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Neuroticism modulates mood responses to pharmacological sex hormone manipulation in healthy women

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ABSTRACT

Background: Women show increased risk of depressive symptoms during hormonal transition phases. The risk mechanisms may include changes in mood in response to fluctuating ovarian hormones moderated by predisposing risk factors for mood disorders, such as personality trait Neuroticism.

Methods: A pooled sample of 92 mentally healthy women (28.3 ± 7.1, mean age ± SD) from two independent cohorts run in our lab, using gonadotropin-releasing hormone agonist (GnRHa) experimentally (n = 28) compared to placebo (n = 27) and as part in vitro fertilization (n = 37), were extracted from the Center for Integrated Molecular Brain Imaging database. All women filled in questionnaires of trait Neuroticism from the NEO personality Inventory-Revised (NEO PI-R) at baseline and self-reported levels of mood disturbances with the Profile of Mood States (POMS) daily during 14 days of GnRHa intervention or placebo. Effects of intervention by trait Neuroticism on serial daily reports of mood disturbances were examined using mixed model analyses.

Results: Personality trait Neuroticism significantly modulated daily mood responses to GnRHa, but not placebo. Women with high and low scores on trait Neuroticism at baseline experienced more pronounced changes in mood when exposed to GnRHa, whereas women with medium trait Neuroticism scores remained relatively stable.

Conclusions: The susceptibility to hormone-triggered mood changes appears to depend upon women's general tendency to experience distress and destabilization of mood, as captured by personality trait Neuroticism. This could aid clinicians evaluate hormone-related vulnerability for mood disorders in women and may guide targeted prevention in reproductive care.

1. Introduction

Major depressive episodes occur twice as frequent in women compared to men (Kessler et al., 2005), and women also tend to exhibit greater symptom severity and higher rates of co-morbid disorders (Marcus et al., 2008). A recent nationwide Danish cohort study of trends in depression replicated the women to men risk ratio of 2 to 1, and further replicated an even higher risk ratio for adolescent girls from expected time of puberty onset (age 12–19) with a girls to boys risk ratio of 2.7 to 1 (Skovlund et al., 2017). The mechanisms involved in this increased risk for depression in females are not clear, but may include a heightened sensitivity to fluctuating ovarian steroid hormones (Douma et al., 2005). This is supported by studies reporting that the risk of developing mood disturbances or major depressive episodes increases in life phases where ovarian steroid hormones fluctuate or decline rapidly, e.g., puberty and across peripartum and perimenopause (Deecher et al., 2008; Freeman et al., 2014; Gavin et al., 2005; Le Strat et al., 2011; Munk-Olsen et al., 2006). Depressive symptoms also appear to be coupled to the magnitude by which estradiol levels fluctuate around a woman's own mean during menopausal transition (Freeman et al., 2006). However, while these findings suggest that fluctuations in ovarian hormones can trigger major depressive episodes and mood disturbances in a subgroup of vulnerable women, little is known about what characterizes the profile of such women beyond estradiol sensitivity (Guintivano et al., 2014; Mehta et al., 2014) and broader environmental and demographic risk factors (Di Florio et al., 2017;

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Guintivano et al., 2018).

The Five-Factor Model (FFM) is a widely applied framework for indexing essential personality features of an individual that continue to influence cognition, emotion and behaviour (Costa and McCrae, 2005). Among the FFM personality traits (Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness), trait Neuroticism is a robust risk factor for major depressive episodes (Christensen and Kessing, 2006; Kendler et al., 2006; Kendler and Myers, 2010; Kotov et al., 2010), which is also associated with the severity of depression (Brown and Rosellini, 2011). High scores on trait Neuroticism has also been associated with increased vulnerability in response to life stress such as infertility (Rockliff et al., 2014), and psychopathology in general (Ormel et al., 2013). Women tend to score higher on trait Neuroticism than men (Costa et al., 2001; Schmitt et al., 2008), a phenomenon that translates across cultures. However, no studies have investigated whether high scores on trait Neuroticism constitute a risk factor for mood disturbances in healthy women undergoing controlled ovarian hormone fluctuations.

In women ovarian hormone production is governed by the hypothalamic-pituitary-gonadal (HPG)-axis (Hoyt and Falconi, 2015). A gonadotrophin-releasing hormone agonist (GnRHa) is a synthetic peptide (Millar et al., 2004) that, when administered pharmacologically in a continuous fashion induces a biphasic ovarian hormone response (Thomas et al., 1986); after initial stimulation of the HPG-axis which peaks around day 4, GnRH receptors desensitize and consequently, ovarian hormone production is suppressed to menopausal levels within 10–14 days. Pretreatment with a GnRHa is essential in in vitro fertilization (IVF) techniques used in reproductive care, where it suppresses spontaneous ovulation as part of a controlled ovarian hyperstimulation procedure to ensure the retrieval of multiple mature oocytes for fertilization. In our previous work, we have used GnRHa as a means of modelling risk mechanisms for depressive symptoms and mood disturbances in healthy women and in healthy women undergoing IVF (Frokjaer et al., 2015; Stenbaek et al., 2016, 2015). For the purpose of this study, such a risk model also provides a unique opportunity to investigate whether fluctuating ovarian hormones affect mood dependent on individual differences in personality trait Neuroticism at baseline.

Here, we evaluate whether trait Neuroticism is a modulator of daily reported mood in 92 mentally healthy premenopausal women undergoing 14 days of pharmacological GnRHa intervention or placebo. We hypothesize that baseline trait Neuroticism will moderate daily mood during GnRHa intervention, but not during placebo. In particular, we expect women with higher trait Neuroticism to exhibit more pronounced mood changes in response to GnRHa intervention.

2. Methods

2.1. Participants and study design

A total of 92 healthy adult women (> 18 years) within an expected reproductive age span (28.3 ± 7.1, mean ± SD) undergoing intervention with GnRHa or placebo were included in the study. Data from the included women was collected as part of two earlier parallel studies run in our laboratory and stored in the Center for Integrated Molecular Brain Imaging database (Knudsen et al., 2016). The 92 women available in the database formed three groups; two groups were formed from 55 women who participated in a randomised, placebo-controlled, double-blind prospective study, where 28 received experimental intervention with GnRHa and 27 received placebo (this study is described in details elsewhere (Frokjaer et al., 2015; Stenbaek et al., 2016)), and one group was formed from 37 women who participated in a randomised prospective IVF study comparing a GnRH agonist with a GnRH antagonist IVF protocol. In the current study we included patients from the arm, where they received GnRHa as part of their IVF protocol (this study is described in details elsewhere (Stenbaek et al., 2015)). Fig. 1 shows a schematic overview of the three groups included in this study and their time course.

In both studies, i.e., in all three groups, we obtained personality and mood measures at baseline and mood measures daily during intervention. For the first study, exclusion criteria were current and previous psychiatric illness, a significant medical history including premenstrual dysphoric disorder (according to DSM-IV criteria for PMDD), alcohol, tobacco, and illegal drug use, and abnormal neurological and gynaecological examination, including ultrasound imaging of the uterus and ovaries. For the second study, exclusion criteria were prior IVF treatment, uterine anomalies, testicular sperm aspiration (TESA) needed for reproductive care, allergy to the ingredients used in the pharmacological treatment, reduced kidney or liver function, women > 40 years of age, prior or current use of antidepressant medication. All women signed an informed consent. The studies were registered and approved by the local ethics committee (protocol ID's: H-2-2010-108 and H-B-2008-109) and were further registered as clinical trials (EudraCT - 2008-005452-24 and NCT - 02661789).

2.2. Intervention

Two of the three groups in the study received active intervention with GnRHa; the first group of 28 healthy women (non-IVF-GnRHa group) received a GnRHa implant (goserelin®, 3.6 mg) as part of an experimental protocol and the second group of 37 healthy women undergoing IVF treatement (IVF-GnRHa group) received nasal GnRHa spray (synarela®, 200 mg. × 3 daily) in a natural cycle during the postovulatory phase to suppress ovarian hormone production. Postovulatory status was confirmed by ultrasound in both groups. The 27 healthy women in the placebo group received a single injection with saline. In the non-IVF-GnRHa group and the placebo group, both women and investigators were blinded to intervention type (GnRHa or placebo), which was randomized between the two groups. In the IVF-GnRHa group women were not blinded to intervention since it was part of their IVF treatment.

2.3. Data collection

Self-reported measures of trait Neuroticism and mood was collected at baseline using the NEO Personality Inventory-Revised (NEO PI-R) (Costa and McCrae, 1992; Skovdahl Hansen et al., 2003) and the Profile of Mood States (POMS) (McNair et al., 1992), respectively. POMS mood reports were further collected on a daily basis during the 14 days intervention. In our analyses, NEO PI-R was included as the independent variable and POMS as the dependent variable. All questionnaires were completed from home through a secured online survey system (https://survey.nru.dk/) (Knudsen et al., 2016).

2.4. Measures

2.4.1. The NEO personality inventory-revised

At baseline all women completed the Danish version (Skovdahl Hansen et al., 2003) of the NEO PI-R (Costa and McCrae, 1992). The NEO PI-R comprises 240 items that measure five major personality traits and for each trait six constitutive sub-facets. To serve the purpose of this study only trait Neuroticism was used. Trait Neuroticism comprises 48 items (e.g. "I am not a worrier" or "I often get angry at the way people treat me") rated on a 5-point Likert scale from 0 (strongly disagree) to 4 (strongly agree).

2.4.2. The profile of mood states

The Profile of Mood States (POMS) is a psychological scale used to rate transient, distinct mood states (McNair et al., 1992). It comprises six factors and a total score of mood disturbance (TMD) rated by 65 adjectives (e.g. "Furious", "Hopeless" and "Carefree") on a 5-point Likert scale from 1 (not at all) to 5 (extremely) based on the recollection

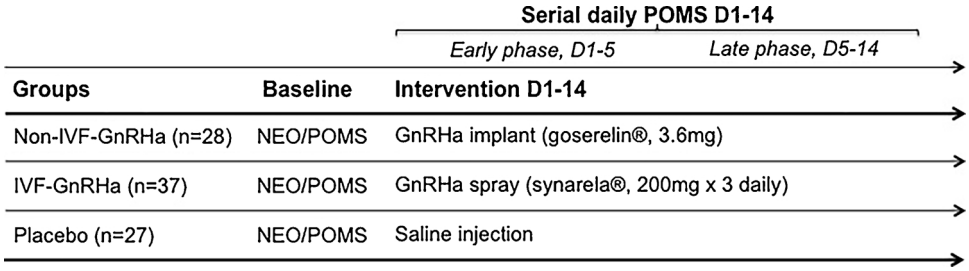

Fig. 1. Schematic overview of the study. GnRHa = gonadotropin-releasing hormone agonist, IVF = in vitro fertilization, NEO PI-R = NEO Personality Inventory-Revised, POMS = Profile of Mood States, D1-14 = day1-14 of intervention, D1–5 = day1–5 of intervention, D5–14 = day5–14 of intervention.

of "the last 24 h".

2.5. Statistics

Group differences in descriptive data were analyzed using ANOVA. Interaction effects between intervention and trait Neuroticism on serial daily reports of TMD for each of the three groups were examined using mixed model analyses.

In a first step, moderation of trait Neuroticism on TMD development over the first 14 days of intervention was modeled for each woman using a piecewise linear model with breakpoint after 5 days which modelled the biphasic hormone response to GnRHa (initial stimulation of HPG-axis 1–5 days and subsequent suppression of HPG-axis 5–14 days). Interaction terms between trait Neuroticism and the temporal covariates were included so that the slopes before and after 5 days were allowed to depend on trait Neuroticism. This model was fitted to data in each of the three groups separately (IVF-GnRHa, non-IVF-GnRHa and placebo), and it was tested whether the slopes for each group were moderated by trait Neuroticism.

In a second step, we then compared the slopes for the three groups in a joint model allowing each of these groups to have its own piecewise linear function describing the moderation of trait Neuroticism on TMD development over the first 14 days of intervention.

Finally, to illustrate interaction effects, in a third step we categorized trait Neuroticism at baseline in three tertiles (low: Neuroticism $< = 73$, moderate Neuroticism: $> 73 < 100$, and high Neuroticism $> = 100$) and re-fitted the first model with this categorized trait Neuroticism (see Fig. 1). From this model we calculated the change in TMD from the estimated slopes of the piecewise linear functions between day 1–5 and day 5–14 across the categorized trait Neuroticism groups: low, moderate and high.

For all models we included a random intercept to model the variation between women. We observed a tendency for more variation in the TMD scores among women reporting higher scores, and therefore re-fitted our models following a modified logarithmic transformation of the TMD scores (log (POMS + 30)). Thus, the reported results are based on the log-transformed data.

All statistical analyses were carried out in SAS version 9.4. The significance level was set at alpha ≤ 0.05 and all reported p-values are uncorrected.

3. Results

3.1. Descriptive data

Descriptive data obtained in the follicular phase for the three groups are shown in Table 1. Differences in age between the three groups were significant. At baseline, women in the IVF-GnRHa group were significantly older than the non-IVF-GnRHa group ($p < 0.001$) and the placebo group ($p < 0.001$). The two latter groups did not differ ($p = 0.53$). The three groups did not differ in trait Neuroticism, TMD at first intervention day or body mass index. Information regarding intervention timing and hormone responses for the non-IVF-GnRHa group and the placebo group has been detailed earlier (Frokjaer et al., 2015).

3.2. Modulation by trait Neuroticism on mood responses to GnRHa or placebo

Results from the first model showed that trait Neuroticism at baseline significantly moderated the development of daily reported TMD (full period of 14 days) during intervention with GnRHa in mentally healthy women (IVF-GnRHa group: $X^2 = 7.57$, df = 2, $p = 0.023$, non-IVF-GnRHa group: $X^2 = 9.96$, df = 2, $p = 0.0069$), but not during placebo intervention ($X^2 = 0.744$, df = 2, $p = 0.69$).

Breaking down the full period of 14 days piecewise, the slopes in the placebo group were close to zero and did not depend on trait Neuroticism neither in the early phase, i.e., 1–5 days ($p = 0.8$) nor in the late phase, i.e., 5–14 days ($p = 0.6$). For women in the IVF-GnRHa group the modulation by trait Neuroticism was significant in the early phase ($p = 0.006$), but not in the late phase ($p = 0.2$), while in the non-IVF-GnRHa group a borderline significant effect of trait Neuroticism was found in the early phase ($p = 0.05$) together with a non-significant effect in the late phase ($p = 0.3$). When we compared the moderation of trait Neuroticism on TMD development across the three groups, we found a significant effect ($p = 0.034$). Post hoc analyses showed that this overall group difference was driven by differences between the two GnRHa groups ($p = 0.004$), while none of the GnRHa groups differed significantly from the placebo group.

For each of the three intervention groups, Fig. 1 illustrates the estimated development of TMD under consideration of baseline trait Neuroticism as categorized in low, moderate and high scores, and Table 2 shows the estimated change in TMD within this matrix. In the placebo group, estimated changes in TMD from day 1–5 and day 5–14 were not significant for any of the trait Neuroticism categories: low, moderate and high. In the IVF-GnRHa group a significant change in TMD (from baseline) was found for low trait Neuroticism ($p = 0.04$) and a borderline significant change for high trait Neuroticism ($p = 0.08$) in the early phase, while no significant changes were observed in the late phase. In the non-IVF-GnRHa group a borderline significant change was found for low trait Neuroticism in the early phase ($p = 0.06$) and a significant change for high trait Neuroticism ($p = 0.004$) in the late phase (Fig. 2).

4. Discussion

In this study we explored whether personality trait Neuroticism modulated daily mood responses to a controlled GnRHa-induced biphasic ovarian hormone fluctuation within and outside an IVF treatment setting or placebo in mentally healthy women. We, for the first time, demonstrated that trait Neuroticism moderated mood responses during 14 days of GnRHa intervention irrespective of concomitant IVF treatment, while it did not moderate mood responses during placebo intervention. In particular, higher and lower scores on trait Neuroticism

Table 1
Descriptive data.

Descriptive variable	Placebo (N = 27)	IVF-GnRHa (N = 37)	Non-IVF-GnRHa (N = 28)	p-value
Age in years	24.4 ± 5.3	34.8 ± 4.4	23.4 ± 3.0	< 0.001
Body Mass Index (kg/m2)	23.3 ± 3.9	25.0 ± 5.6	23.2 ± 3.8	0.3
TMD score	5.0 ± 15.3	9.3 ± 22.3	1.9 ± 17.1	0.3
Trait Neuroticism score	87.2 ± 22.3	84.0 ± 21.1	86.8 ± 21.1	0.8

Notes: Information obtained at baseline with means ± standard deviations and ANOVA p-values of group differences. TMD = total mood disturbance score. GnRHa = gonadotropin-releasing hormone agonist, IVF = in vitro fertilization.

were associated with mood changes during GnRHa intervention, which was not observed for medium Neuroticism scores.

Based on our results, the susceptibility to sex hormone triggered mood reactions depends, at least partially, on women's general tendency to experience distress. High trait Neuroticism indexes the tendency to experience frequent, intense negative emotions and thoughts (Mroczek and Almeida, 2004). It is associated with inadequate coping due to a more intense experience of uncontrollability in response to various stressors (Barlow et al., 2014; Lahey, 2009; Mroczek and Almeida, 2004), which proposedly reflects a magnified perception of threat (Drabant et al., 2011). In support of this latter proposition, we and other labs have previously demonstrated a coupling between higher trait Neuroticism in healthy individuals and increased reactivity of the amygdala to threat-related stimuli (Everaerd et al., 2015) and decreased amygdala functional connectivity to orbitofrontal and prefrontal cortex, suggesting a reduced capacity for cortical top-down control over the amygdala response to threat (Madsen et al., 2016). It is therefore plausible that women in our study with higher trait Neuroticism had more limited capacity for top-down control over GnRHa-induced limbic activation, such as we have previously shown for anterior insula in the GnRHa (non-IVF) cohort (Henningsson et al., 2015), and consequently were more vigilant and alert in response to changes in sex hormones. A heightened state of vigilance and alertness is likely to affect mood, as then reflected by the observed changes in TMD scores.

Interestingly, and contrary to our expectation, women with high trait Neuroticism undergoing GnRHa showed an improvement of mood from day 5–14, which was most prominent in the non-IVF-GnRHa group. Taken together this suggests that GnRHa provokes a mood response that peaks in concert with the intense biologic stimulation of the HPG-axis and not the hypogonadal suppressed state as such. Supporting this, we found an adverse effect on mood of HPG-axis *stimulation* in an earlier independent group of women undergoing IVF treatment with no prior GnRHa treatment (i.e, short protocol), where mood fluctuations were more pronounced during stimulation (Stenbaek et al., 2015). In the current study, we speculate that factors related to IVF treatment could explain the observed difference in mood relaxation between the IVF-GnRHa and non-IVF-GnRHa group. Infertility is a significant stressor (Domar et al., 1993; Lund et al., 2009) and for women undergoing IVF treatment, improvement in mood may not occur until a pregnancy has been achieved at the end of treatment (Verhaak et al., 2005). As such, it should not be surprising that women undergoing GnRHa intervention as part of their IVF protocol did not experience a relaxation of mood in the late phase of GnRHa exposure to the same extent as women undergoing GnRHa experimentally.

No significant mood responses to intervention were observed in the placebo group, while women in this group with higher trait Neuroticism still reported higher levels of mood disturbances on a daily basis, which is consistent with the notion of a general negative impact of trait Neuroticism on mood.

Interestingly, in our study, not only high trait Neuroticism but also low trait Neuroticism was associated with mood changes in response to GnRHa, although in opposite directions for the IVF-GnRHa and non-IVF-GnRHa group. Contrary to commonly held belief that Neuroticism is a maladaptive trait, some authors argue for a more balanced view in which a moderate degree of trait Neuroticism is adaptive and beneficial, and extreme scores in either direction may become maladaptive (Watson and Casillas, 2003). In such a view low trait Neuroticism also marks increased vulnerability to various potential stressors (McCleery and Goodwin, 2001) and emotional maladjustment (Daspe et al., 2013). In support of our present findings, we showed earlier in a partly overlapping cohort that both high and low trait Neuroticism scores at baseline showed a significant trend towards subsequent negative pregnancy test in women undergoing IVF treatment (Stenbaek et al., 2015). We speculate that low trait Neuroticism reflects a combination of lower temperamental reactivity together with mood regulation strategies such as distraction and redirecting attention on external factors away from internal subjective states (Larsen, 2000). This may paradoxically increase negative emotional states due to inefficient coping. However, since very little evidence is available regarding effects of low trait Neuroticism, future studies should elucidate the mechanisms potentially involved in sex hormone-triggered mood dysregulation in individuals with low trait Neuroticism. This could for example be done by studying functional connectivity changes in perinatal women with low trait Neuroticism, elucidating the role of limbic under- or over-reactivity induced by sex hormone changes.

Overall, an individual vulnerability approach based on trait Neuroticism appears to provide a useful framework for understanding

Table 2
Mood changes during intervention.

Group	Trait Neuroticism	Change, day 1-5	95% CI	p-value	Change, day 5-14	95% CI	p-value
Placebo	Low	2.72	−2.92 ; 8.36	0.35	3.73	−2.24 ; 9.70	0.22
Placebo	Medium	−4.39	−11.3 ; 2.49	0.21	−2.05	−8.21 ; 4.10	0.51
Placebo	High	2.22	−8.80 ; 13.24	0.69	0.612	−10.1 ; 11.30	0.91
IVF-GnRHa	Low	−5.25	−10.3 ; -.19	0.04	0.472	−3.70 ; 4.64	0.82
IVF-GnRHa	Medium	1.1	−4.35 ; 6.552	0.69	−0.67	−5.87 ; 4.53	0.8
IVF-GnRHa	High	9.74	−1.19 ; 20.68	0.08	−4.92	−15.9 ; 6.01	0.38
Non-IVF-GnRha	Low	7.46	−.189 ; 15.10	0.06	−1.42	−9.35 ; 6.51	0.73
Non-IVF-GnRha	Medium	−4.33	−11.2 ; 2.54	0.22	3.45	−2.80 ; 9.73	0.28
Non-IVF-GnRha	High	4.85	−6.17 ; 15.87	0.39	−14.7	−24.6 ; -4.74	0.004

Notes: Changes in total mood disturbance scores calculated from the estimated slopes of the piecewise linear functions between day 1–5 and day 5–14 across groups and trait Neuroticism categories: Low, medium and high with p-values and 95% confidence intervals. GnRHa = gonadotropin-releasing hormone agonist, IVF = in vitro fertilization.

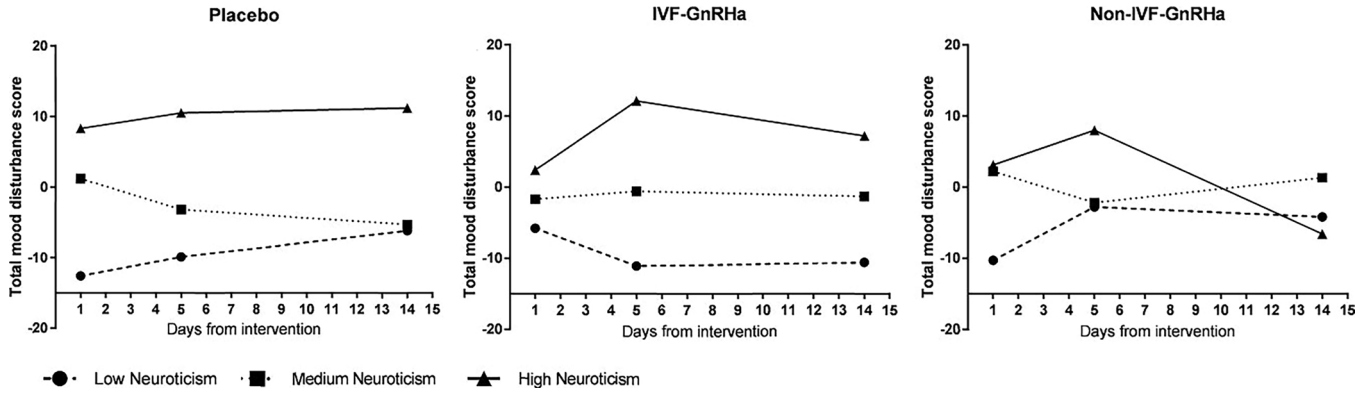

Fig. 2. Illustration of mood development during 14 days of intervention for the three study groups across three categories of trait Neuroticism: Low, medium and high. The numbers of days are shown on the x-axis and total mood disturbances scores are shown on the y-axis. GnRHa = gonadotropin-releasing hormone agonist, IVF = in vitro fertilization.

how psychological and hormonal factors combine to place women at risk for depression. Such a rationale is further supported by longitudinal studies attesting that high trait Neuroticism is associated with increased risk of post-partum depression (Iliadis et al., 2015) and mental health problems during menopausal transition (Rossler et al., 2016). Our studies are, to our knowledge, the first studies to collect serial daily mood measurements from mentally healthy reproductive women while undergoing a controlled ovarian hormone fluctuation. We propose future studies to expand such a design to elucidate phase specific changes and not solely the hypogonadal state per se.

In summary, our findings that personality trait Neuroticism modulates mood responses to GnRHa intervention highlight the importance of considering where women in on the Neuroticism spectrum in relation to hormone-altering treatments or therapies, as well as when approaching problems related to hormonal life-transitions. The ease of administration and the clinical relevance make ratings of trait Neuroticism with NEO PI-R (the instrument is available in both a long and short version) an applicable tool for health care professionals. Future studies are needed to evaluate whether personalized prevention based on information about trait Neuroticism could help support and sustain women's mental health during hormonal transition phases, e.g., IVF treatments.

4.1. Methodological considerations

Strengths of this study include the within-subject design with reliable psychometric instruments covering serial daily reports throughout controlled pharmacological treatment. Our results depend on within subject differences and are therefore likely to be robust to (effects of time constant) confounding variables. However, some potentially important methodological limitations should be mentioned. First, women with current and previous depressive disorders were excluded from our study population. This is likely to have biased our study population, so that we may have missed potential interactive effects of trait Neuroticism and GnRHa-induced hormone fluctuations in more vulnerable populations, i.e., women recovered from depression or with a family history of mood disorders and also women with known hormone-triggered disturbance of mood such as premenstrual symptoms or premenstrual dysphoric disorder. Second, although the NEO PI-R and POMS are considered golden standard for measuring personality and mood in both clinical and research settings, subjective self-report is an inherent part of this methodology. However, evidence support the stability of NEO PI-R over time, and the repeated measure design with daily mood reports adds substantial credibility to the obtained results.

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Conflict of interest

None.

Author contributions

Stenbæk, DS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Writing - original draft, Writing – review & editing

Budtz-Jørgensen, E: Formal analysis, Methodology, Software, Writing – review & editing.

Pinborg A: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Jensen, PS: Data curation, Investigation, Project administration, Software, Writing – review & editing.

Frokjaer, VG: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing - original draft, Writing – review & editing.

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