your clinician. Free daily tracking: **MAC-PMSS** app (iPhone). **iapmd.org** for the patient treatment guidebook, provider directory and support. Crisis support (US): **call or text 988**.

IF YOU'RE A CLINICIAN

ncrptraining.org (National Curriculum in Reproductive Psychiatry) · **nabrp.org** (efforts to create a standard reproductive psychiatry subspecialty) · **iapmd.org** (clinician guidelines)

IF YOU'RE A RESEARCHER

menstrualcycleR (cycle timing) and **cpass** (PMDD scoring) R packages · CLEAR Lab: **clearlabresearch.com**

IF YOU WANT TO GIVE

BBRF funds critical science. **bbrfoundation.org** · IAPMD serves patients directly. **iapmd.org** · To support the CLEAR Lab specifically: **temo@uchicago.edu**