Pràcticum: Recerca Neurociència Cognitiva

Memòria Projecte Final

Improving Affective Symptomatology and Hormonal Alterations with Mindfulness and Acceptance VR-program

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Recerca Neurociència Cognitiva i Tecnologies de la Informació

Universitat Oberta de Catalunya

Title

Improving Affective Symptomatology and Hormonal Alterations with Mindfulness and Acceptance VR-program

Acronym

IASHAMA-VR

Abstract

This project aims to contribute more evidence to understand the bidirectionality between the nervous and endocrine systems and the potential of this knowledge to improve the treatment of psychoneuroendocrine disorders in women more effectively. Specifically, this research proposal aims to assess whether there is a significant correlation between the incidence and prevalence of depressive and anxiety disorders in women of menstrual age and alterations in the neuroendocrine system.

First of all, it will be observed if there is comorbidity between the symptomatological expression in these disorders and alterations at the hormonal and neuroendocrine level and the differences between men and women. Second, it is intended to analyse whether there is bidirectionality between the psychoemotional state and the neuroendocrine state so that hormonal alterations and changes in the HPA axis are modulated through psychological treatment. To do this, psychometric tests will be used to measure anxious (STAI) and depressive (HDRS) symptomatology, as well as the coping strategies used (CRI-A) and stress reactivity (IRE-32) in situations perceived as stressful; and tests to assess the status of the HPA axis (MRI) and the existence of hormonal changes (hormonal analyses).

To evaluate the effectiveness of the psychological treatment, a design composed of two experimental groups and a control group will be carried out, where one group will receive a treatment based on VR-Mindfulness and the other a therapy based on Cognitive Behavioral Therapy. The control group will not receive any treatment. With these results and evaluating the bidirectionality between both systems, it is intended to know the effectiveness of a Mindfulness-based Virtual Reality program for the clinical improvement of both disorders compared to CBT, which has already shown its efficacy in previous studies.

Key words

psychoneuroendocrinology, anxiety, depression, coping strategies, HPA axis.

Abstract for a non-specialized public

In recent decades, a higher incidence of anxiety and depression disorders has been observed in women than in men. This may be due to various reasons, such as the masculinisation of science, where diagnoses and treatments have been designed in a general and historical way based on the male gender, without taking gender differences into account. The bibliography has shown a correlation between the hormonal state and the psychoaffective state in recent years, as shown in more detail in the following sections. This research proposal aims to test the hypothesis that there is a significant correlation between these mental disorders and hormonal changes in women of menstrual age. If its existence is proven, it is intended to assess whether this correlation is explained with bidirectionality that would allow modulation and prevent endocrine alterations through psychological treatment, that is, if a healthy psycho-emotional state could be a preventive factor of altered hormonal states.

For these purposes, the research will be divided into two major stages, the first aimed at observing whether there are significant differences between men and women regarding the relationship between endocrine status and psycho-emotional status; the second aimed at evaluating the efficacy of a treatment based on VR and another based on CBT to improve the symptoms in both disorders and, being so, to observe what repercussion occurs in the evaluations of the HPA axis and the hormonal alterations in case of existing.

In detail, the research design will be carried out for a treatment of 18 months. In each of the experimental groups, a different therapeutic program will be used to evaluate the effectiveness of each one for the clinical improvement of each disorder and a control group that will not receive any specific treatment by the research. However, their status and related actions will be monitored throughout the treatment. This project collaborates with Amelia Virtual Care, a company that provides a Virtual Reality tool designed for psychological treatment. From this, virtual environments of psychoeducation and Mindfulness will be used as a support tool for the clinical therapist. This research is expected to improve knowledge in psychoneuroendocrinology and test this new perspective of treatment for working with patients with anxiety and depression through Mindfulness and psychoeducation.

Background

Context

Affective diseases, such as depression and anxiety disorders, are the most common in current societies. Moreover, women show twice the lifetime rates of most of these disorders (Kessler, 2005). For example, depression is more frequent in women in a proportion of 5 to 1 after twelve years (del Barrio, 2017), and according to some epidemiological studies about anxiety disorders, 66% of diagnosed patients are women (APA, 2013). Third generation CBT, such as Mindfulness-based programs (i.e. Goldberg et al., 2019; Ghahari et al., 2020) and psychoeducation techniques (Donker et al., 2009), have been demonstrated to improve anxiety and depression symptoms. On the other hand, women are very different in their endocrine system, and their hormonal changes are more frequent and complex than those of men.

Most medical and mental illnesses have been studied from the male anatomy throughout history. However, a wide range of sexual differentiation, such as sexual behaviour, physiology, the endocrine system and neurophysiology (Redolar, 2009), affect the diagnosis and treatment of different medical and clinical disorders. The woman has a more complex organism than the man; she is designed to create life, so her endocrine system is more activated. For more than six decades, it has been known that both corticotropin-releasing hormone (CRH) and the hypothalamic-pituitary-adrenal (HPA) axis are involved in some psychiatric disorders. Recently reviews and studies (e.g. Naughton et al., 2014; Hogervorst et al., 2009; Hsu et al., 2021) have provided evidence in a wide range of areas about the interaction between hormonal and psychological states, such as dementia, cognitive function or PTSD. The psychological and hormonal disorders in women could be more related than professionals take into account in their offices. The disease continues to be addressed by maintaining disciplinary divisions in treating mental disorders, and non-psychological variables are not considered to understand and treat the condition.

Conceptual framework

a. Psychoneuroendocrinology

Psychoneuroendocrinology is a construction minted in science for more than 70 years ago. Its object of study is the inextricable structural and functional relationships between the neuroendocrine system and the central nervous system and the behaviours in continuous interaction (Reus, 1989; Fava, 1994). This project aims to take a further step towards transdisciplinarity in health.

b. Sex differences in anxiety and depression disorders.

As we have mentioned, there is a higher prevalence of anxiety in women than in men; for

example, 6.6% vs 3.6% in generalized anxiety disorder (APA, 2013). It has been seen that the increased risk of anxiety disorders in girls begins in middle childhood (Lewinsohn et al., 1998, as cited in Altemus et al., 2014), and the sex differences emerge in mid-adolescence (Beesdo et al., 2009). On the other hand, the majority of treatment for this disease is pharmacological treatment, which has efficacy limitations and side effects (Dilbaz et al., 2011).

In contrast to anxiety disorders, depression has an increased prevalence in girls beginning in mid-puberty (Lewinsohn et al., 1998, as cited in Altemus et al., 2014), coinciding with the data provided by del Barrio (2017), which indicates a difference in the prevalence of 5 against 1 from the age of twelve. It has been seen that psychological and pharmacological treatments show the same efficacy immediately after treatment ends. However, there are suggestions of greater longitudinal effectiveness in psychological than pharmacological treatment after discontinuation of treatment (Barlow et al., 2016).

c. Hormones, depression and anxiety

Depressive symptomatology has been related to different hormonal alterations. It has been seen that the autonomic symptoms observed in major depression are probably conditioned by prolonged orexin signalling (Lutter et al., 2008), a neuropeptide hormone related to wakefulness and sleep. Also, some studies claim that menopausal changes predispose women to a higher risk of depression (Weber et al., 2014; Balzer et al., 2015; Whedon et al., 2017 Morssinkhof et al., 2020; Padda et al., 2021). Because of this relationship between menopause and mood disorders, novel treatments for anxiety and depression in menopausal women are being investigated using ERβ-targeted therapies; beta estrogen receptors (Vargas et al., 2016). There are several hormones related to depression. In addition, their action can be simultaneous and linked according to different interoceptive conditions; (for example, in depressive states, excessive levels of the corticotropin-releasing hormone have been observed, acting in an inhibitory manner on the hypothalamic-pituitary-gonadal (HPG) axis and increasing cortisol levels; these changes, in turn, imply others at the neural and hormonal. On the other hand, there is a wide variety of literature that has reviewed anxiety sensitivity related to the menstrual cycle, as well as the regulatory effects of progesterone, estradiol, and other sexual hormones (Nillni et al., 2011; Tang & Graham, 2020; Maqbool et al., 2021) and the impact of altered emotional states, such as anxiety and depression, on menstrual periods has been observed, showing other somatic symptoms in women who suffer from them (Maqbool et al., 2021). On the other hand, Maeng and Milad (2015) concluded in their study that the high risk of anxiety may depend on fluctuations in estrogen levels rather than on their absolute levels. This data is very interesting for future research where it will be necessary to pay special attention to these fluctuations concerning anxiety and depression. Finally, given the bidirectionality of the neuroendocrine system with emotional states, studies have been carried out (e.g., Gabb et al., 2006) where the efficacy of psychological techniques such as cognitive behavioral stress management has been

observed not only to reduce psychological and somatic symptoms but also to improve hormonal regulation, for example in the cortisol response.

d. Hypothalamic–pituitary–adrenal axis

The hypothalamic-pituitary-adrenal axis is a subsystem of the neuroendocrine system formed by a complex set of interactions between the hypothalamus and the pituitary and adrenal glands. For more than five decades, the relationship of the HPA axis with a variety of psychiatric illnesses has been studied. Thanks to the extensive literature, stress could be an integral component of various psychiatric conditions, including depression and anxiety. Various studies explained that stress could play an essential role in the etiology of these mental disorders (Naughton et al., 2014), altering different brain regions and neural networks (Magalhães et al., 2017). It is known that the activity of the HPA axis is influenced by stressful stimuli (Jaferi & Bhatnagar, 2007; Jaferi & Bhatnagar, 2007), which explains the function of this system to respond to perceived threats. In many cases, these only come from the individual's perception, which defines a poor regulation and management of stress with its subsequent hyper-response of cortisol. Different studies have suggested that pituitary volume can serve as an indicator of some psychiatric disorders; for example, it is suggested that anxiety could reduce pituitary volume (Gapp, 2022). In this document, we will not go into much detail about the functioning of the HPA axis since an entire article would be necessary for this task. However, it is worth mentioning that different cortical and limbic regions are involved in processing cognitive information relevant to coping with stress, such as the medial prefrontal cortex (mPFC), which plays an important role in modulating processes behavior related to stress (Jaferi & Bhatnagar, 2007). Different tests have suggested that this region is responsible for regulating HPA responses induced by stress and have observed the relationship of the activity of this axis with behaviors related to anxiety (Jaferi & Bhatnagar, 2007).

e. VR Mindfulness-based treatment

Finally, we must dedicate a few lines to describe the benefits observed in the extensive literature about the benefits of Mindfulness and its application through virtual reality. For example, Modrego et al. (2021) has shown the efficacy of treatment based on Mindfulness and self-compassion to reduce stress in Exam Anxiety conditions, showing increases in adherence to treatment when applied through VR. More recent studies (Arpaia et al., 2022) support the potential of VR-MBT for anxiety and depression. However, they highlight the need for future research that provides evidence that validates this technique in specific conditions.

General aims

1. The general long-term aim is to identify the bidirectional influence of the psychological and affective state on some endocrine system alterations in women to promote research in this direction.

2. The general short-term aim is to determine the effectiveness of the psychological treatment to improve anxiety and depression symptomatology and hormonal alterations in women of menstrual age.

Specific aims

1. To investigate the relationship between affective symptomatology, coping strategies and hormonal alterations in women of menstrual age.

Psychological variables will be assessed by HDRS (Ramos-Brieva and Cordero, 1988), STAI (Spielberger et al., 1982), CRI-Adult (Moos, 2010) and IRE-32 (Gonzalez de Ribera, 1990). In addition, neuroendocrine alterations will be evaluated by hormonal analyses and the MRI technique.

2. Determine the effectiveness of the VR-Mindunfulness based program to improve behavorial and emotional state with respect to traditional psychotherapy and a control group.

Coping strategies and stress responses will be measured by CRI-Adult (Moos, 2010) and IRE-32 (Gonzalez de Ribera, 1990), respectively.

3. Determine the effectiveness of the VR-Mindunfulness based program to reduce anxiety and depressive symptomatology.

Anxiety and depression symptomatology will be measured by STAI (Spielberger et al., 1982) and HDRS (Ramos-Brieva and Cordero, 1988), respectively.

4. Determine the effectiveness of both psychological therapies to repair the HPA axis and regulate hormonal alterations in cases of damage.

The HPA axis state will be measured by MRI and the hormonal state with hormonal analyses.

Hypothesis

Related to the short-term general aim

1. We hypothesise that the VRMindfulness-psychoeducation based program can improve the homeostasis of participants better than traditional psychologic treatments.

Related to the specific aims

1. We hypothesise that anxious and depressive symptomatology, coping strategies and stress response are more associated with hormonal alterations in women of menstrual age than in men.

2. We hypothesise that VR-Mindfulness treatment will be more effective than traditional psychotherapy in improving coping strategies and stress responses.

3. We hypothesise that VR-Mindfulness treatment will be more effective than traditional psychotherapy in reducing anxiety and depression symptomatology.

4. We hypothesise that psychological VRM treatment can promote homeostasis and HPA recovery and that we will find correlations between the HPA axis state and the psychological variables measured in the baseline.

Methods and materials

1. Study design

This project is designed in two different phases. First, related to Objective 1, is a transversal design to investigate and compare hormonal alterations between men and women, with affective symptomatology related to depression and anxiety. We will compare the correlation in these variables between women and men. Second, related to the rest of the objectives is based on a longitudinal repeated measures design with two treatment groups and one control group. We will analyse if a VRMindfulness-psychoeducation based program can improve the homeostasis of participants better than traditional psychologic treatments.

All the participants will be recruited from the Public Health Service of Catalonia and all recruited candidates will receive a study information sheet to obtain informed consent (*see **Annex 1***).

2. Inclusion and exclusion criteria

The participants will be females and males (males just for aim 1) from 18 to 45 years old. They all present anxious or depressive symptomatology (measured with HDSR and STAI) and declare the same symptomatology for more than two months. All of them will come from the Public Health Service of the Barcelona Health Region. In addition, they will understand and speak Catalan, Spanish or English. Candidates with psychopharmacological treatment who have previous experience in VR for therapy and meditation and a history of abuse of alcohol and narcotic substances will be discarded. Also, we will discard participants who are

doing some hormonal treatment and women who are pregnant.

3. Sample

Objective 1: We will collect a sample of 500 people (250 women and 250 men) who will do psychometric tests and we will 300 who meet the inclusion criteria. A random distribution will be made into two equivalent groups taking into account age and HDRS and STAI scores. *women_group (150); men group (150)*

Objectives 2 to 4: We will carry out a randomized distribution with the group of women mentioned in the Objective 1 sample. Also, we will apply a randomized distribution to divide the sample into three equivalent groups considering the same criteria of the previous distribution. *women_group: 150 → VR_group (50); PSY_group (50) and C_group (50)*

4. Instruments and techniques

4.1. Phase 1

Obj.1 The first step for this objective is to evaluate all the candidates in their affective symptomatology. For this, the HDRS (Ramos-Brieva and Cordero, 1988) and the STAI (Spielberger et al., 1982) will be administered. The next step is to select the sample that meets the inclusion and exclusion criteria related to psychometric scores (*see **Annex 2***). Once selected, psychometric tests will also be administered to evaluate coping strategies (CRI-A, Moos, 2010) and the usual cognitive, emotional, vegetative and behavioral responses to stressful situations (IRE-32; Gonzalez de Ribera, 1990), in addition to hormonal analysis and magnetic resonance evaluation to determine the values of hormones associated with the emotional state, such as; estrogens, progesterone, cortisol, and thyroid or HPA alterations, such as hippocampal and pituitary volume (Colla, 2007). The duration of this phase is 4 months approximately.

4.2. Phase 2

In this phase of the project, we will randomly distribute the women's sample into three equivalent groups described in the Sample section to determine the efficacy of VRM and psychoeducation-based program in improving psychological and neuroendocrine variables.

4.2.1. Intervention

Psychoeducation based program (VR_group and PSY_group)

This project collaborates with Amelia Virtual Care, a company that provides a VR tool for treatment, including hardware and software. This program is distributed in different stages, as described below;

1) Depression and Anxiety Psychoeducation

The first technique in the treatment programs (VR and non-VR) is Psychoeducation. There is consense the efficacy of this technique and relaxation intervention in reducing stress and diminishing depressive and anxiety symptomatology (Daele et al., 2012; Shah et al, 2014). The first month of the treatment (month 5), both groups will start one day per week of Psychoeducation and Relaxation sessions. In the six first Psychoeducation sessions, the clinician and patient will work around Depression and anxiety diseases, including topics such as Coping strategies and Stress and their influence on emotional behavior. After each session clinician will carry out a relaxation exercise different for each group.

2) Relaxation exercises

- VR_group: At the end of each Psychoeducation session, participants of this group will join a 15' intervention on Relaxation' VR-environment named Progressive muscle relaxation (Amelia Virtual Care, 2022)
- PSY_group: Ending each Psychoeducation session, participants will join a 15' intervention on Jacobson Progressive Relaxation technique.

3) VR-Mindfulness Psychoeducation (only VR_group)

As of the seventh session of psychoeducation, the topics of the sessions will be Virtual Reality for treatment and its use and effectiveness through mindfulness. The duration of this stage is three weeks. At the end of each session, participants will join the VR-relaxation intervention again. In these sessions, clinicians will explain the three VR environments (Amelia Virtual Care, 2022) described below that they will use.

- Attentional focus: This environment is directed to practice mindfulness and acceptance exercises as a walk through a peaceful meadow (duration: 15 min)
- Emotional regulation: This environment contains two interconnected scenarios directed to practice mindfulness exercises focused on emotions (duration: 22 min)
- Deep roots: This environment is focused on deeper meditation exercises.

4) VR-Mindfulness treatment (VR_group)

Participants will start this stage of treatment for 14 months in the seventh month. The roadmap is described below:

a) Starting with focused attention (months 7 to 10)

The sessions of these three months will be distributed in 10 min talking, one session in the Attentional focus environment with eyes open (15min), 5 minutes of feedback and 15 minutes of VR-Relaxation on Progressive muscle relaxation environment.

b) Integrating emotional regulation (months 11 to 15)

In the next five months, the session will be distributed in 10 min talking, 1 session in the Emotional Regulation Environment (22 minutes) with eyes open (on this part of the program, patients will be able to choose open eyes or closed eyes meditation), 5 minutes of feedback and 10 minutes on Imagery for relaxation environment of VR-Relaxation.

c) Into a deep meditation state (months 16 to 20)

The differences in this stage are that patients will be able to choose the VR environment and all the Mindfulness sessions and all the Mindfulness tasks will have to be done with the eyes closed, for at least three-quarters of the session.

5) Cognitive Behavioral Therapy with Psychoeducation (PSY_group)

Participants of the PSY_group will receive 15-months Cognitive-Behavioral intervention that will include techniques such as Cognitive Restructuring, Stress inoculation, Self-instruction and Problem-solving training and Autocontrol techniques. At the end of all sessions, they will do 15 min of relaxation exercises such as Jacobson's technique and Deep breathing.

6) Control group

The C_group following will be carried out through family doctors in Primary Attention Centers a minimum of two times per month for sixteen months (from month 5 to 20). The research will guide no specific intervention in this group. It is a controlled follow-up of the participant,

including collecting data on the start of psychological or pharmacological treatment, the patient's condition and the evaluation tests foreseen in the project.

4.2.2. Assessment

4.2.2.1. The psychological assessment will be carried out every two months. We will use scores of tests applied in month four as a baseline. After, we will administrate the psychometric tests every two months, distributed in HDRS or STAI first week, IRE-32 second week and CRI-A in the third week during the treatment program. We will use the assessment on the 20th month as a posttest. After that, A follow-up control will be carried out three months later to evaluate the effect of the treatment.

a) Hamilton Depression Rating Scale (HDRS; Ramos-Brieva and Cordero, 1988): It is a 17-items scale directed to assess the severity of symptoms quantitatively and assess changes in the depressed patient.
b) State-Trait Anxiety Inventory (STAI; Spielberger et al., 1982): This inventory can be used in clinical settings to diagnose anxiety and distinguish symptoms related to a temporary state or those related to personality traits. In addition, it helps distinguish anxiety from depressive syndromes.
c) Stress Reactivity Scale (IRE-32; Gonzalez de Ribera, 1990): The test consists of a brief introduction in which reactivity to stress is conceptualized, followed by a list of the 32 most common reaction patterns. The participant will have to read and choose those closest to their usual behaviours. They will also be able to modify or add something if needed.
d) Adult Coping Responses Inventory (CRI-A; Moos, 2010): This inventory assesses the coping strategies on eight scales (such as Logical analysis, Positive reevaluation, Problem-solving, etc.), and it is divided into two parts.

4.2.2.2. Neuroendocrine assessment

Hormonal analyzes and magnetic resonance neuroimaging techniques will be performed to evaluate hormonal alterations and visible alterations in the HPA axis, respectively. These tests will be administered three times during the program. The first on the fourth month of the research project (Phase 1) will be used as the baseline and subsequently, the tests will be applied in the thirteenth and twentieth months.

a) Hormonal analyses: Based on the studies reviewed, hormonal values will be analysed three times during the project (months 4, 13 and 20). This is a complete hormonal analysis that includes orexin (Lutter et al., 2008), estrogen (Vargas et al., 2016; Maeng and Milad, 2015), cortisol, progesterone and estradiol (Nillni et al., 2011; Tang & Graham, 2020; Maqbool et al., 2021).

b) MRI technique: It will be applied this technique focused on the HPA axis to analyze the volume and alterations of regions such as the pituitary gland and hypothalamus.

4.3. Phase 3 Follow up

A follow-up will be carried out 3 and 6 months after the end of the treatment. The psychometric tests, the hormonal analyses, and the MRI will be administered in both sessions.

4.4. Phase 4 Data analysis

In order to analyse the correlation between psychological scores (STAI or HDRS, IRE-32, and CRI-A) and neuroendocrine values we will use Pearson/Spearman statistics. To analyse the effect of treatment in psychological and neuroendocrine assessments we will use Linial regression. Finally, we will apply ANOVA to evaluate and compare the differences between groups.

We hypothesise that VR_group and PSY_group will improve psychological scores better than the control group. Also, we hypothesise that there is a significant positive relationship between psychological variables and neuroendocrine state (related to hormones and HPA analised). Better scores on psychometric tests are related to better scores on hormonal analyses and MRI results.

5. Materials

The material used in the project will be composed of:

A) Psychometric tests and licenses to assess anxiety (STAI) and depression (HDRS) symptomatology, and coping strategies (CRI-A) and stress reactivity (IRE-32);

B) Agreements with Quirón Salud to perform an MRI evaluation and hormonal analyses;

C) Pico Samsung VR, eSense biofeedback sensor and Amelia Virtual Care license for the VR_group.

D) Computers with SPSS and JASP for the analysis of the study data.

Human resources: Four clinician therapists and two PhD fellows in Neuropsychology.

Justification of the team of researchers and institutions involved

The team of researchers and the personnel for the treatments will be made up of:

- Two PhD fellows in Neuropsychology with wide experience in MRI and DATA analyses.
- Four clinician therapists to carry out psychological interventions. Two with experience in VRT and two experts in CB treatment.
- Two Master in Cognitive Neuroscience students to perform assistant tasks such as psychometric tests administration and correction.
- Two PhD in Neurosciences with experience in DATA analysis will carry out the organisation, control, and monitor the research.

Institutions involved:

- The Public Health Service of the Barcelona Health Region collaborates with us to collect the pre-sample and monitor and transfer the information of the participants of the control group who participate in the research and who attend the Primary Care Centers for this purpose.
- This project collaborates with Amelia Virtual Care company, which provides us with the software, hardware and license to apply VR based treatment through their platform. Also, they offer us a formation to apply VRT based on their experience. The collaboration contract includes the transfer of data results and the recognition of the use of their platform in the final paper.

Project impact

This project aims to examine our body's capacity to regulate neuroendocrine alterations through psychoemotional and behavioural regulation, for this will use a Mindfulness and Psychoeducation VR-based program. We consider that this study shows a potential impact on scientific, clinical, social and technological levels.

First, there is little literature on this topic, this study will provide new data on the influence of emotional behaviour on neuroendocrine disorders, favouring its study in future research on these or other mental disorders.

Second, this study will compare the efficacy of CBT-based treatment and third-generation CBT-based treatment with VR for anxiety and depression disorders. If the null hypothesis is rejected, this research will provide conclusions for clinicians seeking treatment alternatives for these disorders, for example, with patients with low treatment adherence. In addition, we intend to bring health professionals closer to more integrative treatments that take into account the influences of the different systems on the symptom.

Finally, we hope that the results are encouraging and that they promote the application of techniques that promote health and do not require professionals for their use. Some of the techniques used, such as mindfulness and relaxation, can be self-applied without the need for professionals. In this way, it is intended to give more power and control to the population over their health. At a technological level, we are still on the path of validating or ruling out VR as a treatment support tool since its use could improve treatments in remote contexts.

Identifying risks and contingency plan

Lack of adherence to the research

In this longitudinal investigation, most participants will have to participate weekly for 18 months. There is a risk that some participants will drop out of the research. Participation through psychological treatment must be a reinforcing condition for the two experimental groups. However, a quarterly interview will be held to evaluate the individual process of each participant in the research to resolve doubts or provide support in what can be addressed. For the control group participants, the procedure will be the same, understanding the decisions they want to make regarding improving their psycho-emotional and emotional states.

Lack of control of extraneous variables that influence the neuroendocrine and psychoemotional state.

Several factors can influence the hormonal and neuroendocrine state, such as the menstrual cycle and psycho-emotional state, eating and sleeping habits, drug and narcotic use, etc. Measurements of these variables are not performed. However, the variation in these extraneous variables is expected to be controlled by the random distribution.

Differences in the course and treatment of both disorders.

The non-specificity in the clinical object of the investigation can be a problem when obtaining the results and drawing conclusions. Each sample disturbs a different course and symptoms,

and the treatment used for both follows the same pattern in both groups. However, it is known that the treatments applied usually show efficacy, but there is still a lack of specificity in this regard.

Ethical implications

This research will be carried out in compliance with the Research Ethics Standards not to violate any code of good practice of the Higher Council for Scientific Research (CSIC) and the regulations of the Department of Health of the Generalitat of Catalonia.

In this way, before the participants sign the informed consent (*see **Annex 1***), we will inform them about the study's objectives and the techniques applied to achieve them.

The participants will know that they will be divided into three groups and the treatment applied in each one. They will also know that one of the groups will not receive treatment, and there will be no blinding in this case.

On the other hand, Organic Law 15/1999 on the Protection of Personal Data is respected, which guarantees the anonymity of the participants and the principle of confidentiality.

Finally, the research ethics committee will review the conditions and the informed consent before approving the study.

Calendar

This longitudinal study is designed to last 28 months. The schedule for the different tasks and phases is specified below:

Phase 1 (Aim 1)

Months 1 and 2: Candidates recruitment (maximum 500 that meet the inclusion criteria)

Month 2: Administration HDRS and STAI tests.

Month 3: Selection of 300 participants who meet scores from inclusion criteria) and distribution in two groups.

Month 4: Administration of psychometric tests (HDRS, STAI, IRE-32 and CRI-A), MRI neuroimaging and hormonal analyses.

Month 4: Data analyses

Phase 2 (Aims 2 to 4)

Month 5, first week: Random distribution to three equivalent groups of women.

Months 5 and 6 (six weeks in both experimental groups): Depression and Anxiety Psychoeducation and Relaxation exercises.

Month 6 and 7 (three weeks in VR_group): Psychoeducation about VR and Mindfulness and Relaxation exercises)

Months 7 to 20 (15 months): Once per week CBT based treatment for PSY_group.

Month 8 to 20 (14 months): Once per week VR-Mindfulness based treatment for VR_group.

- *Months 8 to 11:* Treatment directed on VR-focused attention.
- *Months 12 to 16:* Treatment directed on VR-emotional regulation.
- *Months 17 to 20:* Treatment directed on VR-deep meditation.

Months 5 to 20: Follow-up C_group in Primary Care Center (two times per month).

Assessments

Psychometric tests every two months in all groups even months from 6 to 20.

- STAI and/or HDRS on the first week; IRE-32 on the second week and CRI-A on the third week.

MRI and hormonal analyses will be applied in months 4, 13 and 20.

Phase 3 (aims 2 to 4)

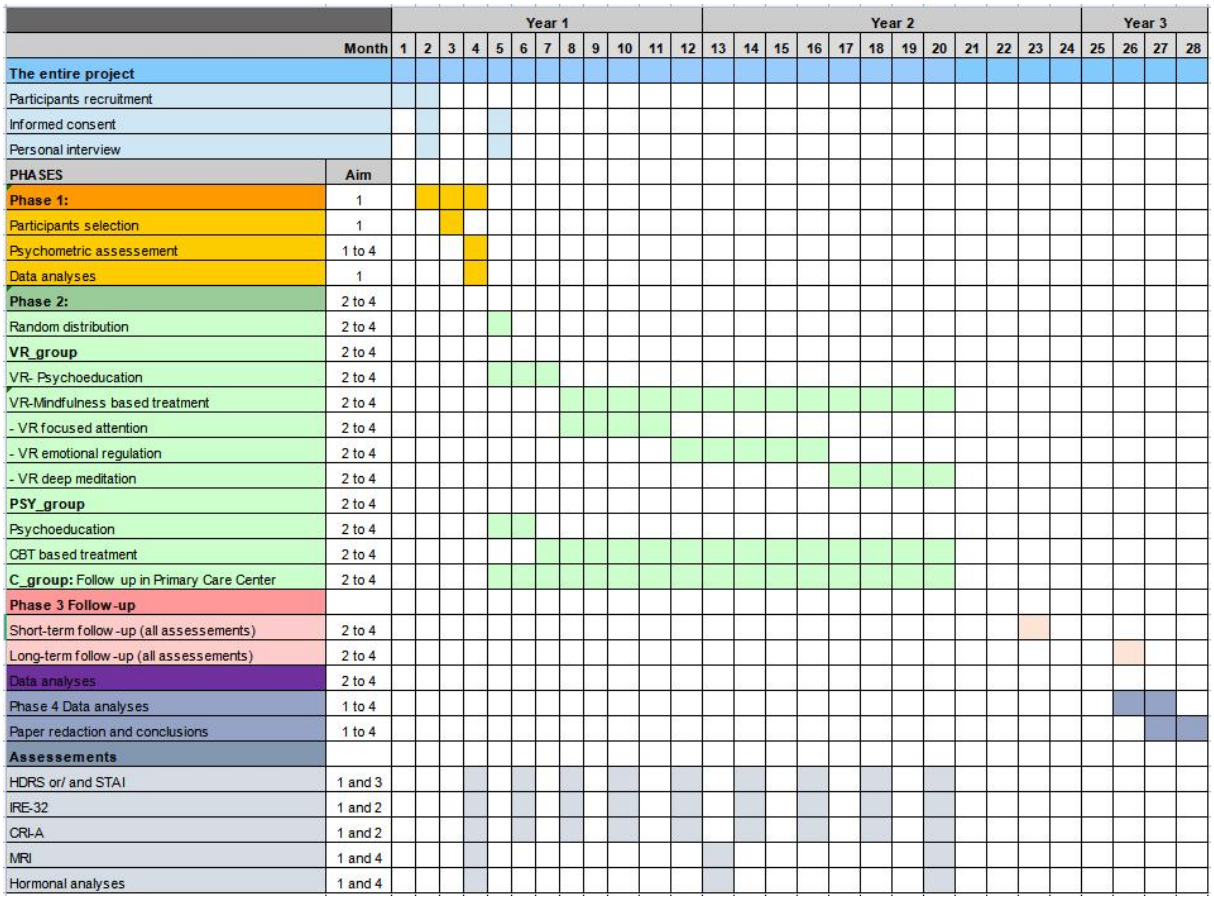
Month 23 and 26: Follow up to assess short-term and long-term efficacy, respectively.

Phase 4

Months 26 and 27: Data analyses.

Months 27 and 28: Paper redaction and conclusions.

Gantt diagram



Budget

Service	Price per sesion	N sessions	N participants or gropus	Total
Psychometric assessment				
STAI	35,55	1		35,55
HDRS	0	1		0
CRI-A	88,56	1		88,56
IRE-32	0	1		0
VR kit				
Pico Sasung VR	0	-	2	0
eSense biofeedback sensor	0	-	2	0
Amelia Virtual Care license	0	-	2	0
Informatics				
Asus ZenBook 14 UX435EAL-KC096T i7-1165G7 16GB 512GB SSD 14"	1199	-	2	2398
JASP	0	-	2	0
SPSS	145	1	2	290
Human resources				
Clinician therapist	1908	15	4	114480
PhD	2064	28	2	115584
MRI	100	3	150	45000
Hormonal analyses	62	3	150	27900
			Total	**305776,11**

VR kit
There is no cost for the hardware provided by Amelia Virtual Care nor for the software, and a collaboration contract has been agreed upon.
Informatics
SPSS purchased from supplier StudentDiscounts.com for12 months.
Human resources:
The budget of the human team based on the planned work time.

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Annexes

Annex 1: Informed consent

INFORMED CONSENT SHEET FOR THE IASHAMA-VR STUDY

INTRODUCTION

We are writing to inform you about a research study you are invited to participate in.
Please read the following information to make sure you fully understand the objectives of this study and sign it if you agree to participate in it.
In summary, this study aims to analyse the correlation between depressive disorder and anxiety disorder with hormonal alterations in women of menstrual age.

PROCESS

This study requires weekly availability for 20 months and two weeks after completion at 3 and 6 months. In addition to meeting the following requirements:
Inclusive criteria:
- Be between 18 and 45 years old.
- Show symptomatology in anxiety or depression measured with HDRS or STAI for more than two months.
- Understand and speak Spanish, Catalan or English.

Exclusive criteria:
- Receive psychopharmacological treatment.
- Have received mindfulness-based treatment.
- Having received treatment based on Virtual Reality.
- Show comorbidity with another psychopathology.
- Have a history of consumption and abuse of alcohol and/or narcotic substances.
- Receiving hormonal treatment.
- Be receiving psychological treatment.
- Be pregnant.

This study will include 300 participants divided into two non-equivalent groups (women and men). In the following phases, only the 150 women divided into three groups will follow, two of them will receive two different psychological treatments, and the third will not receive any treatment. Still, it will receive monthly monitoring at its Primary Care Center.
Specific non-invasive tests will be carried out to assess levels of anxiety and depression, as well as coping strategies used and reactivity to stress. On the other hand, hormonal analyzes and Magnetic Resonance tests will be performed, both on three occasions.
These will assess the hormonal and neuroendocrine status, precisely the HPA axis.
Do not continue and request information if you have not received such information.

GENERAL RISKS

Risks and possible complications of MRI include Problems with metallic implants or undetected foreign bodies. Reaction, such as headaches, chills, and vomiting, to the sedative or anaesthesia. Allergic responses include hives, itching, or wheezing from the contrast dye.

The different psychometric tests do not produce any adverse effects by themselves.

The different treatments themselves do not produce any adverse side effects. However, one of the treatments will use Virtual Reality, which can cause side effects, such as eyestrain, dizziness or fatigue. However, these effects are temporary and are reduced depending on the time of exposure to the virtual environment.

Suppose an unexpected situation or complication arises during the study that requires a procedure other than those provided. In that case, I request and authorize the scientific team to carry out whatever it deems necessary or convenient, including my transfer to a hospital centre.

VOLUNTARY PARTICIPATION

Your participation in the study is entirely voluntary, so there is no penalty for your non-participation.

BENEFITS

The treatment is expected to produce some psychoemotional improvement in you. If so, it could also have benefits for other people with anxiety or depression. However, you cannot be sure until you get the results at the end of it.

EXPENSES

All expenses will be fully assumed by the parties involved in the study.

RIGHT TO WITHDRAW

You have the right to withdraw from the study at any time, and you only have to notify the person responsible for it.

CONFIDENTIALITY

All data will be treated confidentially and processed by current regulations on the protection of personal data (Organic Law 3/2018, Protection of Personal Data and Guarantee of Digital Rights, and Regulation [EU] 2016/679 of the European Parliament and the Council, regarding the protection of natural persons concerning the processing of personal data and the free circulation of these data).

The data collected for the study will be identified by a code so that it does not include information that can identify you, and only your study doctor/collaborators will be able to relate said data to you and your medical history. Therefore, your identity will not be revealed to anyone except for exceptions in case of a medical emergency or legal requirement. The

treatment, communication and transfer of personal data of all participants will comply with the provisions of the law.
Access to your identified personal information will be restricted to the study doctor/collaborators, health authorities, the Research Ethics Committee and personnel authorized by the sponsor (study monitors, auditors) when required to verify the data and procedures of the study, but always maintaining their confidentiality by current legislation.
The data will be collected in a research file under the institution's responsibility and will be processed within the framework of its participation in this study.
In accordance with the provisions of the data protection legislation, you can exercise the rights of access, modification, opposition and cancellation of data, for which you should contact your study doctor.
If you decide to withdraw your consent to participate in this study, no new data will be added to the database, but those that have already been collected will be used.
The coded data can be transmitted to third parties, but in no case will they contain information that can directly identify you, such as name and surname, initials, medical record number, etc.

If this assignment occurs, it will be for the same purposes of the study described or used in scientific publications but always maintaining their confidentiality by current legislation.

IN CASE OF DOUBT
If you have any questions, consult with Dr…....., from the Service.....… with a telephone number…....., he is responsible for this research and will answer any questions you may have related to this study.
Whatever your decision, both the promoter and the research team want to thank you for your time and attention.

Universitat Oberta de Catalunya

INFORMED CONSENT

STUDY TITLE: IASHAMA-VR
STUDY CODE:

Me, ……. ……. …… (name and surname of the patient), I declare that

• I have read the information sheet provided to me;
• was able to ask questions about the study;
• received enough information about the study;
• I have spoken with …… .. …… .. …… (name of the researcher);
• I understand that my participation is voluntary;
• I understand that I can withdraw from the study
or when you want,
or without having to give explanations,
or without this affecting my medical care.

By signing this document, I freely consent to participate in the study, and I give my consent for the access and use of my data as stipulated in the information sheet given to me.

I will receive a signed and dated copy of this informed consent document.

Participant sign
Date: ……/……/……
(Name, sign and date in the handwritting of the participant)

Resercher sign
Date: ……/……/……

Annex 2: Inclusion criteria scores

The following table shows the proportions of the STAI and HDRS tests that will be used as a reference to include or eliminate the candidates for the first phase of the investigation.

Table 1

Inclusion criteria scores			
STAI		**HDRS**	**Notes**
Anxiety state	*Anxiety trait*	*Both sex*	This table shows scores considered in the inclusion criteria for HDRS and STAI. These scores include values representing moderate, severe and very severe depression and moderate and high scores in anxiety.
women: >27	women: >29	> 16	
men: >24	men: >23		

Note: *This information is based on the STAI (Spielberg et al., 1982) and HDRS (Ramos-Brieva and Cordero, 1988) correction manuals .*