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Note from the Editors: Instructions for reviewers of study protocols

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Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scored as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

Adaptability to acute stress among women victims of intimate partner violence: protocol for a mixed-methods cross-sectional study in a laboratory setting.

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ABSTRACT

Introduction: Intimate partner violence (IPV) is the most common and alarming form of violence against women, affecting around 25% of all women around the world. Using an integrative methodology, we approach IPV as a form of chronic exposure to severe stress that alters the stress-response system of exposed women. The aim of this study is to identify potential vulnerabilities that may clarify the association between IPV and increased prevalence of health issues in this population. Results are expected to help build resilience strategies with a long-lasting impression on women's healthy functioning.

Methods and analysis: The study aims at testing the hypothesis that sustained exposure to IPV in women confers a vulnerability-to-stress profile characterized by: i) attentional bias towards threat, associated with ii) altered hypothalamic-pituitary-adrenal response to acute stress and iii) altered behavioural responses to acute stress. A sample of 90 women exposed to IPV and 45 women not exposed to IPV will be included and assessed for attentional bias and response to acute stress in a laboratory condition (the Trier Social Stress Task). The study will include quantitative and qualitative measures of cognitive performance, neuroendocrine activity and face-to-face interviews to obtain an integrative description of the stress-response profile of these women.

Ethics and dissemination: The study has obtained the approval of the local Ethics Committee ('Comité de Ética de la Investigación Parc Taulí de Sabadell'; 2018551 version 1.2 June 2018). Besides the communication of results in peer-reviewed papers and scientific congresses, the project will inform guidelines and recommendations for future work and prevention strategies. Participants will be invited to be an active part in the dissemination strategy focused on raising awareness of coping limitations and abilities that women themselves will be able to identify throughout the study. The study has been registered at the ClinicalTrails.gov database (Identifier number: NCT03623555).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The design combines biological and psychosocial data in an integrative model of the health consequences of intimate partner violence.
- A mixed-methods approach allows to incorporate the voices of the victims in the research process.

- Stress reactivity is measured in the laboratory using the goal standard Trier Social Stress Task
- The limited sample size will prevent exploring possible modulatory effects of relevant variables (i.e. other stressful experiences).

INTRODUCTION

The burden and prevalence of violence against women and girls worldwide has helped recognized this issue as a global public health problem [1]. Consistent evidence confirms that victims of intimate partner violence (IPV), compared to women who have not suffered IPV, more frequently present chronic diseases such as diabetes, chronic pain, asthma, cardiovascular disease, stroke and joint disease [2,3]. Furthermore, mental health-related consequences are largely common among IPV victims [4]. It has been estimated that up to 28% of the cases of depression can be attributed to lifetime exposure to IPV [5]. Only in the United Kingdom this translates into 1 million cases of depression per year that could be completely averted if no women had been exposed to IPV.

This background clearly supports a relationship between IPV and disease. But the biological correlates of such association are still unclear. The most widely acknowledged theoretical approach proposes a model of chronic stress. Indeed, the victims of IPV are repetitively exposed to physical, emotional and sexual violence in the context of an intimate relationship that may last for years [6]. Each single exposure to IPV is expected to trigger the typical neurobiological response to stressful stimuli, which includes a wide range of neural and peripheral stress biological responses, including the activation of the sympathetic-adrenomedullary and hypothalamic-pituitary-adrenal (HPA) axes [7], and the subsequent release of catecholamines and cortisol, respectively. When this stress response presents frequently or persists continuously for an extended period of time, the mechanisms that were initially activated to cope with acute stress extend over time and can eventually lead to pathophysiology and psychiatric diseases [8]. However, the impact of chronic stress on basal cortisol secretion appears to be dependent on several critical factors, including the time since stress onset, the type of challenge and the possibility of control [9].

Stress-related biological dysregulations specific to IPV victims has been addressed for the first time in a recent systematic review [10]. Authors reveal that this population present flattened diurnal cortisol rhythm and an overall higher diurnal secretion - a pattern expected after exposure to chronic stress. The extent to which these changes persist once exposure to the situation has finished is unclear. Interestingly, in IPV victims that developed PTSD, but not in those without overt psychopathology, reduced baseline cortisol levels and enhanced suppression by dexamethasone has been reported [11]. In sum, previous literature consistently supports that the neurobiological mechanisms involved in the stress-response system are

altered following IPV. Importantly, these alterations can be placed in the core of the neurobiological pathogenesis of the associated health disorders [9].

Why our study?

Despite the critical importance of the stress-response system, most research on IPV has only evaluated basal activity of the HPA and other biological systems. This has left unanswered the question of whether women previously exposed to IPV have difficulties when coping with new emotional situations and whether this is reflected in an altered HPA responsiveness. The activation of the stress system in response to novel stressful situations is a central matter as it reflects the person's capacity to respond to the changing demands that commonly occur at work and at home. For example, a job interview could be a stressful circumstance that affected women may have to face after recovering from IPV. The performance during the interview (i.e. getting or losing the job opportunity) will largely depend on the current person's vulnerability to emotionally stressful situations or, on the contrary, on the successful strategies women may present to cope with acute stress.

A history of chronic stress can alter responsiveness to further acute stressors in a way not predicted by basal HPA activity. These alterations can be either sensitization or blunting[12]. In this regard, experimental findings indicate that both acute and chronic exposure of adult rats to severe stress induce HPA cross-sensitization; that is, enhanced response to new acute stressors [13,14]. Human studies focused on the consequences of exposure to chronic stress also adopt this perspective. Evidence suggests that the chronic stress exposure implicated in caregiving is associated with dysfunctional psychosocial behaviour related to maladaptive coping strategies when facing novel stressful circumstances. A key phenomenon in this respect is selective attentional processing [15], which refers to an attentional bias early on the process of the cognitive approach to any given situation that predisposes a person to an enhanced vigilance for threat. This bias towards threat has been linked to being a victim of interpersonal violence [16,17], and is associated with higher HPA axis activity [18]. Quite surprisingly, no study has yet evaluated selective attentional bias in association to acute stress responsiveness among women exposed to IPV.

In the present proposal we aim at identifying these learnt vulnerabilities and resources for resilience among IPV-exposed women using valid measures of psychosocial and neuroendocrine response to acute stress. Also, we will assess the long-termed marks of chronic

stress on the global basal levels of cortisol in IPV victims using hair-cortisol analysis, following previous studies on other stress-related situations [19,20].

Objectives of the study

The main hypothesis of our study is that women exposed to IPV present a vulnerability-to- stress profile, characterized by: i) attentional bias towards threat, associated with ii) a sensitized HPA axis response to acute stress and iii) altered behavioural responses to acute stress.

To test this hypothesis, we aim to compare a group of women with a history of IPV as opposed to women without such history from the same community in order to:

1) Examine global basal cortisol alterations in the group of IPV-exposed women using hair-cortisol analysis;
2) Assess the patterns of psychosocial and neuroendocrine coping in IPV-exposed women (selective attentional processing bias, HPA axis response to acute stress);
3) Identify potential relationships between exposure to IPV, patterns of stress response, and health status;
4) Ascertain the strategies used by resilient women in terms of psychosocial schemes and neuroendocrine regulation to cope with acute stress.

METHODS AND ANALYSIS

Study Design and Participants

We will use a case-control design, where cases will be defined as women who have been exposed to IPV, and controls will be defined as women who have not been exposed to IPV. The definition of exposure to IPV will follow the World Health Organization guidelines: "IPV refers to any behaviour within an intimate relationship that causes physical, psychological and sexual harm to those in the relationship" [21] and will include physical violence, sexual violence, emotional/psychological abuse and controlling behaviours. These forms of violence will also follow WHO's definitions [22] including but not limited to: 1) Acts of physical violence: the woman has been pushed, beaten up, choked or burnt by an intimate partner; 2) sexual violence: any form of sexual coercion by the intimate partner; 3) emotional/psychological abuse: the woman has been humiliated, intimidated, threatened by her intimate partner; 4) controlling

behaviours: the woman has been isolated, monitored for her actions by her intimate partner, and restricted her access to financial resources, employment, education or medical care. In order to warrant chronic exposure to stress as proposed in the rationale of the study [9], the minimum of time of duration of the violent relationship will be set at one year.

Exclusion criteria will be as following: age below 21 and over 50, having any pituitary and/or adrenal gland disorder, currently using of steroid-based medications, being currently pregnant, lactating or menopausal, and having a severe illness that may affect cognitive performance and/or consciousness. No participant will be excluded on the basis of disability, ethnicity, religion or sexual orientation. To avoid including women who might be still in a relationship with the violent partner at the time of the assessment [23], only women who have already ended the violent relationship for at least one year will be allowed in the study.

Procedures

Participants will be women from the general population who will be recruited through advertisements in the community and in social media. Because social media will be an important tool for recruitment, participants in the study are expected to belong to areas in Catalonia that will exceed the catch zone of the reference Centre (Parc Taulí University Hospital).

Women interested in participating will actively contact us by the email address that will be detailed in the advertisement. At first contact, a researcher will assess eligibility according to inclusion/exclusion criteria. If all criteria are met, a first face-to-face session will be scheduled for an in-depth interview, followed by a second session two weeks later to complete the assessment of response to acute stress exposure (See Figure).

Session 1:

All participants will obtain a full description of the study's aims and procedures and all questions will be answered. Only those women willing to participate who sign an informed consent will be included in the study. Sociodemographic data will be collected through the use of a standardized self-report questionnaire. History of IPV will be extensively described combining standard measures of screening (PVS, [24]) and an in-depth structured interview among women identified as victims (WHO Violence Against Women Instrument, [6,25]). Exposure to other forms of interpersonal violence will also be collected at this point using the Childhood Trauma Questionnaire (CTQ, [26]) and the Life-events Scale [27]. A description of

coping styles and resilient behaviour will be assessed using the COPE Inventory [28] and the CD-RISC [29].

A comprehensive health profile will also be assessed during the initial interview that will provide information on physical and mental health status and history of clinical treatment. The MAPSAIS [30] and SF-36 [31,32] scales will be used for the assessment of physical symptoms and perception of general health. The GHQ-12 [33,34] will be used for screening of mental health status and the MINI [35] for in-depth assessment when GHQ-12 suggests mental health disorders. Personality traits will be assessed using the NEO-FFI [36].

As part of the comprehensive health profile assessment, a full laboratory test will be included to obtain a description of biochemistry markers. For this objective, peripheral blood samples will be collected by a nurse in 15 mL of capacity tubes. Finally, a hair sample with an approximate diameter of 30 single hairs will be taken from the upper part of the scalp. This technique provides a measure of the integrated release of steroid over the growth period of a specific hair segment, typically 1 cm/month [37]. As glucocorticoid levels cannot be experimentally manipulated in humans, we have experimentally validated the technique measuring hair corticosterone in rats [38] and validated measurement of hair cortisol in humans using the well-characterized Salimetric kit assay for cortisol (unpublished).

At this point of the assessment we will examine selective attentional processing by means of the Visual Probe Task (VPT) [39,40]. Briefly, participants are presented simultaneously with a pair of stimuli, one emotionally salient and one neutral for 500 ms time, followed by a probe that replaces one of the two stimuli. Participants are required to respond as accurately and as quickly as possible to the probe. Reaction times are recorded and contrasted. A decreased reaction time to a probe replacing emotional stimuli compared to the neutral stimuli provide a measure of bias to be vigilant for threatening information. Assessment of the VPT will be accompanied by a brief complementary cognitive examination that will include semantic memory (RAVLT, [41], intelligence quotient (WAIS, [42]), and executive functioning [43,44].

Session 2:

After two weeks, a second appointment will be scheduled focused on the assessment of the response to acute stress. In order to control for potential differences in circadian rhythm associated with endocrine activity, all participants will have a light lunch in the cafeteria of the Centre one hour before the start of the laboratory phase. To control for inter-individuals

differences in cortisol levels, no meals neither heavy physical activity 2 hours before lunch, no coffee consumption the same day are allowed [45,46].

Acute psychosocial stress response will be assessed using the Trier Social Stress Task [47]. This is the gold standard in biopsychological stress research, and can be briefly described as a mock job interview. The participants are instructed to imagine that having applied for their "dream job", they are now invited to a job interview. Participants are aware of no real job is at issue. The TSST consists of three successive phases: (1) A preparation period (3 minutes), (2) a free speech task in which the participants have to argue why they are the best candidate for the (5 minutes), and (3) a mental arithmetic task in which participants have to sequentially subtract an odd two-digit number from an odd four-digit number (e.g., 17 from 2023; 5 minutes). The two tasks are performed in front of a selection committee consisting of two members, one male and one female, dressed in white lab coats, acting in a reserved manner and providing no facial or verbal feedback [48]. The interview is recorded in a video camera, a procedure that has been demonstrated effective in triggering further threat [49].

The primary measure of the stress response will be the activation of the HPA axis by assessing the release of cortisol immediately before the TSST (T0), immediately after (T1), and at recovery (T2). Saliva samples will be obtained by means of Salivette collection devices (Sarstedt, UK) and will be stored at -20°C on the same day of recollection. Salivary cortisol levels will be determined by means of a competitive radio-immunoassay technique with a polyclonal anticortisol-antibody (K7348) developed in our laboratory that has been validated against a widely used kit (Salimetrics).

Secondary measures of response to acute stress will be the level of perceived stress and anxiety. To fulfil this aim, the individuals' responses to two different scales will be registered. The first of these scales will be the state examination of the State-Trait Anxiety Inventory (STAI, [50]), which will allow to examine the self-perceived level of state anxiety at baseline (T0) and after the task (T1). The second scale will be the Self-Assessment Manikin (SAM, [51]), which is a picture-oriented scale to register an emotional response in its three key features: valence/pleasure of the response, arousal, and dominance/control.

The final half hour of the second appointment will be dedicated to a face-to-face interview aiming to systematically register subjective experience-based issues related to stress and coping strategies that may have not been included in the quantitative assessment. This interviewer will have had no previous contact with the women up to this moment Participants will be invited to follow a semi-structured interview regarding their feelings, perceptions and

attitudes during exposure to the acute stress (TSST), generating a personal narrative of the experience by women themselves [52]. Conversations will be recorded and the transcripts will be used for analysis.

Sample size calculation

Sample size has been calculated with a focus on the primary outcome measure, the response to acute stress that will be assessed by means of the changes in the levels of salivary cortisol during TSST. It has been estimated that the TSST reliably activates the HPA axis and triggers a two- to three-fold increase in cortisol in about 70-80% of participants [49]. Assuming an increase in hormones with the task of about 70% [53] and a standard deviation of 30% of the mean, if we want to detect differences among the two groups of half of this increase with a power of 0.80 and an alpha of 0.05, we will need a sample size of 43/group to detect a significant effect [54]. Because women victims of IPV are more likely to report a history of childhood trauma (Odds Ratio ranging from 0.7 to 3.8 [55]), and violence during childhood also affects the stress system of women [56], the sample size of the exposed group (cases) will be increased to include an even number of women with and without a history of childhood violence, as assessed by the CTQ. Therefore, the complete sample will include: i) the group of women exposed to IPV (cases) composed of 90 women, 45 of them with history of childhood abuse and 45 of them without such history, and ii) the non-exposed group (control) composed of 45 women. Total sample size: 135 women.

Patient and public involvement

The study has been designed with a focus on exposure to IPV as a main risk factor for a number of health-related issues, particularly mental health disorders. During the design stage the research team was particularly concerned that the exposure to acute stress was clearly justified, and the information obtained through this laboratory condition could not be collected in other forms. It was also highly important that the experimental condition would resemble a situation that any person could be presented with in real life. The team consulted local experts in the field of violence against women before deciding on the use of the TSST.

During the recruitment period, different local governmental and non-governmental organizations will be involved as consultants and sources of identification of potential participants. They will also be contacted to discuss the final results and potential recommendations.

The final stage of the study will include a workshop session where the participants will be placed in the centre of the experience and will invited to contribute to possible solutions. This session will have two parts with different purposes. The first will be an open session aiming at disseminating the results of the study, including specific interventions to raise awareness about the consequences of IPV. This first part will target all the participants as well as other stakeholders and social agents that may benefit from this information. The second session will be a closed participatory session targeting the participants with history if IPV aimed at gathering resilient behaviour and discussing prevention strategies. The session will end with the co-creation of an inventory of prevention strategies (from victims and for victims) and ideas to communicate them.

Data analysis plan

The primary outcome variable in the study is the response to acute stress, measured on the basis of salivary cortisol at T0, T1 and T2. The secondary outcome variables are the responses to acute stress as measured by self-reported behavioural scales: perceived levels of anxiety at T0 and T1 (STAI), perceived levels of valence/pleasure, arousal and control al T0 and T1 (SAM). Hence, these will be the dependent variables in all analyses. Data will be analysed using SPSS software (SPSS, IL, Chicago, version 21).

Firstly, a detailed descriptive analysis will be run that will include the information from: i) the initial interview, ii) hair-cortisol analysis, iii) the results of the VPD task, iv) the neuroendocrine response trajectories during the TSST, v) the self-reported levels of behavioural responses during the TSST. This information will be presented in the form of contingency tables, and group-comparison analysis will be run between the group of IPV-exposed women and non-exposed women. Tests will be selected according to the nature of the variables and their sample distributions. The main hypothesis being tested at this stage will be that both groups differ in the measures of response to stress both at the neuroendocrine (hair cortisol, salivary cortisol) and behavioural (VPD, STAI, SAM) levels.

The following stage will be to test the hypothesis that bias towards threat as measured by the VPD task is associated with the response to acute stress in the group of women with IPV. To test this hypothesis, we will use a generalized lineal model, specifically a repeated measures design. Two independent analysis will be run for salivary cortisol and for behavioural outcomes. The dependent variables of interest will be the score of VPD and group (IPV or non-IPV). Other

variables will be included as covariates in the model: age, level of education, history of other life events.

Regarding the semi-structured interviews that follow the TSST, content analysis will be used to extract the fundamental aspects of the discourse on the experience of women and their resilience strategies [57]. The aim will be to search discourse's saturation, this is, when new interviews don't provide new findings on the results. Transcriptions will be analyzed using software for qualitative analysis, Atlas.ti (Scientific Software Development GmbH). Following on this data, a second tier for analysis will focus on profile differentiation in order to capture the different narratives and profiles that may arise across participants, and related to other variables (childhood abuse, socio-economic position, education). This will lead to highlight the common traits within each profile as well as strengths and weaknesses. Finally, a mixed-methods analysis will be run to explore relevant aspects identified in the Post-TSST interviews and that may have not been fully considered in the original design [58]. The selection of the specific variables at this point will be determined by results of the previous stages.

Ethics and dissemination:

This study has been approved by the Ethics Committee of reference ('Comité de Ética de la Investigación Parc Taulí de Sabadell'). Written informed consent as approved by the Ethics Committee will be obtained after a full description of the study's aims and design. Participants will be informed of the confidentiality of their comments following the European Data Protection legislation (2016/679; Ley Orgánica de Protección de Datos de Carácter Personal, 15/1999 del 13 de Diciembre, LOPD). Registry and use of information resulting from this study will follow the Declaration of Helsinki agreements. All biological samples will be collected according to the corresponding legislation (Llei 14/2007 de Recerca Biomèdica). The study will follow WHO's recommendations for research on violence against women [23].

The dissemination of the results of our project will start at the level of the participants during the final workshop, which is expected to act as a first step for developing prevention tools and information resources that are essentially built by women themselves. We will carry out policy-dialogues and workshops with relevant regional and national representatives aimed at enhancing the current policies and roadmaps regarding the training and management in the educational and healthcare areas. At the level of the dissemination of results in the scientific community, the strategy includes the publication of the results in international peer-reviewed scientific journals and the presentation in national and international congresses. Also, the

project is expected to strengthen the way health-care providers respond to women who have experienced violence. The complete set of results from the study will be used to develop guidelines and recommendations for actions that will be distributed among professionals.

Discussion:

The prevention of violence against women in general, and of IPV in particular, has risen as a priority on the international public health agenda, and research is playing a key role in the detection of protective factors and the development of effective interventions [59]. Are there cognitive implications of exposure to gender-based violence? Which systems underlie these effects, what causes them? Can they be reversed? These are questions that exceed the laboratory settings and impact "the real world". Our proposal aims at targeting these traits, which not only impair women's daily functioning but also feed a cycle of attitudes, norms and beliefs that justify dominant notions of masculinity and stigmatise victims [60,61]. Hence, the inclusion of a mixed-methods approach that integrates subjective reports with neurobiological data is a key aspect of this protocol.

Regarding methodological issues, the TSST is a powerful tool to identify dysfunctional patterns of coping that may help explain some critical aspects of the behavioural responses of IPV-exposed women. However, we have included the TSST only after extensively discussing the possible distress that may be caused to women, and the benefits of including the measure in the study. Our decisions throughout the project have been guided by the WHO Practical Guide for Researchers and Activists [62]. This document summarizes all aspects of research in this field and provides with useful recommendations to assure the project achieves the objective of serving the target women. The safety of respondents and the research team is our priority and it is our advice that it be that of any other study working with this population. The identification of any problem in this respect must result in the immediate interruption of the assessment of the case. The research team must be trained, and the assessment must be conducted in a location different to that where women receive health and social assistance.

Our study has the potential to provide evidence to serve a deeper understanding of IPV and the vulnerability and resilience processes these women present. This information will allow professionals and institutions to better understand and address this reality. Ultimately, it is expected that the results of this research will serve as the foundation to build evidence-based tools for the prevention of re-victimization among women exposed to IPV and of IPV in at-risk groups.

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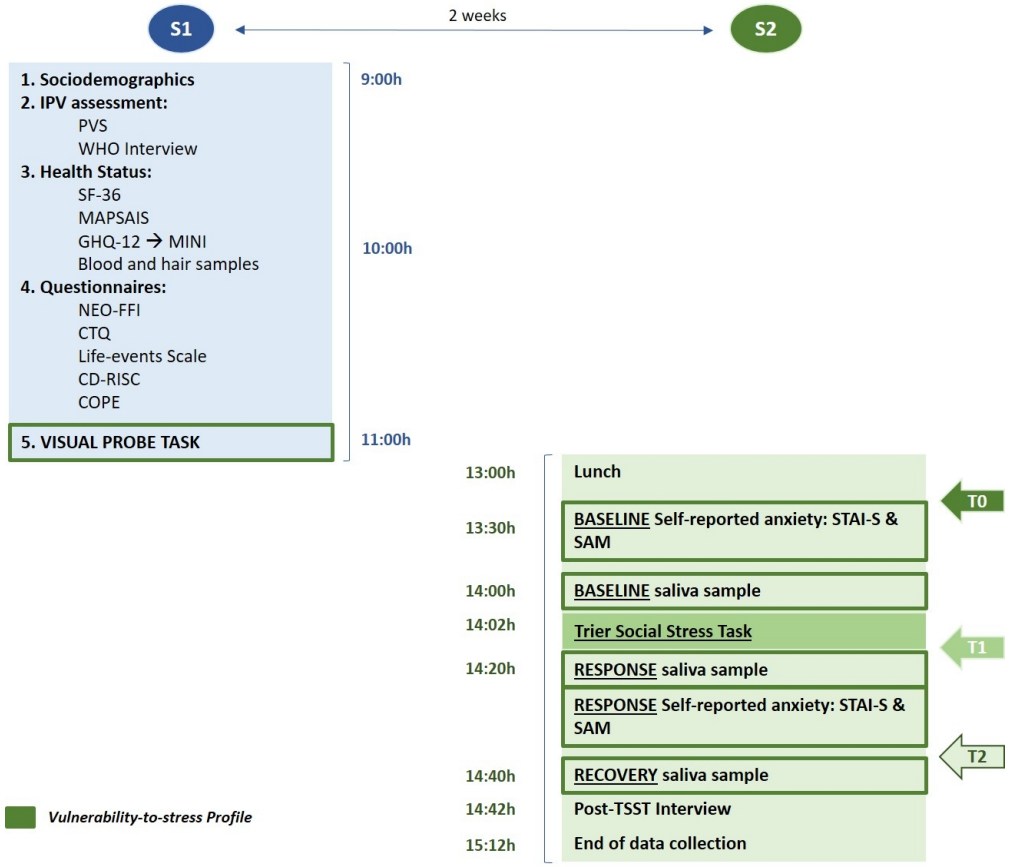
Caption Figure: Procedures of the study. Session 2 (S2) will be scheduled 2 weeks after session 1 (S1) and will take place in the afternoon. PVS: Partner violence screen; WHO Interview: World Health Organization Violence Against Women Instrument; SF-36: Short form 36 health survey; MAPSAIS: Miller Abuse Physical Symptom and Injury Scale; GHQ-12: General Health Questionnaire; MINI: Mini-International Neuropsychiatric Interview; NEO-FFI: NEO five-factor inventory; CTQ: Childhood Trauma Questionnaire; CD-RISC: Connor-Davidson Resilience scale; COPE: COPE Inventory.



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Adaptability to acute stress among women victims of intimate partner violence: protocol for a mixed-methods cross-sectional study in a laboratory setting (BRAW study)

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ABSTRACT

Introduction: Intimate partner violence (IPV) is the most common and alarming form of violence against women, affecting around 30% of all women around the world. Using an integrative methodology, we approach IPV as a form of chronic exposure to severe stress that alters the stress-response system of exposed women. The aim of this study is to test the hypothesis that sustained exposure to IPV in women confers a vulnerability-to-stress profile characterized by higher neuroendocrine and behavioural responsiveness associated with a selective attentional processing bias towards threat.

Methods and analysis: Women between 21 and 50 years old from the area of Barcelona (Spain) will be invited to participate. A sample of 82 women exposed to IPV and 41 women not exposed to IPV will be included and assessed for attentional bias and response to acute stress in a laboratory condition (the Trier Social Stress Task). The study will include quantitative and qualitative measures of cognitive performance, neuroendocrine activity and face-to-face interviews to obtain an integrative description of the stress-response profile of these women. Results are expected to help build resilience strategies with a long-lasting impression on women's healthy functioning.

Ethics and dissemination: The study has obtained the approval of the local Ethics Committee ('Comité de Ética de la Investigación Parc Taulí de Sabadell'; 2018551 version 1.2 June 2018). Besides the communication of results in peer-reviewed papers and scientific congresses, the project will inform guidelines and recommendations through policy-dialogues and workshops with relevant regional and national representatives for future work and prevention strategies. Participants will be invited to be an active part in the dissemination strategy focused on raising awareness of coping limitations and abilities that women themselves will be able to identify throughout the

study. The study has been registered at the ClinicalTrails.gov database (Identifier number: NCT03623555).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The design combines biological and psychosocial data in an integrative model of the health consequences of intimate partner violence.
- A mixed-methods approach allows to incorporate the voices of the victims in the research process.
- Stress reactivity is measured in the laboratory using the gold standard Trier Social Stress Task
- The limited sample size will prevent exploring possible modulatory effects of relevant variables (i.e. other stressful experiences).

INTRODUCTION

The burden and prevalence of violence against women and girls worldwide has helped raise this issue as a global public health problem [1]. While women are exposed to several types of gender-based violence, almost 1 in 3 ever-partnered women worldwide (30%) have experienced intimate partner violence (IPV) [2]. This alarming reality applies to the territory of the European Union, where a recent EU-wide survey has estimated the prevalence of IPV to be 22% [3]. It also reflects on the IPV-estimates in Spain: 13% of women report suffering physical or sexual violence, and over 26.4% have suffered psychological and economic IPV [4].

Consistent evidence confirms that victims of IPV, compared to women who have not suffered IPV, more frequently present chronic diseases such as diabetes, chronic pain, asthma, or cardiovascular disease [5,6]. Furthermore, mental health-related consequences are largely common among IPV victims [7]. It has been estimated that up to 28% of the cases of depression can be attributed to lifetime exposure to IPV [8]. Only in the United States this translates into 1 million cases of depression per year that could be completely averted if no women had been exposed to IPV. In this regard, the possibility to suffer traumatic brain injury has to be considered as this is frequently associated with mental health problems, mostly depression [9]. Also relevant to the present study, women victims of IPV are more likely to report a history of childhood trauma, which per se has long-term consequences in mental health [10,11]. In Europe, almost one third of women exposed to sexual IPV report having experienced sexual victimisation during childhood [3]. A recent multi-country study reported an Odds Ratios ranging from 1.41 to 3.8 in six out of seven study sites [12].

This background clearly supports a relationship between IPV and disease. But the biological correlates of such association are still unclear. The most widely acknowledged theoretical approach proposes a model of chronic stress. Indeed, the victims of IPV are repetitively exposed to physical, emotional and sexual violence in the context of an intimate relationship that may last for years [13]. Each single exposure to IPV is expected to trigger the typical neurobiological response to stressful stimuli, which includes a wide range of neural and peripheral stress biological responses, including the activation of the sympathetic-adrenomedullary and hypothalamic-pituitary-adrenal (HPA) axes [14], and the subsequent release of catecholamines and cortisol, respectively. When this stress response presents frequently or persists continuously for an extended period of time, the mechanisms that were initially activated to cope with acute stress extend over time and can eventually lead to pathophysiology and psychiatric diseases [15]. However, the impact of chronic stress on basal cortisol secretion appears to be dependent on several critical factors, including the time since stress onset, the type of challenge and the possibility of control [16].

Stress-related biological dysregulations specific to IPV victims have been addressed for the first time in a recent systematic review [17]. Authors reveal that this population present flattened diurnal cortisol rhythm and an overall higher diurnal secretion - a pattern expected after exposure to chronic stress. The extent to which these changes persist once exposure to the situation has finished is unclear. Interestingly, in IPV victims that developed PTSD, but not in those without overt psychopathology, reduced baseline cortisol levels and enhanced suppression by dexamethasone has been reported [18]. In sum, previous literature consistently supports that the neurobiological mechanisms involved in the stress-response system are altered following IPV.

Importantly, these alterations can be placed in the core of the neurobiological pathogenesis of the associated health disorders [16].

Why our study?

Despite the critical importance of the stress-response system, most research on IPV has only evaluated basal activity of the HPA and other biological systems. This has left unanswered the question of whether women previously exposed to IPV present behavioural difficulties when coping with new emotional situations (i.e. anxiety, emotional arousal) and whether this is reflected in an altered HPA responsiveness. The activation of the stress system in response to novel stressful situations is a central matter as it reflects the person's capacity to respond to the changing demands that commonly occur at work and at home. For example, a job interview could be a stressful circumstance that affected women may have to face after recovering from IPV. The performance during the interview (i.e. getting or losing the job opportunity) will largely depend on the current person's neuroendocrine and behavioural vulnerability to emotionally stressful situations or, on the contrary, on the successful, resilient strategies women may present to cope with acute stress.

A history of chronic stress can alter responsiveness to further acute stressors in a way not predicted by basal HPA activity. These alterations can be either sensitization or blunting [19]. In this regard, experimental findings indicate that both acute and chronic exposure of adult rats to severe stress induce HPA cross-sensitization; that is, enhanced response to new acute stressors [20,21]. Human studies focused on the consequences of exposure to chronic stress also adopt this perspective. Evidence suggests that the chronic stress exposure implicated in caregiving is associated with dysfunctional

psychosocial behaviour related to maladaptive coping strategies when facing novel stressful circumstances. A key phenomenon in this respect is selective attentional processing [22], which refers to an attentional bias early on the process of the cognitive approach to any given situation that predisposes a person to an enhanced vigilance for threat. This bias towards threat has been linked to being a victim of interpersonal violence [23], and is associated with higher HPA axis activity [24]. Quite surprisingly, no study has yet evaluated selective attentional bias in association to acute stress responsiveness among women exposed to IPV.

In the present proposal we aim at identifying potential alterations in the adaptive response to acute stress among IPV-exposed women using valid measures of neuroendocrine and behavioural response to acute stress. We propose that these alterations persist in the long term even when the exposure to IPV has ceased. Also, we will assess the long-termed marks of chronic stress on the global basal levels of cortisol in IPV victims using hair-cortisol analysis, following previous studies on other stress-related situations [25,26].

Objectives of the study

The main (general) objective of our study is to compare the response to acute stress in a group of women with a history of IPV as opposed to women without such history from the same community. The specific objectives are:

1) To assess the neuroendocrine (HPA axis) and behavioural response to acute stress.
2) To study whether IPV women show selective attentional processing bias towards threat.

3) To identify the resilience strategies used by women in terms of psychosocial schemes and neuroendocrine regulation to cope with acute stress and their relationship with health status.
4) To examine global basal cortisol alterations in the group of IPV-exposed women using hair-cortisol analyses.

The main hypothesis of our study is that women exposed to IPV, in contrast to a group of women without a history of IPV, will present a vulnerability-to-stress profile. The specific sub-hypotheses of the study are:

1) The group of women exposed to IPV will present higher neuroendocrine and behavioural responsiveness to stress than the non-exposed group, as measured by self-reported behavioural scales and salivary cortisol, respectively.
2) A selective attentional processing bias towards threat will be associated with a higher response to acute stress in the group of women exposed to IPV, as opposed to the group of non-exposed women.
3) The performance and resilience strategies during an acute stress task will be self-perceived as poorer/weaker among the group of women exposed to IPV in contrast with the self-perceptions of the group of non-exposed women. Resilience will be related to health status.
4) Women exposed to IPV will present higher levels of hair cortisol indicating global basal cortisol alterations.

STUDY CONTEXT

Participants will be women from the general population who will be recruited through advertisements in the community and in social media. The interviews will take place in the facilities of Parc Taulí Foundation, the research branch of the Parc Taulí Healthcare Corporation (Corporació Sanitària Parc Taulí, CSPT). Participants will not receive monetary compensation for their participation in the research.

CSPT is a public healthcare legal entity that manages the third-level Parc Taulí Hospital along with primary healthcare centres, diagnostic and emergency units, and several transversal services including sexual and reproductive health programmes. It is the single healthcare provider for the area of the Catalan Eastern Occidental Vallès, which counts a total population of close to 500,000 people. Parc Taulí Foundation (Fundació Parc Taulí, FPT) provides support to CSPT in areas of research, teaching and innovation, and has been recognized as a University Institute affiliated to the Universitat Autònoma de Barcelona. FPT has a strong background in the promotion of healthy habits and social awareness in the community, and for the last decade has dedicated special efforts to enhance this line of work in the area of mental health.

Because social media will be an important tool for recruitment, participants in the study are expected to belong to areas in Catalonia that will exceed the catch zone of the reference Centre. In particular, we expect participants based in the area of Barcelona, which covers a population of approximately 1,620,000 inhabitants.

METHODS AND ANALYSIS

Study Design and Participants

We will use a mixed-methods, cross-sectional design. The key element in the study is the inclusion of the Trier Social Stress Task (TSST), which provides a laboratory

setting to measure the neuroendocrine and behavioural responses to acute stress. Quantitative data will be generated from various sources, including biological samples (hair, saliva) and clinical and behavioural scales that are described in detail in the procedures section below. Semi-structured interviews will be used to register the participants' impressions regarding their experience during the TSST, with a focus on identifying emerging themes. While the sample size for the quantitative analysis has been calculated during the design phase of the study, the total number of semi-structured interviews may vary. Interviews will continue until data saturation has been reached in the analyses (i.e. no new emerging themes are identified from new interviews) [27]. The methods for each stage of the study are presented in more detail in the following sections.

Criteria for the inclusion of women in the study will be mainly guided by their previous exposure to IPV, which will define two groups of participants: an IPV-exposed group with an estimated sample size of 82 women, and a non-exposed IPV group with an estimated sample size of 41 women (see sample size calculation for further details). The definition of exposure to IPV will follow the World Health Organization guidelines: "IPV refers to any behaviour within an intimate relationship that causes physical, psychological and sexual harm to those in the relationship" [28] and will include physical violence, sexual violence, emotional/psychological abuse and controlling behaviours. These forms of violence will also follow WHO's definitions [29] including but not limited to: 1) Acts of physical violence: the woman has been pushed, beaten up, choked or burnt by an intimate partner; 2) sexual violence: any form of sexual coercion by the intimate partner; 3) emotional/psychological abuse: the woman has been humiliated, intimidated, threatened by her intimate partner; 4) controlling behaviours: the woman has been

isolated, monitored for her actions by her intimate partner, and restricted her access to financial resources, employment, education or medical care. In order to warrant chronic exposure to stress as proposed in the rationale of the study, the minimum time of duration of the violent relationship will be set at one year [16]. Also, to allow the study of the long-term effects of IPV once the exposure has ceased, only women who have already ended the violent relationship for at least one year will be included.

Exclusion criteria will be as following: age below 21 and over 50, having any pituitary and/or adrenal gland disorder, currently using of steroid-based medications, being currently pregnant, lactating or menopausal, and having a severe illness that may affect cognitive performance and/or consciousness. No participant will be excluded on the basis of disability, ethnicity, religion or sexual orientation.

Procedures

Women interested in participating will actively contact us by the email address that will be detailed in the advertisement. At first contact, a researcher will assess eligibility according to inclusion/exclusion criteria. If all criteria are met, a first face-to-face session will be scheduled for an in-depth interview, followed by a second session two weeks later to complete the assessment of response to acute stress exposure. A visual depiction of the procedures is presented in Figure 1, and a detailed description of the measures along with the reference for the Spanish translations of the scales is available as Supplementary Materials.

Session 1:

All participants will obtain a full description of the study's aims and procedures and all questions will be answered. Only those women willing to participate who sign an informed consent will be included in the study. Sociodemographic data will be collected through the use of a standardized self-report questionnaire. History of IPV will be extensively described combining standard measures of screening (Partner Violence Screen [30]) and an in-depth structured interview among women identified as victims that include onset and frequency of IPV among other details (WHO Violence Against Women Instrument [28]). Exposure to other forms of interpersonal violence will also be collected at this point using the Childhood Trauma Questionnaire (CTQ, [31]) and the Life-events Scale [32]. A description of coping styles and resilient behaviour will be assessed using the Coping Orientation to Problems Experienced Inventory [33] and the Connor-Davidson Resilience Scale [34].

A comprehensive health profile will also be assessed during the initial interview that will provide information on physical and mental health status and history of clinical treatment. The Miller Abuse Physical Symptom and Injury Scale [35] and Short Form 36 Scale for self-perceived health status [36] scales will be used for the assessment of physical symptoms and perception of general health. As part of the comprehensive health profile assessment, a full laboratory test will be included to obtain a description of biochemistry markers. For this objective, peripheral blood samples will be collected by a nurse in 15 mL of capacity tubes. The General Health Questionnaire (12 items version, GHQ-12) [37] will be used for screening of mental health status and the Mini International Neuropsychiatric Interview [38] for in-depth assessment when GHQ-12 suggests mental health disorders. Personality traits will be assessed using the Neuroticism-Extraversion Openness Inventory (Five Factor version, NEO-FFI [39]).

Finally, a hair sample of more than 3 cm length with an approximate diameter of 30 single hairs will be taken from the upper part of the scalp. This technique provides a measure of the integrated global basal cortisol over the growth period of a specific hair segment, typically 1 cm/month [40]. As glucocorticoid levels cannot be experimentally manipulated in humans, we have biologically validated this variable measuring hair corticosterone in rats [41]. Moreover, we have also technically validated in our laboratory the measurement of hair cortisol in humans using the well-characterized Salivary Cortisol Elisa Kit (Salimetrics, LCC, PA, USA). Reliability of the measure taken at different times is good, with correlations of 0.68-0.79 [40].

At this point of the assessment we will examine selective attentional processing by means of the Visual Probe Task (VPT) [42,43]. Briefly, participants are presented simultaneously with a pair of stimuli, one emotionally salient and one neutral for 500ms time, followed by a probe that replaces one of the two stimuli. Participants are required to respond as accurately and as quickly as possible to the probe. Reaction times are recorded and contrasted. A decreased reaction time to a probe replacing emotional stimuli compared to the neutral stimuli provide a measure of bias to be vigilant for threatening information. Assessment of the VPT will be accompanied by a brief complementary cognitive examination that will include semantic memory [44], intelligence quotient [45], and executive functioning [46,47].

Session 2:

After two weeks, a second appointment will be scheduled focused on the assessment of the response to acute stress. In order to control for potential differences in circadian rhythm associated with endocrine activity, all participants will have a light

lunch in the cafeteria of the centre one hour before the start of the laboratory phase. To control for inter-individuals differences in cortisol levels meals, heavy physical activity 2 hours before lunch, and coffee consumption the same day are not allowed [48,49].

Acute psychosocial stress response will be assessed using the TSST [50]. This is the gold standard in biopsychological stress research, and can be briefly described as a mock job interview. The participants are instructed to imagine that having applied for their "dream job", they are now invited to a job interview. Participants are aware of no real job is at issue. The TSST consists of three successive phases: (1) a preparation period (3 minutes), (2) a free speech task in which the participants have to argue why they are the best candidate for the job (5 minutes), and (3) a mental arithmetic task in which participants have to sequentially subtract an odd two-digit number from an odd four-digit number (e.g., 17 from 2023; 5 minutes). The two tasks are performed while standing in an upright position in front of a selection committee consisting of two members, one male and one female, dressed in white lab coats, acting in a reserved manner and providing no facial or verbal feedback [51]. The interview is recorded in a video camera, a procedure that has been demonstrated effective in triggering further threat [52].

The primary measure of the stress response will be the activation of the HPA axis by assessing the release of cortisol immediately before the TSST (T0), immediately after (20 minutes after the start of TSST, T1), and at recovery (40 minutes after the start of TSST, T2). Saliva samples will be obtained by means of Salivette© Cortisol collection devices (Sarstedt AG & Co., Germany) and will be stored at -20°C on the same day of recollection. Salivary cortisol levels will be determined by means of a competitive radio-immunoassay (RIA) technique developed in our laboratory that uses anti-cortisol

antibody (121116) and Iodinated cortisol (121126) from MP-Biomedicals (Valiant Co., Ltd., USA). We have validated this RIA against the Salivary Cortisol Elisa Kit (Salimetrics, LCC, PA, USA), showing a high correlation of r=0.95. The reliability of the salivary cortisol TSST response is moderated, with Spearman correlations over the days between 0.38-0.60 [53].

The behavioural response to acute stress will be the level of anxiety and perceived stress. To fulfil this aim, the individuals' responses to two different scales will be registered. The first of these scales will be the state examination of the State-Trait Anxiety Inventory (STAI, [54]), which will allow to examine the self-perceived level of state anxiety at baseline (T0) and after the task (T1). Cronbach's alpha reliability of the Spanish adaptation of this measure is high: 0.90 for the Trait Inventory and 0.94 for State Inventory. The second scale will be the Self-Assessment Manikin (SAM, [55]), which is a picture-oriented scale to register an emotional response in its three key features: valence/pleasure of the response, arousal, and dominance/control. This is a nonverbal scale specifically designed to be applied in transcultural settings.

The final half hour of the second appointment will be dedicated to a face-to-face interview aiming to systematically register subjective experience-based issues related to stress and coping strategies that may have not been included in the quantitative assessment. This interviewer will have had no previous contact with the women up to this moment Participants will be invited to follow a semi-structured interview regarding their feelings, perceptions and attitudes during exposure to the acute stress (TSST), generating a personal narrative of the experience by women themselves [56]. Conversations will be recorded and the transcripts will be used for analysis.

Sample size calculation

Sample size has been calculated using a priori power analysis conducted in G*Power [57], with a focus on the neuroendocrine response to acute stress that will be assessed by means of the changes in the levels of salivary cortisol during TSST at T0, T1 and T2. It has been estimated that the TSST reliably activates the HPA axis and triggers a two- to three-fold increase in cortisol in about 70%-80% of participants [58]. Assuming a conservative effect size of 0.2 based on this reference, and the correlation between measures of 0.38 mentioned above [53], if we want to detect differences among the two groups with a power of 0.95 and an alpha of 0.05, we will need a sample size of 41/group to detect a significant effect (repeated measures ANOVAs for the predictor analysis). Because violence during childhood can also affect the stress system of women [59], the sample size of the group exposed to IPV will be doubled to include an even number of women with and without a history of childhood violence, as assessed by the CTQ. Therefore, the complete sample will include: i) the group of women exposed to IPV composed of 82 women, 41 of them with history of childhood abuse and 41 of them without such history, and ii) the group of women not exposed to IPV, composed of 41 women. The total sample size will equal 123 women.

Patient and public involvement

The study has been designed with a focus on exposure to IPV as a main risk factor for a number of health-related issues, particularly mental health disorders. During the design stage the research team was particularly concerned that the exposure to acute stress was clearly justified, and the information obtained through this laboratory condition could not be collected in other forms. It was also highly important that the

experimental condition would resemble a situation that any person could be presented with in real life. The team consulted local experts in the field of violence against women before deciding on the use of the TSST.

During the recruitment period, different local governmental and non-governmental organizations will be involved as consultants and sources of identification of potential participants. They will also be contacted to discuss the final results and potential recommendations.

The final stage of the study will include a workshop session where the participants will be placed in the centre of the experience and will be invited to contribute to possible solutions. This session will have two parts with different purposes. The first will be an open session aiming at disseminating the results of the study, including specific interventions to raise awareness about the consequences of IPV. This first part will target all the participants as well as other stakeholders and social agents that may benefit from this information. The second session will be a closed participatory session targeting the participants with history of IPV aimed at identifying strategies to build resilience and discussing prevention strategies. The session will end with the co-creation of an inventory of prevention strategies (from victims and for victims) and ideas to communicate them.

Data analysis plan

All participants will be assigned a code at the moment of inclusion in the study, and the identification information will be saved separately to warrant confidentiality. Original data will be transferred to databases that will be archived in PTF applying the

standard processes of the centre. These same standard processes will be used to secure data quality throughout the study.

The primary outcome variable in the study is the neuroendocrine response to acute stress, measured on the basis of salivary cortisol at T0, T1 and T2. The secondary outcome variables are the behavioural responses to acute stress as measured by self-reported behavioural scales: perceived levels of anxiety at T0 and T1 (STAI), perceived levels of valence/pleasure, arousal and control at T0 and T1 (SAM). Hence, these will be the dependent variables in all analyses. Data will be analysed using SPSS software (IBM SPSS Statistics for Windows, Version 23.0. Armonk; NY: IBM Corp).

Firstly, a detailed descriptive analysis will be run that will include the information from: i) the initial interview, ii) hair-cortisol analysis, iii) the results of the VPT task, iv) the neuroendocrine response trajectories during the TSST, v) the self-reported levels of behavioural responses during the TSST. This information will be presented in the form of contingency tables, and group-comparison analysis will be run between the group of IPV-exposed women and non-exposed women. Tests will be selected according to the nature of the variables and their sample distributions. The hypothesis being tested at this stage will be that both groups differ in the measures of response to stress both at the neuroendocrine (salivary cortisol) and behavioural (self-reported behavioural scales) levels.

The following stage will be to test the hypothesis that bias towards threat as measured by the VPT task is associated with the response to acute stress in the group of women with IPV. To test this hypothesis, we will use a generalized lineal model, specifically a repeated measures design. Two independent analysis will be run for salivary cortisol and for behavioural outcomes. The dependent variables of interest will

be the score of VPT and group (IPV or non-IPV). Other variables will be included as covariates in the model: age, level of education, history of other life events.

Regarding the semi-structured interviews that follow the TSST, the research team will develop the general guidelines before the start of the study. All interviews will be recorded, and the transcriptions of these recordings will be conducted by trained professionals. Content analysis will be used to extract the fundamental aspects of the discourse on the experience of women and their resilience strategies [60]. The aim will be to search data saturation, this is, when new interviews do not provide new findings on the results. Transcriptions will be analyzed using software for qualitative analysis, Atlas.ti (Scientific Software Development GmbH). Following on these data, a second tier for analysis will focus on profile differentiation in order to capture the different narratives and profiles that may arise across participants, and related to other variables (childhood abuse, socio-economic position, education). This will lead to highlight the common traits within each profile as well as strengths and weaknesses. Finally, a mixed-methods analysis will be run to explore relevant aspects identified in the Post-TSST interviews and that may have not been fully considered in the original design [61]. The selection of the specific variables at this point will be determined by results of the previous stages.

Ethics and dissemination:

This study has been approved by the Ethics Committee of reference ('Comité de Ética de la Investigación Parc Taulí de Sabadell'). Written informed consent as approved by the Ethics Committee will be obtained after a full description of the study's aims and design. Participants will be informed of the confidentiality of their comments and of the contact information of the principal investigators to exercise their rights of access,

modification, opposition and cancellation of data following the European Data Protection legislation (2016/679; Ley Orgánica de Protección de Datos de Carácter Personal, 15/1999 del 13 de Diciembre, LOPD). Registry and use of information resulting from this study will follow the Declaration of Helsinki agreements. All biological samples will be collected and stored according to the corresponding legislation (Llei 14/2007 de Recerca Biomèdica). The study will follow WHO's recommendations for research on violence against women [62].

The dissemination of the results of our project will start at the level of the participants during the final workshop, which is expected to act as a first step for developing prevention tools and information resources that are essentially built by women themselves. We will carry out policy-dialogues and workshops with relevant regional and national representatives aimed at enhancing the current policies and roadmaps regarding the training and management in the educational and healthcare areas. Spain counts with relevant programs in the field of violence against women [63], and we expect to provide these initiatives with evidence-based data that can help build innovative solutions. At the level of the dissemination of results in the scientific community, the strategy includes the publication of the results in international peer-reviewed scientific journals and the presentation in national and international congresses. Also, the project is expected to strengthen the way health-care providers respond to women who have experienced violence. A series of courses will be developed based on the results of this project and others with similar objectives to inform the work of psychologists, psychiatrists, social workers, nurses and any professional association that might be willing to receive the training. The complete set of results from the study

will be used to develop guidelines and recommendations for actions that will be distributed among professionals.

Discussion:

The prevention of violence against women in general, and of IPV in particular, has risen as a priority on the international public health agenda, and research is playing a key role in the detection of protective factors and the development of effective interventions [64]. Are there cognitive implications of exposure to gender-based violence? Which systems underlie these effects, what causes them? Can they be reversed? These are questions that exceed the laboratory settings and impact "the real world". Our proposal aims at targeting these traits, which not only impair women's daily functioning but also feed a cycle of attitudes, norms and beliefs that justify dominant notions of masculinity and stigmatise victims [65,66]. Hence, the inclusion of a mixed-methods approach that integrates subjective reports with neurobiological data is a key aspect of this protocol.

Regarding methodological issues, the TSST is a powerful tool to identify dysfunctional patterns of coping that may help explain some critical aspects of the behavioural responses of IPV-exposed women. However, we have included the TSST only after extensively discussing the possible distress that may be caused to women, and the benefits of including the measure in the study. Our decisions throughout the project have been guided by the WHO Practical Guide for Researchers and Activists [67]. This document summarizes all aspects of research in this field and provides with useful recommendations to assure the project achieves the objective of serving the target women. The safety of respondents and the research team is our priority and it is our

advice that it be that of any other study working with this population. The identification of any problem in this respect must result in the immediate interruption of the assessment. The research team must be trained, and the assessment must be conducted in a location different to that where women receive health and social assistance.

The main limitation in our study is that the limited sample size will prevent exploring putative modulatory effects of relevant variables such as other lifetime stressful experiences. Also, we will not be able to test our hypothesis among women over 50 years of age due to restrictions in the inclusion/exclusion criteria. We would like to acknowledge the need for further information and research regarding IPV in the population of women aged 50 years and older, as has been highlighted by others before us [2]. In turn, our study has the potential to provide evidence to serve a deeper understanding of IPV and the vulnerability and resilience processes that IPV-exposed women present. This information will allow professionals and institutions to better understand and address this reality. Ultimately, it is expected that the results of this research will serve as the foundation to build evidence-based tools for the prevention of re-victimization among women exposed to IPV and of IPV in at-risk groups.

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Authors' contributions: XG, RN and AA were responsible for determining the content and scope of the study, and for the design. CE and DP were involved in the definition of the protocol. All authors were involved in study methods and tools. XG drafted the manuscript with critical input from the rest of authors, who read and approved the final manuscript.

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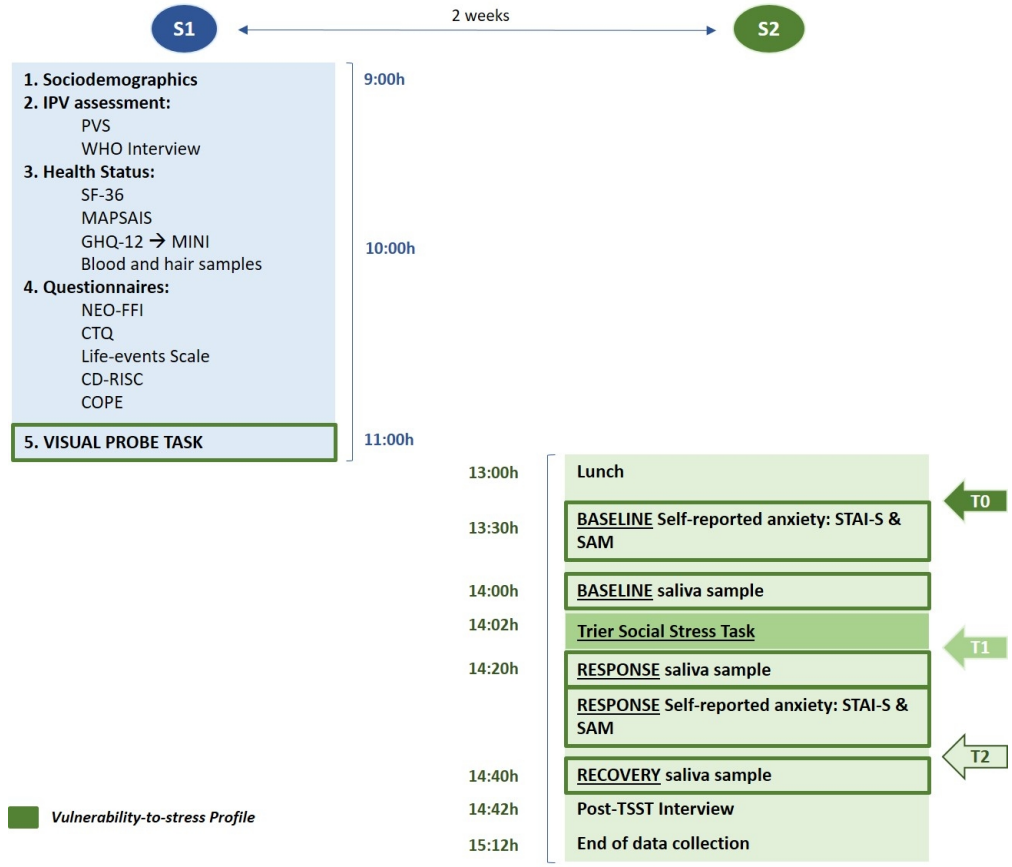
Caption Figure 1: Procedures of the study. Session 2 (S2) will be scheduled 2 weeks after session 1 (S1) and will take place in the afternoon. CD-RISC: Connor-Davidson Resilience scale; COPE: COPE Inventory; CTQ: Childhood Trauma Questionnaire; GHQ-12: General Health Questionnaire; MAPSAIS: Miller Abuse Physical Symptom and Injury Scale; MINI: Mini-International Neuropsychiatric Interview; NEO-FFI: NEO five-factor inventory; PVS: Partner violence screen; SAM: Self-Assessment Manikin; SF-36: Short form 36 health survey; STAI: State-Trait Anxiety Inventory; TSST: Trier

Social Stress Task; WHO Interview: World Health Organization Violence Against Women Instrument.



Caption Figure 1: Procedures of the study. Session 2 (S2) will be scheduled 2 weeks after session 1 (S1) and will take place in the afternoon. CD-RISC: Connor-Davidson Resilience scale; COPE: COPE Inventory; CTQ: Childhood Trauma Questionnaire; GHQ-12: General Health Questionnaire; MAPSAIS: Miller Abuse Physical Symptom and Injury Scale; MINI: Mini-International Neuropsychiatric Interview; NEO-FFI: NEO five-factor inventory; PVS: Partner violence screen; SAM: Self-Assessment Manikin; SF-36: Short form 36 health survey; STAI: State-Trait Anxiety Inventory; TSST: Trier Social Stress Task; WHO Interview: World Health Organization Violence Against Women Instrument.

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Supplementary material: detailed description of variables and measures.

1. Main outcome variables

The main hypothesis of our study is that women exposed to IPV, in contrast to a group of women without a history of IPV, will present a vulnerability-to-stress profile characterized by higher neuroendocrine and behavioural responsiveness to stress associated with a selective attentional bias towards threat. Hence, the main outcome variables in our study are:

Variables	Measures	Reference for Validation
Neuroendocrine response to acute stress during the Trier Social Stress Task	Salivary cortisol will be collected at T0, T1 and T2 using Salivette© Cortisol collection devices (Sarstedt AG & Co., Germany). Salivary cortisol levels will be determined in our laboratory by means of a competitive radio-immunoassay (RIA) technique highly correlated with the Salivary Cortisol Elisa Kit (Salimetrics, LCC, PA, USA).	The Trier Social Stress Task reliably activates the HPA axis and triggers a two- to three-fold increase in cortisol in about 70%-80% of participants. Reference: Kudielka BM, Hellhammer DH, Kirschbaum C. Ten years of research with the Trier Social Stress Test (TSST) - revisited. In: Harmon-Jones E, Winkielman P, eds. *Social Neuroscience: Integrating Biological and Psychological Explanations of Social Behavior*. 2007. 512. The reliability of the salivary cortisol TSST response shows correlations over the days between 0.38-0.60. Reference: Kirschbaum C, Prussner JC, Stone AA, *et al.* Persistent high cortisol responses to repeated psychological stress in a subpopulation of healthy men. *Psychosom Med* 1995;**57**:468–74.
Behavioural response to acute stress during the Trier Social Stress Task	Anxiety and emotional response to stress will be measured using the State-Trait Anxiety Inventory (STAI) and the Self-Assessment Manikin (SAM)	The State-Trait Anxiety Inventory (STAI) presents a high reliabilty in both trait and state subscale, reporting in the Spanish version Cronbach's α coefficients between 0.90 and 0.94. Reference for the original version: Spielberger CD, Sydeman SJ. State-trait anxiety inventory and state-trait anger expression inventory. In: Maruish EM, ed. *The use of psychological testing for treatment planning and outcome assessment*. Hillsdale, NJ: : Lawrence Erlbaum Associates, Inc. 1994. 292–321. Reference for the Spanish adaptation: Guillen, A. & Buela, G. Actualización psicométrica y funcionamiento diferencial de los ítems en el State Trait Anxiety Inventory (STAI). *Psicothema* 2011;**23**: 510-515. The Self-Assessment Manikin (SAM) was specifically designed to assess emotional states using a non-verbal measure that can be applied across transcultural settings with diverse populations. Reference for the original version: Bradley MM, Lang PJ. Measuring emotion: The self-assessment manikin and the semantic differential. *J Behav Ther Exp Psychiatry* 1994;**25**:49–59.
Selective attentional bias	Visual Probe Task (VPT)	The Visual Probe Task used in our study is the non-verbal version described in: Sipos ML, Bar-Haim Y, Abend R, *et al.* Postdeployment threat-related attention bias interacts with combat exposure to account for PTSD and anxiety symptoms in soldiers. *Depress Anxiety* 2014; **31**:124-9. Reference for original version: MacLeod C, Mathews A, Tata P. Attentional bias in emotional disorders. *J Abnorm Psychol* 1986;**95**:15–20. doi:10.1037//0021-843x.95.1.15 Although meta-analyses have proven the validity of the task (Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M.J., & van IJzendoorn, M.H. Threat-related attentional bias in anxious and non-anxious individuals: A meta-analytic study. *Psychol Bull* 2007;**133**:1–24.), some concerns have been reported regarding the retest reliability of the bias score (Schmukle SC. Unreliability of the dot probe task. *Eur J Pers* 2005;**19**:595–605). We will test the reliability of the VPT in our study against the included measures of anxiety and cognition presented below.

2. Explanatory variables: assessment of exposure to IPV and childhood maltreatment

The main explanatory variable is exposure to IPV, which will be screened in all participants and described in detail among the exposed women. Because women victims of IPV are more likely to report a history of childhood trauma (European Agency for Fundamental Rights. Violence against women: an EU-wide survey Main results. Vienna, Austria: 2014), and violence during childhood also affects the stress system of women (Mielock AS, Morris MC, Rao U. *J Affect Disord* 2017;**209**:46-52) exposure to childhood violence will also be included as an independent variable in the assessment.

Variables	Measures	Reference for validation
Initial screening of exposure to IPV	Partner Violence Screen (PVS)	The inter-test reliability of the Spanish adaptation of the PVS has shown kappa values between 0.7 and 0.8. Reference for the original version: Feldhaus, KM., Kozoil-McLain, J., Amsbury, HL., *et al.* Accuracy of 3 brief screening questions for detecting partner violence in the emergency department. *J Am Med Assoc* 1997;**3**:104-5. Spanish adaptation: Garcia-Esteve, L., Torres, A., Navarro, P., Ascaso, C., Imaz, M. L., Herreras, L., & Valdés, M. Validación y comparación de cuatro instrumentos para la detección de la violencia de pareja en el ámbito sanitario. *Med Clin (Bar)* 2011;**137***:390–397.*
Detailed description of exposure to IPV including onset, frequency, time since last exposure	In-depth structured interview: WHO Violence Against Women Instrument (VAWI)	The questionnaire was translated during the original study before assessment to ensure transcultural, cross-country comparability. More details about the translation process can be found in Chapter 2: Definitions and questionnaire development of the original document. Reference for the original version: Garcia-Moreno C, Jansen HA, Ellsberg M, *et al*. WHO Multi-Country Study on Women's Health and Domestic Violence against Women. Initial results on prevalence, health outcomes and women's responses. Geneva: 2005. The Cronbach's α coefficients for the measures included in the VAWI are between 0.66 and 0.81 according to the validation of the instrument as reported in Garcia-Moreno C, Jansen HA, Ellsberg M, *et al.* Prevalence of intimate partner violence: findings from the WHO multi-country study on women's health and domestic violence. *Lancet* 2006;**368**:1260–9.
Exposure to childhood maltreatment including abuse and neglect	Childhood Trauma Questionnaire Short Form (CTQ-SF)	The Cronbach's α coefficients reported for the Spanish adaptation range from 0.66 to 0.94 for the different subscales of the CTQ-SF. Reference for the original version: Bernstein D, Stein J, Newcomb M, *et al.* Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Negl,* 2003;**27**:169–190. Spanish adaptation: Hernandez A, Gallardo-Pujol D, Pereda N, Arntz A, Bernstein D, Gaviria AM, Labad A, Valero J. & Gutiérrez-Zotes JA. Initial Validation of the Spanish Childhood Trauma Questionnaire-Short Form. *J Interper Viol,* 2012;**28**:1498–1518.

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3. Control variables: other variables of potential interest to the study

Variables	Measures	Reference for validation
Exposure to other relevant life events	Life-events Scale	The Spanish adaptation of the Life-events scale shows high test-retest reliability (Kappa between 0.61 and 0.87) and a Cronbach's α internal consistency coefficient of 0.44. Reference for the original version: Brugha T, Bebbington P, Tennant C, *et al.* The List of Threatening Experiences: A subset of 12 life event categories with considerable long-term contextual threat. *Psychol Med* 1985;**15**:189–49. Spanish adaptation: Monroy E, Moreno B, Luna J, *et al.* Psychometric properties of the List of Threatening Experiences--LTE and its association with psychosocial factors and mental disorders according to different scoring methods. *J Affect Disord*, 2013;**150**:931–940.
Coping styles	Brief Coping Orientation to Problems Experienced Inventory (Brief-COPE)	The Spanish adaptation of the Brief-COPE shows Cronbach's α coefficient of 0.7. Reference for the original version: Carver CS. You want to measure coping but your protocol's too long: Consider the brief COPE. *Int J Behav Med* 1997;**4**:92–100. Spanish adaptation: Perczek R, Carver CS, Price A, *et al.* Coping, mood, and aspects of personality in Spanish translation and evidence of convergence with English versions. *J Pers Assess* 2000;**74**:63–87.
Resilient behaviour	Connor-Davidson Resilience Scale (CD-Risc)	The Cronbach's α coefficient reported for the Spanish adaptation is 0.86. Reference for the original version: Connor, KM. & Davidson, JRT. Development of a new Resilience scale: The Connor-Davidson Resilience scale (CD-RISC). *Depress Anxiety* 2003;**18**:76–82. Spanish adaptation: Garcia MA, Gonzalez A, Robles H, Padilla JL, Peralta MI. Psychometric properties of the Connor-Davidson Resilience Scale (CD-RISC) in the Spanish Population. *Annals of psychology* 2019;**35**:33-40.
Health status: physical symptoms	Miller Abuse Physical Symptom and Injury Scale (MAPSAIS)	Test-restest reliability of the MAPSAIS is 0.63. For the present study we translated and back-translated the 25 items included in the original study. Reference for the original version: Miller C, Campbell J. *Reliability and Validity of the Miller Abuse Physical Symptom and Injury Scale (MAPSAIS)*. Chicago: Midwest Nursing Research Society 1993.
Global cortisol (hair concentration)	Elisa Kit (Salimetrics, LCC, PA, USA).	The reliability of the measure taken at different times is good, with correlations of 0.68-0.79. Reference: Stalder T, Kirschbaum C. Analysis of cortisol in hair--state of the art and future directions. *Brain Behav Immun* 2012;**26**:1019–29.
Self-perception of general health	Short Form 36 Scale for self-perceived health status (SF-36)	The Cronbach's α coefficients reported for the Spanish adaptation are all above 0.7, with the exception of the social relations dimension (0.45). Intraclass coefficients between 0.58-0.99. Reference for the original version: McHorney, CA., Ware, JE. & Raczek, AE. (1993). The MOS 36-item short-form health survey (Sf-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;**31**:247-263. Spanish adaptation: Alonso J, Prieto L. & Antó, JM. La versión española del SF-36 Health Survey (Cuestionario de Salud SF-36): un instrumento para la medida de los resultados clínicos. *Med Clin* 1995;**104**:771-776.
Current mental health state screening	General Health Questionnaire , 12 items version (GHQ-12)	The Cronbach's α coefficient reported for the Spanish adaptation is 0.78. Reference for the original version: Goldberg DP, Gater R, Sartorius N, *et al.* The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychol Med* 1997;**27**, 191–197. Spanish adaptation: Sánchez-López, MP. & Dresch, V. (2008). The 12-item General Health Questionnaire (GHQ-12): Reliability, external validity and factor structure in the Spanish population.

		Psicothema 2008;**20**:839–43.
In-depth assessment of mental health disorders	Mini International Neuropsychiatric Interview (MINI)	The kappa values for inter-observer reliability of the Spanish version range around 0.75, whereas test-retest reliability was close to 0.75. Reference for the original version: Sheehan D V., Lecrubier Y, Sheehan KH, *et al.* The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. In: *Journal of Clinical Psychiatry*. 1998. Spanish translation: Ferrando, L., Bobes, J., Gibert, J., Soto, M. Y Soto, O. (2000). *MINI. Entrevista Neuropsiquiátrica Internacional. Versión en Español 5.0.0. DSM-IV*. Traducida por, L. Franco-Alfonso.
Personality traits	Neuroticism-Extraversion-Openness Inventory, Five Factor version (NEO-FFI)	Cronbach's α internal consistency coefficients are above 0.85 for the NEO PI-R dimension scales, whereas they range between 0.60 and over 0.80 for 25 out of 30 NEO PI-R facet scales. Reference for the original version: Costa PT, McCrae RR. *Revised NEO personality inventory (NEO-PI-R) and NEO five-factor inventory (NEO-FFI)*. Odessa, FL: : Psychological Assessment Resources, Inc. 1992. Spanish adaptation: Cordero A, Pamos A & Seisdedos N. *NEO PI-R Manual. Adaptación Española.* Madrid, España: TEA Ediciones 2008. Spanish normative data: Sanz J & Garcia-Pera MP. New Norms for the Spanish Adaptation of the NEO Personality Inventory-Revised (NEO PI-R): Reliability and Normative Data in Volunteers From the General Population. *Clinica y Salud* 2009;**20**:131-144.
Cognition: semantic memory	Rey Auditory Verbal Learning Test (RAVLT)	Cronbach's α coefficient is 0.80. Reference for the original version: Rey, A. (1964). *L'examen clinique en psychologie (The Clinical Psychological Examination).* Paris, FR: Presse Universitaires de France. Spanish adaptation: Valencia R. Prueba de Aprendizaje Auditivo-Verbal de Rey. *Hispanic Journal of Behavioral Sciences,* 1997;**19:**171-181.
Cognition: intelligence quotient	Wechsler Adult Intelligence Scale, 4th version (WAIS-IV)	The internal consistency of the test is very high, reaching Cronbach's α coeffcients of 0.9. Reference for the original version: Wechsler D, Coalson D, Raiford S. *Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV)*; Administering and Scoring Manual. San Antonio, TX, USA: Pearson. 2008. Spanish adaptation: De la Guia E, Hernánde, A, Paradell E & Vallar F. *WAIS-IV (Escala de Inteligencia de Wechsler para adultos-IV).* España: Pearson Educación 2012.
Cognition: executive function	Stroop Color and Word Test & Trail Making Test	The Stroop Color and Word Test presents a very high internal consistency, reaching Cronbach's α coefficient of 0.8. Reference for the original version: Golden CJ. Stroop Color and Word Test: A manual for clinical and experimental uses. *Chicago: Stoelting* 1978. Spanish adaptation: Golden, C. J. *Stroop test de colores y palabras, manual* (5° Ed.). Madrid, España: TEA Ediciones. 2007. The correlation of the Trail Making Test with other tests measuring similar constructs is between 0.36 and 0.48. Reference for the original version: Reitan RM. Validity of the Trail Making test as and indicator of organic brain damage. *Percept Mot Skills* 1958;**8**:271–6. Spanish adaptation: Fernández AL, Marino JC & Alderete AM. Estandarización y validez conceptual del test de trazo en una muestra de adultos argentinos. *Revista de Neurología Argentina* 2002;**27**:83-88.

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Adaptability to acute stress among women survivors of intimate partner violence: protocol for a mixed-methods cross-sectional study in a laboratory setting (BRAW study)

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Adaptability to acute stress among women survivors of intimate partner violence: protocol for a mixed-methods cross-sectional study in a laboratory setting (BRAW study)

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ABSTRACT

Introduction: Intimate partner violence (IPV) is the most common and alarming form of violence against women, affecting around 30% of all women around the world. Using an integrative methodology, we approach IPV as a form of chronic exposure to severe stress that alters the stress-response system of exposed women. The aim of this study is to test the hypothesis that sustained exposure to IPV in women confers a vulnerability-to-stress profile characterized by higher neuroendocrine and behavioural responsiveness associated with a selective attentional processing bias towards threat.

Methods and analysis: Women between 21 and 50 years old from the area of Barcelona (Spain) will be invited to participate. A sample of 82 women exposed to IPV and 41 women not exposed to IPV will be included and assessed for attentional bias and response to acute stress in a laboratory condition (the Trier Social Stress Task). The study will include quantitative and qualitative measures of cognitive performance, neuroendocrine activity and face-to-face interviews to obtain an integrative description of the stress-response profile of these women. Results are expected to help build resilience strategies with a long-lasting impression on women's healthy functioning.

Ethics and dissemination: The study has obtained the approval of the local Ethics Committee ('Comité de Ética de la Investigación Parc Taulí de Sabadell'; 2018551 version 1.2 June 2018). Besides the communication of results in peer-reviewed papers and scientific congresses, the project will inform guidelines and recommendations through policy-dialogues and workshops with relevant regional and national representatives for future work and prevention strategies. Participants will be invited to be an active part in the dissemination strategy focused on raising awareness of coping limitations and abilities that women themselves will be able to identify throughout the

study. The study has been registered at the ClinicalTrails.gov database (Identifier number: NCT03623555).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The design combines biological and psychosocial data in an integrative model of the health consequences of intimate partner violence.
- A mixed-methods approach allows to incorporate the voices of the survivors in the research process.
- Stress reactivity is measured in the laboratory using the gold standard Trier Social Stress Task
- The limited sample size will prevent exploring possible modulatory effects of relevant variables (i.e. other stressful experiences).

INTRODUCTION

The burden and prevalence of violence against women and girls worldwide has helped raise this issue as a global public health problem [1]. While women are exposed to several types of gender-based violence, almost 1 in 3 ever-partnered women worldwide (30%) have experienced intimate partner violence (IPV) [2]. This alarming reality applies to the territory of the European Union, where a recent EU-wide survey has estimated the prevalence of IPV to be 22% [3]. It also reflects on the IPV-estimates in Spain: 13% of women report suffering physical or sexual violence, and over 26.4% have suffered psychological and economic IPV [4].

Consistent evidence confirms that survivors of IPV, compared to women who have not suffered IPV, more frequently present chronic diseases such as diabetes, chronic pain, asthma, or cardiovascular disease [5,6]. Furthermore, mental health-related consequences are largely common among IPV survivors [7]. It has been estimated that up to 28% of the cases of depression can be attributed to lifetime exposure to IPV [8]. Only in the United States this translates into 1 million cases of depression per year that could be completely averted if no women had been exposed to IPV. In this regard, the possibility to suffer traumatic brain injury has to be considered as this is frequently associated with mental health problems, mostly depression [9]. Also relevant to the present study, women survivors of IPV are more likely to report a history of childhood trauma, which per se has long-term consequences in mental health [10,11]. In Europe, almost one third of women exposed to sexual IPV report having experienced sexual victimisation during childhood [3]. A recent multi-country study has reported an Odds Ratios ranging from 1.41 to 3.8 in six out of seven study sites [12].

This background clearly supports a relationship between IPV and disease. But the biological correlates of such association are still unclear. The most widely acknowledged theoretical approach proposes a model of chronic stress. Indeed, the victims of IPV are repetitively exposed to physical, emotional and sexual violence in the context of an intimate relationship that may last for years [13]. Each single exposure to IPV is expected to trigger the typical neurobiological response to stressful stimuli, which includes a wide range of neural and peripheral stress biological responses, including the activation of the sympathetic-adrenomedullary and hypothalamic-pituitary-adrenal (HPA) axes [14], and the subsequent release of catecholamines and cortisol, respectively. When this stress response presents frequently or persists continuously for an extended period of time, the mechanisms that were initially activated to cope with acute stress extend over time and can eventually lead to pathophysiology and psychiatric diseases [15]. However, the impact of chronic stress on basal cortisol secretion appears to be dependent on several critical factors, including the time since stress onset, the type of challenge and the possibility of control [16].

Stress-related biological dysregulations specific to IPV survivors have been addressed for the first time in a recent systematic review [17]. Authors reveal that this population present flattened diurnal cortisol rhythm and an overall higher diurnal secretion - a pattern expected after exposure to chronic stress. The extent to which these changes persist once exposure to the situation has finished is unclear. Interestingly, in IPV survivors that developed PTSD, but not in those without overt psychopathology, reduced baseline cortisol levels and enhanced suppression by dexamethasone has been reported [18]. In sum, previous literature consistently supports that the neurobiological mechanisms involved in the stress-response system are altered following IPV.

Importantly, these alterations can be placed in the core of the neurobiological pathogenesis of the associated health disorders [16].

Why our study?

Despite the critical importance of the stress-response system, most research on IPV has only evaluated basal activity of the HPA and other biological systems. This has left unanswered the question of whether women previously exposed to IPV present behavioural difficulties when coping with new emotional situations (i.e. anxiety, emotional arousal) and whether this is reflected in an altered HPA responsiveness. The activation of the stress system in response to novel stressful situations is a central matter as it reflects the person's capacity to respond to the changing demands that commonly occur at work and at home. For example, a job interview could be a stressful circumstance that affected women may have to face after recovering from IPV. The performance during the interview (i.e. getting or losing the job opportunity) will largely depend on the current person's neuroendocrine and behavioural vulnerability to emotionally stressful situations or, on the contrary, on the successful, resilient strategies women may present to cope with acute stress.

A history of chronic stress can alter responsiveness to further acute stressors in a way not predicted by basal HPA activity. These alterations can be either sensitization or blunting [19]. In this regard, experimental findings indicate that both acute and chronic exposure of adult rats to severe stress induce HPA cross-sensitization; that is, enhanced response to new acute stressors [20,21]. Human studies focused on the consequences of exposure to chronic stress also adopt this perspective. Evidence suggests that the chronic stress exposure implicated in caregiving is associated with dysfunctional

psychosocial behaviour related to maladaptive coping strategies when facing novel stressful circumstances. A key phenomenon in this respect is selective attentional processing [22], which refers to an attentional bias early on the process of the cognitive approach to any given situation that predisposes a person to an enhanced vigilance for threat. This bias towards threat has been linked to being a victim of interpersonal violence [23], and is associated with higher HPA axis activity [24]. Quite surprisingly, no study has yet evaluated selective attentional bias in association to acute stress responsiveness among women exposed to IPV.

In the present proposal we aim at identifying potential alterations in the adaptive response to acute stress among IPV-exposed women using valid measures of neuroendocrine and behavioural response to acute stress. We propose that these alterations persist in the long term even when the exposure to IPV has ceased. Given the innovative nature of this project, we will register the perceptions of the participants regarding their experience of acute stress. This qualitative information will allow the identification of variables that may be overlooked during the design of the study. Also, we will assess the long-termed marks of chronic stress on the global basal levels of cortisol in IPV survivors using hair-cortisol analysis, following previous studies on other stress-related situations [25,26].

Objectives of the study

The main (general) objective of our study is to compare the response to acute stress in a group of women with a history of IPV as opposed to women without such history from the same community. The specific objectives are:

1) To assess the neuroendocrine (HPA axis) and behavioural response to acute stress.
2) To study whether IPV women show selective attentional processing bias towards threat.
3) To identify the resilience strategies used by women in terms of psychosocial schemes (i.e. quantitative and qualitative information) and neuroendocrine regulation to cope with acute stress and their relationship with health status.
4) To examine global basal cortisol alterations in the group of IPV-exposed women using hair-cortisol analyses.

The main hypothesis of our study is that women exposed to IPV, in contrast to a group of women without a history of IPV, will present a vulnerability-to-stress profile. The specific sub-hypotheses of the study are:

1) The group of women exposed to IPV will present higher neuroendocrine and behavioural responsiveness to stress than the non-exposed group, as measured by self-reported behavioural scales and salivary cortisol, respectively.
2) A selective attentional processing bias towards threat will be associated with a higher response to acute stress in the group of women exposed to IPV, as opposed to the group of non-exposed women.
3) The performance and resilience strategies during an acute stress task will be self-perceived as poorer/weaker among the group of women exposed to IPV in contrast with the self-perceptions of the group of non-exposed women, as assessed using semi-structured interviews and quantitative scales. Weaker resilience strategies will be related to poorer health status.

4) Women exposed to IPV will present higher levels of hair cortisol indicating global basal cortisol alterations.

STUDY CONTEXT

Participants will be women from the general population who will be recruited through advertisements in the community and in social media. The interviews will take place in the facilities of Parc Taulí Foundation, the research branch of the Parc Taulí Healthcare Corporation (Corporació Sanitària Parc Taulí, CSPT). Participants will not receive monetary compensation for their participation in the research.

CSPT is a public healthcare legal entity that manages the third-level Parc Taulí Hospital along with primary healthcare centres, diagnostic and emergency units, and several transversal services including sexual and reproductive health programmes. It is the single healthcare provider for the area of the Catalan Eastern Occidental Vallès, which counts a total population of close to 500,000 people. Parc Taulí Foundation (Fundació Parc Taulí, FPT) provides support to CSPT in areas of research, teaching and innovation, and has been recognized as a University Institute affiliated to the Universitat Autònoma de Barcelona. FPT has a strong background in the promotion of healthy habits and social awareness in the community, and for the last decade has dedicated special efforts to enhance this line of work in the area of mental health.

Because social media will be an important tool for recruitment, participants in the study are expected to belong to areas in Catalonia that will exceed the catch zone of the reference Centre. In particular, we expect participants based in the area of Barcelona, which covers a population of approximately 1,620,000 inhabitants.

METHODS AND ANALYSIS

Study Design and Participants

We will use a mixed-methods, cross-sectional design in compliance with the Good Reporting of a mixed methods study (GRAMMS) framework [27]. The key element in the study is the inclusion of the Trier Social Stress Task (TSST), which provides a laboratory setting to measure the neuroendocrine and behavioural responses to acute stress. Quantitative data will be generated from various sources, including biological samples (hair, saliva) and clinical and behavioural scales that are described in detail in the procedures section below. Qualitative data will be generated from semi-structured interviews that will be used to register the participants' impressions regarding their experience during the TSST, with a focus on identifying emerging themes. The integration of these sources of data is the main justification for proposing a mixed-methods approach. While the sample size for the quantitative analysis has been calculated during the design phase of the study, the total number of semi-structured interviews may vary. Interviews will continue until data saturation has been reached in the analyses (i.e. no new emerging themes are identified from new interviews, expected 30 interviews [28]). The methods for each stage of the study are presented in more detail in the following sections.

Criteria for the inclusion of women in the study will be mainly guided by their previous exposure to IPV, which will define two groups of participants: an IPV-exposed group with an estimated sample size of 82 women, and a non-exposed IPV group with an estimated sample size of 41 women (see sample size calculation for further details). The definition of exposure to IPV will follow the World Health Organization guidelines: "IPV refers to any behaviour within an intimate relationship that causes physical,

psychological and sexual harm to those in the relationship" [29] and will include physical violence, sexual violence, emotional/psychological abuse and controlling behaviours. These forms of violence will also follow WHO's definitions [30] including but not limited to: 1) Acts of physical violence: the woman has been pushed, beaten up, choked or burnt by an intimate partner; 2) sexual violence: any form of sexual coercion by the intimate partner; 3) emotional/psychological abuse: the woman has been humiliated, intimidated, threatened by her intimate partner; 4) controlling behaviours: the woman has been isolated, monitored for her actions by her intimate partner, and restricted her access to financial resources, employment, education or medical care. In order to warrant chronic exposure to stress as proposed in the rationale of the study, the minimum time of duration of the violent relationship will be set at one year [16]. Also, to study of the long-term effects of IPV once the exposure has ceased, only women who have already ended the violent relationship for at least one year will be included.

Exclusion criteria will be as following: age below 21 (to allow a margin of accumulated relationship experience during adulthood) and over 50 (excluding menopause), having any pituitary and/or adrenal gland disorder, currently using steroid-based medications, being currently pregnant, lactating or menopausal, and having a severe illness that may affect cognitive performance and/or consciousness. No participant will be excluded on the basis of disability, ethnicity, religion or sexual orientation.

Procedures

Women interested in participating will actively contact us by the email address that will be detailed in the advertisement. At first contact, a researcher will assess

eligibility according to inclusion/exclusion criteria. If all criteria are met, a first face-to-face session will be scheduled for an in-depth interview, followed by a second session two weeks later to complete the assessment of response to acute stress exposure. A visual depiction of the procedures is presented in Figure 1, and a detailed description of the measures along with the reference for the Spanish translations of the scales is available as Supplementary Materials.

Session 1:

All participants will obtain a full description of the study's aims and procedures and all questions will be answered. Only those women willing to participate who sign an informed consent will be included in the study. Sociodemographic data will be collected through the use of a standardized self-report questionnaire. History of IPV will be extensively described combining standard measures of screening (Partner Violence Screen [31]) and an in-depth structured interview among women identified as survivors that include onset and frequency of IPV among other details (WHO Violence Against Women Instrument [29]). Exposure to other forms of interpersonal violence will also be collected at this point using the Childhood Trauma Questionnaire (CTQ, [32]) and the Life-events Scale [33]. A description of coping styles and resilient behaviour will be assessed using the Coping Orientation to Problems Experienced Inventory [34] and the Connor-Davidson Resilience Scale [35].

A comprehensive health profile will also be assessed during the initial interview that will provide information on physical and mental health status and history of clinical treatment. The Miller Abuse Physical Symptom and Injury Scale [36] and Short Form 36 Scale for self-perceived health status [37] scales will be used for the assessment of

physical symptoms and perception of general health. As part of the comprehensive health profile assessment, a full laboratory test will be included to obtain a description of biochemistry markers. For this objective, peripheral blood samples will be collected by a nurse in 15 mL of capacity tubes. The General Health Questionnaire (12 items version, GHQ-12) [38] will be used for screening of mental health status and the Mini International Neuropsychiatric Interview [39] for in-depth assessment when GHQ-12 suggests mental health disorders. Personality traits will be assessed using the Neuroticism-Extraversion Openness Inventory (Five Factor version, NEO-FFI [40]).

Finally, a hair sample of more than 3 cm length with an approximate diameter of 30 single hairs will be taken from the upper part of the scalp. This technique provides a measure of the integrated global basal cortisol over the growth period of a specific hair segment, typically 1 cm/month [41]. As glucocorticoid levels cannot be experimentally manipulated in humans, we have biologically validated this variable measuring hair corticosterone in rats [42]. Moreover, we have also technically validated in our laboratory the measurement of hair cortisol in humans using the well-characterized Salivary Cortisol Elisa Kit (Salimetrics, LCC, PA, USA). Reliability of the measure taken at different times is good, with correlations of 0.68-0.79 [41].

At this point of the assessment, we will examine selective attentional processing by means of the Visual Probe Task (VPT) [43,44]. Briefly, participants will presented simultaneously with a pair of stimuli, one emotionally salient and one neutral for 500ms time, followed by a probe that replaces one of the two stimuli. Participants will be required to respond as accurately and as quickly as possible to the probe. Reaction times will be recorded and contrasted. A decreased reaction time to a probe replacing emotional stimuli compared to the neutral stimuli will provide a measure of bias to be vigilant for

threatening information. Assessment of the VPT will be accompanied by a brief complementary cognitive examination that will include semantic memory [45], intelligence quotient [46], and executive functioning [47,48].

Session 2:

After two weeks, a second appointment will be scheduled focused on the assessment of the response to acute stress. In order to control for potential differences in circadian rhythm associated with endocrine activity, all participants will have a light lunch in the cafeteria of the centre one hour before the start of the laboratory phase. To control for inter-individuals differences in cortisol levels meals, heavy physical activity 2 hours before lunch, and coffee consumption the same day are not allowed [49,50].

Acute psychosocial stress response will be assessed using the TSST [51]. This is the gold standard in biopsychological stress research, and can be briefly described as a mock job interview. The participants are instructed to imagine that having applied for their "dream job", they are now invited to a job interview. Participants are aware of no real job is at issue. The TSST consists of three successive phases: (1) a preparation period (3 minutes), (2) a free speech task in which the participants have to argue why they are the best candidate for the job (5 minutes), and (3) a mental arithmetic task in which participants have to sequentially subtract an odd two-digit number from an odd four-digit number (e.g., 17 from 2023; 5 minutes). The two tasks are performed while standing in an upright position in front of a selection committee consisting of two members, one male and one female, dressed in white lab coats, acting in a reserved manner and providing no facial or verbal feedback [52]. The interview is recorded in a video camera, a procedure that has been demonstrated effective in triggering further

threat [53]. The researchers in charge of the TSST are blinded to the condition (IPV-exposed or not exposed) of the participants.

The primary measure of the stress response will be the activation of the HPA axis by assessing the release of cortisol immediately before the TSST (T0), immediately after (20 minutes after the start of TSST, T1), and at recovery (40 minutes after the start of TSST, T2). Saliva samples will be obtained by means of Salivette© Cortisol collection devices (Sarstedt AG & Co., Germany) and will be stored at -20°C on the same day of recollection. Salivary cortisol levels will be determined by means of a competitive radio-immunoassay (RIA) technique developed in our laboratory that uses anti-cortisol antibody (121116) and Iodinated cortisol (121126) from MP-Biomedicals (Valiant Co., Ltd., USA). We have validated this RIA against the Salivary Cortisol Elisa Kit (Salimetrics, LCC, PA, USA), showing a high correlation of r=0.95. The reliability of the salivary cortisol TSST response is moderated, with Spearman correlations over the days between 0.38-0.60 [54].

The behavioural response to acute stress will be the level of anxiety and perceived stress. To fulfil this aim, the individuals' responses to two different scales will be registered. The first of these scales will be the state examination of the State-Trait Anxiety Inventory (STAI, [55]), which will allow to examine the self-perceived level of state anxiety at baseline (T0) and after the task (T1). Cronbach's alpha reliability of the Spanish adaptation of this measure is high: 0.90 for the Trait Inventory and 0.94 for State Inventory. The second scale will be the Self-Assessment Manikin (SAM, [56]), which is a picture-oriented scale to register an emotional response in its three key features: valence/pleasure of the response, arousal, and dominance/control. This is a nonverbal scale specifically designed to be applied in transcultural settings.

The final half hour of the second appointment will be dedicated to a face-to-face interview aiming to systematically register subjective experience-based issues related to stress and coping strategies that may have not been included in the quantitative assessment. This interviewer will have no previous contact with the women up to this moment Participants will be invited to a semi-structured interview regarding their feelings, perceptions and attitudes during exposure to the acute stress (TSST), generating a personal narrative of the experience by women themselves [57]. Conversations will be recorded and the transcripts will be used for analysis.

Sample size calculation

Sample size has been calculated using a priori power analysis conducted in G*Power version 3.1.9.2 for Windows [58], with a focus on the neuroendocrine response to acute stress that will be assessed by means of the changes in the levels of salivary cortisol during TSST at T0, T1 and T2. It has been estimated that the TSST reliably activates the HPA axis and triggers a two- to three-fold increase in cortisol in about 70%-80% of participants [59]. Assuming a conservative effect size of 0.2 based on this reference, and the correlation between measures of 0.38 mentioned above [54], if we want to detect differences among the two groups with a power of 0.95 and an alpha of 0.05, we will need a sample size of 41/group to detect a significant effect (repeated measures ANOVAs for the predictor analysis: Test Family: F tests, Statistical test: ANOVA, Repeated measures, within-between interaction, Type of power analysis: A priori, 2 groups, 3 measurements). Because violence during childhood can also affect the stress system of women [60], the sample size of the group exposed to IPV will be doubled to include an even number of women with and without a history of childhood

violence, as assessed by the CTQ. Therefore, the complete sample will include: i) the group of women exposed to IPV composed of 82 women, 41 of them with history of childhood abuse and 41 of them without such history, and ii) the group of women not exposed to IPV, composed of 41 women. The total sample size will equal 123 women. Data collection will continue until the minimum sample is reached.

Participants and public involvement

The study has been designed with a focus on exposure to IPV as a main risk factor for a number of health-related issues, particularly mental health disorders. During the design stage the research team was particularly concerned that the exposure to acute stress was clearly justified, and the information obtained through this laboratory condition could not be collected in other forms. It was also highly important that the experimental condition would resemble a situation that any person could be presented with in real life. The team consulted local experts in the field of violence against women before deciding on the use of the TSST.

During the recruitment period, different local governmental and non-governmental organizations will be involved as consultants and sources of identification of potential participants. They will also be contacted to discuss the final results and potential recommendations.

The final stage of the study will include a workshop session where the participants will be placed in the centre of the experience and will be invited to contribute to possible solutions. This session will have two parts with different purposes. The first will be an open session aiming at disseminating the results of the study, including specific interventions to raise awareness about the consequences of IPV. This first part will target

all the participants as well as other stakeholders and social agents that may benefit from this information. The second session will be a closed participatory session targeting the participants with history of IPV aimed at identifying strategies to build resilience and discussing prevention strategies. The session will end with the co-creation of an inventory of prevention strategies (from survivors and for survivors) and ideas to communicate them.

Data management plan and measures

All participants will be assigned a code at the moment of inclusion in the study, and the identification information will be saved separately to warrant confidentiality. Original data will be transferred to databases that will be archived in FPT applying the standard processes of the centre. These same standard processes will be used to secure data quality throughout the study.

Firstly, a detailed descriptive analysis will be run that will include the information from: i) the initial interview, ii) hair-cortisol analysis, iii) the results of the VPT task, iv) the neuroendocrine response trajectories during the TSST, v) the self-reported levels of behavioural responses during the TSST. This information will be presented in the form of contingency tables. Group-comparison analysis will be run between the groups of IPV-exposed women (with and without history of childhood maltreatment) and non-exposed women. Tests will be selected according to the nature of the variables and their sample distributions.

The primary outcome variable in the study is the neuroendocrine response to acute stress, measured on the basis of salivary cortisol at T0, T1 and T2. The secondary outcome variables are the behavioural responses to acute stress as measured by self-

reported behavioural scales: perceived levels of anxiety at T0 and T1 (STAI), perceived levels of valence/pleasure, arousal and control at T0 and T1 (SAM). Hence, these will be the dependent variables in all analyses (Supplementary Table 1). The hypothesis being tested at this stage will be that the three groups differ in the measures of response to stress both at the neuroendocrine (salivary cortisol) and behavioural (self-reported behavioural scales) levels. To test this hypothesis, we will use a generalized lineal model, specifically a repeated measures design [61], using group and time as the explanatory variables (Supplementary Table 2).

The following stage will test the hypothesis that bias towards threat as measured by the VPT task is associated with the response to acute stress in the group of women with IPV. To test this hypothesis, an independent analysis will be run with VPT, group and time as explanatory variables. Two independent analysis will be run for salivary cortisol and for behavioural outcomes.

Other variables of potential interest will be included as covariates in the models: age, level of education, exposure to other relevant life events, copying styles, resilient behaviour, general health status (physical symptoms, global cortisol hair concentration, self-perception), mental health status, personality traits, and cognition (semantic memory, intelligence quotient, executive function) (Supplementary Table 3). Data will be analysed using SPSS software (IBM SPSS Statistics for Windows, Version 23.0. Armonk; NY: IBM Corp).

Regarding the semi-structured interviews that follow the TSST, the research team will develop the general guidelines before the start of the study. All interviews will be recorded, and the transcriptions of these recordings will be conducted by trained professionals. Content analysis will be used to extract the fundamental aspects of the

discourse on the experience of women and their resilience strategies [62]. The aim will be to search data saturation, this is, when new interviews do not provide new findings on the results. Transcriptions will be analyzed using software for qualitative analysis, Atlas.ti (Atlas.ti 8 Windows, Scientific Software Development GmbH). Following on these data, a second tier for analysis will focus on profile differentiation in order to capture the different narratives and profiles that may arise across participants, and related to other variables (childhood abuse, socio-economic position, education). This will lead to highlight the common traits within each profile as well as strengths and weaknesses. Finally, the integration of quantitative and qualitative data will take place through a mixed-methods analysis that will be run to explore relevant aspects identified in the Post-TSST interviews and that may have not been fully considered in the original design [63]. The selection of the specific variables at this point will be determined by results of the previous stages. Integration of the different sources of data will also be performed during the interpretation of the results using data presented in theme-by-statistics joint display [64]

Ethics and dissemination:

This study has been approved by the Ethics Committee of reference ('Comité de Ética de la Investigación Parc Taulí de Sabadell'). Written informed consent as approved by the Ethics Committee will be obtained after a full description of the study's aims and design. Participants will be informed of the confidentiality of their comments and of the contact information of the principal investigators to exercise their rights of access, modification, opposition and cancellation of data, and withdrawal from the study without any repercussions, following the European Data Protection legislation (2016/679; Ley

Orgánica de Protección de Datos de Carácter Personal, 15/1999 del 13 de Diciembre, LOPD). Registry and use of information resulting from this study will follow the Declaration of Helsinki agreements. All biological samples will be collected and stored according to the corresponding legislation (Llei 14/2007 de Recerca Biomèdica). The study will follow WHO's recommendations for research on violence against women [65]. Participants will be compensated for their transportation expenses, but no other compensation will be included in the study. They will be asked about their experience with the study immediately after completion of the interviews, and this information will be collected and used to provide feedback upon evaluation of the study. Finally, all participants will be provided with information regarding counselling services and other resources as appropriate.

The dissemination of the results of our project will start at the level of the participants during the final workshop, which is expected to act as a first step for developing prevention tools and information resources that are essentially built by women themselves. We will carry out policy-dialogues and workshops with relevant regional and national representatives aimed at enhancing the current policies and roadmaps regarding the training and management in the educational and healthcare areas. Spain counts with relevant programs in the field of violence against women [66], and we expect to provide these initiatives with evidence-based data that can help build innovative solutions. At the level of the dissemination of results in the scientific community, the strategy includes the publication of the results in international peer-reviewed scientific journals and the presentation in national and international congresses. Also, the project is expected to strengthen the way health-care providers respond to women who have experienced violence. A series of courses will be developed

based on the results of this project and others with similar objectives to inform the work of psychologists, psychiatrists, social workers, nurses and any professional association that might be willing to receive the training. The complete set of results from the study will be used to develop guidelines and recommendations for actions that will be distributed among professionals.

Discussion:

The prevention of violence against women in general, and of IPV in particular, has risen as a priority on the international public health agenda, and research is playing a key role in the detection of protective factors and the development of effective interventions [67]. Are there cognitive implications of exposure to gender-based violence? Which systems underlie these effects, what causes them? Can they be reversed? These are questions that exceed the laboratory settings and impact "the real world". Our proposal aims at targeting these traits, which not only impair women's daily functioning but also feed a cycle of attitudes, norms and beliefs that justify dominant notions of masculinity and stigmatise survivors [68,69]. Hence, the inclusion of a mixed-methods approach that integrates subjective reports with neurobiological data is a key aspect of this protocol.

Regarding methodological issues, the TSST is a powerful tool to identify dysfunctional patterns of coping that may help explain some critical aspects of the behavioural responses of IPV-exposed women. However, we have included the TSST only after extensively discussing the possible distress that may be caused to women, and the benefits of including the measure in the study. Our decisions throughout the project have been guided by the WHO Practical Guide for Researchers and Activists

[70]. This document summarizes all aspects of research in this field and provides with useful recommendations to assure the project achieves the objective of serving the target women. The safety of respondents and the research team is our priority and it is our advice that it be that of any other study working with this population. The identification of any problem in this respect must result in the immediate interruption of the assessment. The research team must be trained, and the assessment must be conducted in a location different to that where women receive health and social assistance.

The main limitation in our study is that the limited sample size will prevent exploring putative modulatory effects of relevant variables such as other lifetime stressful experiences. Also, we will not be able to test our hypothesis among women over 50 years of age due to restrictions in the inclusion/exclusion criteria. We would like to acknowledge the need for further information and research regarding IPV in the population of women aged 50 years and older, as has been highlighted by others before us [2]. The mixed-methods approach proposed in our project is expected to be challenging because the qualitative perspective tends to emphasise an inductive method that highlights subjective information while the quantitative perspective is based on a deductive method largely based on objectivity and generalisation. In turn, our study has the potential to provide evidence to serve a deeper understanding of IPV and the vulnerability and resilience processes that IPV-exposed women present. This information will allow professionals and institutions to better understand and address this reality. Ultimately, it is expected that the results of this research will serve as the foundation to build evidence-based tools for the prevention of re-victimization among women exposed to IPV and of IPV in at-risk groups.

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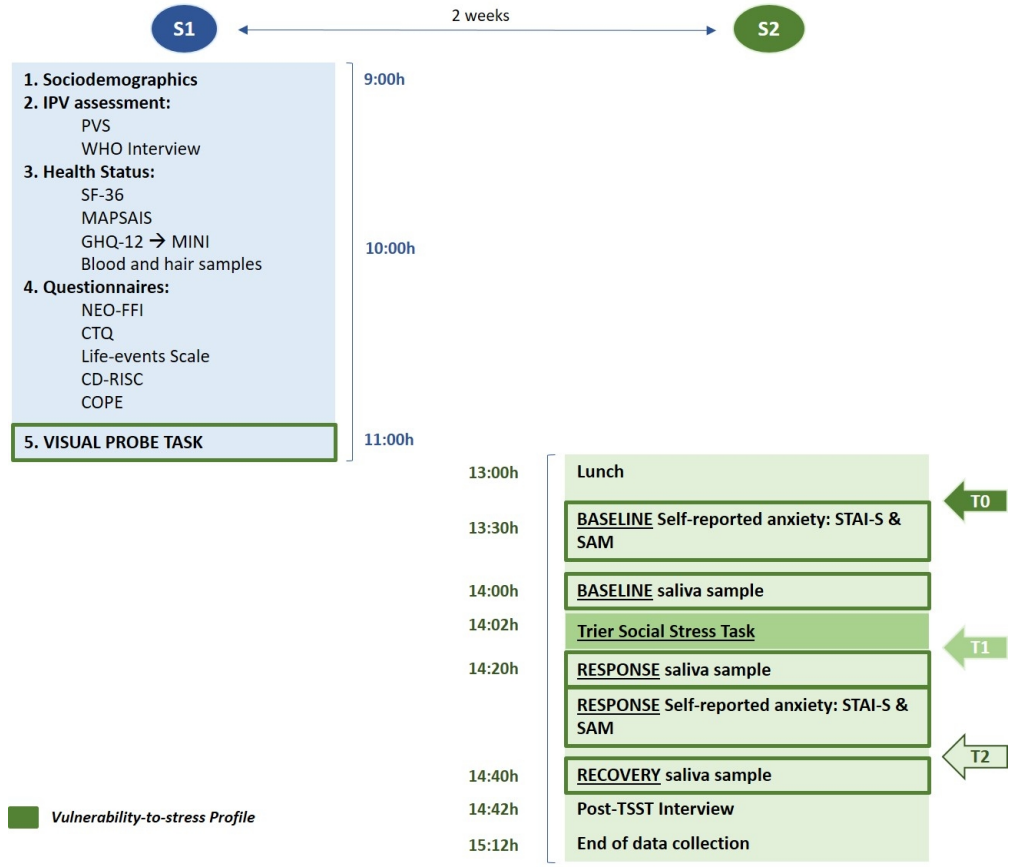
Caption Figure 1: Procedures of the study. Session 2 (S2) will be scheduled 2 weeks after session 1 (S1) and will take place in the afternoon. CD-RISC: Connor-Davidson Resilience scale; COPE: COPE Inventory; CTQ: Childhood Trauma Questionnaire; GHQ-12: General Health Questionnaire; MAPSAIS: Miller Abuse Physical Symptom and Injury Scale; MINI: Mini-International Neuropsychiatric Interview; NEO-FFI: NEO five-factor inventory; PVS: Partner violence screen; SAM: Self-Assessment Manikin; SF-36: Short form 36 health survey; STAI: State-Trait Anxiety Inventory; TSST: Trier

Social Stress Task; WHO Interview: World Health Organization Violence Against Women Instrument.



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Supplementary material: detailed description of variables and measures.

Supplementary Table 1. The outcome variables in this study are the neuroendocrine response to acute stress and the behavioural response to acute stress. All the outcome variables are listed including measures and references:

Variables	Measures	Reference for Validation
Neuroendocrine response to acute stress during the Trier Social Stress Task	Salivary cortisol will be collected at T0, T1 and T2 using Salivette© Cortisol collection devices (Sarstedt AG & Co., Germany). Salivary cortisol levels will be determined in our laboratory by means of a competitive radio-immunoassay (RIA) technique highly correlated with the Salivary Cortisol Elisa Kit (Salimetrics, LCC, PA, USA).	The Trier Social Stress Task reliably activates the HPA axis and triggers a two- to three-fold increase in cortisol in about 70%-80% of participants. Reference: Kudielka BM, Hellhammer DH, Kirschbaum C. Ten years of research with the Trier Social Stress Test (TSST) - revisited. In: Harmon-Jones E, Winkielman P, eds. *Social Neuroscience: Integrating Biological and Psychological Explanations of Social Behavior*. 2007. 512. The reliability of the salivary cortisol TSST response shows correlations over the days between 0.38-0.60. Reference: Kirschbaum C, Prussner JC, Stone AA, *et al.* Persistent high cortisol responses to repeated psychological stress in a subpopulation of healthy men. *Psychosom Med* 1995;**57**:468–74.
Behavioural response to acute stress during the Trier Social Stress Task	Anxiety and emotional response to stress will be measured using the State-Trait Anxiety Inventory (STAI) and the Self-Assessment Manikin (SAM)	The State-Trait Anxiety Inventory (STAI) presents a high reliabilty in both trait and state subscale, reporting in the Spanish version Cronbach's α coefficients between 0.90 and 0.94. Original version: Spielberger CD, Sydeman SJ. State-trait anxiety inventory and state-trait anger expression inventory. In: Maruish EM, ed. *The use of psychological testing for treatment planning and outcome assessment*. Hillsdale, NJ: : Lawrence Erlbaum Associates, Inc. 1994. 292–321. Spanish adaptation: Guillen, A. & Buela, G. Actualización psicométrica y funcionamiento diferencial de los ítems en el State Trait Anxiety Inventory (STAI). *Psicothema* 2011;**23**: 510-515. The Self-Assessment Manikin (SAM) was specifically designed to assess emotional states using a non-verbal measure that can be applied across transcultural settings with diverse populations. Original version: Bradley MM, Lang PJ. Measuring emotion: The self-assessment manikin and the semantic differential. *J Behav Ther Exp Psychiatry* 1994;**25**:49–59.

Supplementary Table 2. The main explanatory variables in this study are group (IPV with and without childhood maltreatment, and controls) and time, while selective attention bias is proposed as explanatory variable for a secondary set of analysis. All explanatory variables are listed including measures and references:

Variables	Measures	Reference for validation
Group	Initial screening of exposure to IPV using the Partner Violence Screen (PVS)	The inter-test reliability of the Spanish adaptation of the PVS has shown kappa values between 0.7 and 0.8. Original version: Feldhaus, KM., Kozoil-McLain, J., Amsbury, HL., *et al.* Accuracy of 3 brief screening questions for detecting partner violence in the emergency department. *J Am Med Assoc* 1997;**3**:04-5. Spanish adaptation: Garcia-Esteve, L., Torres, A., Navarro, P., Ascaso, C., Imaz, M. L., Herreras, Z., & Valdés, M. Validación y comparación de cuatro instrumentos para la detección de la violencia de pareja en el ámbito sanitario. *Med Clin (Bar)* 2011;**137***:390–397.*
	Detailed description of exposure to IPV including onset, frequency, time since last exposure using the in-depth structured interview: WHO Violence Against Women Instrument (VAWI)	The questionnaire was translated during the original study before assessment to ensure transcultural, cross-country comparability. More details about the translation process can be found in Chapter 2: Definitions and questionnaire development of the original document. Original version: Garcia-Moreno C, Jansen HA, Ellsberg M, *et al*. WHO Multi-Country Study on Women's Health and Domestic Violence against Women. Initial results on prevalence, health outcomes and women's responses. Geneva: 2005. The Cronbach's α coefficients for the measures included in the VAWI are between 0.66 and 0.81 according to the validation of the instrument as reported in Garcia-Moreno C, Jansen HA, Ellsberg M, *et al.* Prevalence of intimate partner violence: findings from the WHO multi-country study on women's health and domestic violence. *Lancet* 2006;**368**:1260–9.
	Exposure to childhood maltreatment including abuse and neglect using the Childhood Trauma Questionnaire Short Form (CTQ-SF)	The Cronbach's α coefficients reported for the Spanish adaptation range from 0.66 to 0.94 for the different subscales of the CTQ-SF. Original version: Bernstein D, Stein J, Newcomb M, *et al.* Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Negl,* 2003;**27**:169–190. Spanish adaptation: Hernandez A, Gallardo-Pujol D, Pereda N, Arntz A, Bernstein DP, Gaviria AM, Labad A, Valero J. & Gutiérrez-Zotes JA. Initial Validation of the Spanish Childhood Trauma Questionnaire-Short Form. *J Interper Viol,* 2012;**28**:1498–1518.
Selective attentional bias	Visual Probe Task (VPT)	The Visual Probe Task used in our study is the non-verbal version described in: Sipos ML, Bar-Haim Y, Abend R, *et al.* Postdeployment threat-related attention bias interacts with combat exposure to account for PTSD and anxiety symptoms in soldiers. *Depress Anxiety* 2014; **31**:124-9. Reference for original version: MacLeod C, Mathews A, Tata P. Attentional bias in emotional disorders. *J Abnorm Psychol* 1986;**95**:15–20. doi:10.1037//0021-843x.95.1.15 Although meta-analyses have proven the validity of the task (Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M.J., & van IJzendoorn, M.H. Threat-related attentional bias in anxious and non-anxious individuals: A meta-analytic study. *Psychol Bull* 2007;**133**:1–24.), some concerns have been reported regarding the retest reliability of the bias score (Schmukle SC. Unreliability of the dot probe task. *Eur J Pers* 2005;**19**:595–605). We will test the reliability of the VPT in our study against the included measures of anxiety and cognition presented below.

Supplementary Table 3. Variables of potential interest to the study are proposed as control variables and will be included as covariates in the statistical analysis. All control variables are listed including measures and references

Variables	Measures	Reference for validation
Exposure to other relevant life events	Life-events Scale	The Spanish adaptation of the Life-events scale shows high test-retest reliability (Kappa between 0.61 and 0.87) and a Cronbach's α internal consistency coefficient of 0.44. Reference for the original version: Brugha T, Bebbington P, Tennant C, *et al.* The List of Threatening Experiences: A subset of 12 life event categories with considerable long-term contextual threat. *Psychol Med* 1985;**15**:189–49. Spanish adaptation: Monroy E, Moreno B, Luna J, *et al.* Psychometric properties of the List of Threatening Experiences--LTE and its association with psychosocial factors and mental disorders according to different scoring methods. *J Affect Disord*, 2013;**150**:931–940.
Coping styles	Brief Coping Orientation to Problems Experienced Inventory (Brief-COPE)	The Spanish adaptation of the Brief-COPE shows Cronbach's α coefficient of 0.7. Reference for the original version: Carver CS. You want to measure coping but your protocol's too long: Consider the brief COPE. *Int J Behav Med* 1997;**4**:92–100. Spanish adaptation: Perczek R, Carver CS, Price A, *et al.* Coping, mood, and aspects of personality in Spanish translation and evidence of convergence with English versions. *J Pers Assess* 2000;**74**:63–87.
Resilient behaviour	Connor-Davidson Resilience Scale (CD-Risc)	The Cronbach's α coefficient reported for the Spanish adaptation is 0.86. Reference for the original version: Connor, KM. & Davidson, JRT. Development of a new Resilience scale: The Connor-Davidson Resilience scale (CD-RISC). *Depress Anxiety* 2003;**18**:76–82. Spanish adaptation: Garcia MA, Gonzalez A, Robles H, Padilla JL, Peralta MI. Psychometric properties of the Connor-Davidson Resilience Scale (CD-RISC) in the Spanish Population. *Annals of psychology* 2019;**35**:33-40.
General health status	Physical symptoms: Miller Abuse Physical Symptom and Injury Scale (MAPSAIS)	Test-restest reliability of the MAPSAIS is 0.63. For the present study we translated and back-translated the 25 items included in the original study. Reference for the original version: Miller C, Campbell J. *Reliability and Validity of the Miller Abuse Physical Symptom and Injury Scale (MAPSAIS)*. Chicago: Midwest Nursing Research Society 1993.
	Hair concentration of global cortisol: Elisa Kit (Salimetrics, LCC, PA, USA).	The reliability of the measure taken at different times is good, with correlations of 0.68-0.79. Reference: Stalder T, Kirschbaum C. Analysis of cortisol in hair--state of the art and future directions. *Brain Behav Immun* 2012;**26**:1019–29.
	Self-perception of general health. Short Form 36 Scale for self-perceived health status (SF-36)	The Cronbach's α coefficients reported for the Spanish adaptation are all above 0.7, with the exception of the social relations dimension (0.45). Intraclass coefficients between 0.58-0.99. Reference for the original version: McHorney, CA., Ware, JE. & Raczek, AE. (1993). The MOS 36-item short-form health survey (Sf-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;**31**:247-263. Spanish adaptation: Alonso J, Prieto L. & Antó, JM. La versión española del SF-36 Health Survey (Cuestionario de Salud SF-36): un instrumento para la medida de los resultados clínicos. *Med Clin* 1995;**104**:771-776.
Mental health	General Health Questionnaire , 12	The Cronbach's α coefficient reported for the Spanish adaptation is 0.78. Reference for the original version: Goldberg

status	items version (GHQ-12)	DP, Gater R, Sartorius N, *et al.* The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychol Med* 1997;**27**, 191–197. Spanish adaptation: Sánchez López, MP. & Dresch, V. (2008). The 12-item General Health Questionnaire (GHQ-12): Reliability, external validity and factor structure in the Spanish population. *Psicothema* 2008;**20**:839–43.
	Mini International Neuropsychiatric Interview (MINI)	The kappa values for inter-observer reliability of the Spanish version range around 0.75, whereas test-retest reliability was close to 0.75. Reference for the original version: Sheehan D V., Lecrubier Y, Sheehan KH, *et al.* The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. In: *Journal of Clinical Psychiatry*. 1998. Spanish translation: Ferrando, L., Bobes, J., Gibert, J., Soto, M. Y Soto, O. (2000). *MINI. Entrevista Neuropsiquiátrica Internacional. Versión en Español 5.0.0. DSM-IV*. Traducida por, L. Franco-Alfonso.
Personality traits	Neuroticism-Extraversion-Openness Inventory, Five Factor version (NEO-FFI)	Cronbach's α internal consistency coefficients are above 0.85 for the NEO PI-R dimension scales, whereas they range between 0.60 and over 0.80 for 25 out of 30 NEO PI-R facet scales. Reference for the original version: Costa PT, McCrae RR. *Revised NEO personality inventory (NEO-PI-R) and NEO five-factor inventory (NEO-FFI)*. Odessa, FL: : Psychological Assessment Resources, Inc. 1992. Spanish adaptation: Cordero A, Pamos A & Seisdedos N. *NEO PI-R Manual. Adaptación Española.* Madrid, España: TEA Ediciones 2008. Spanish normative data: Sanz J & Garcia-Pera MP. New Norms for the Spanish Adaptation of the NEO Personality Inventory-Revised (NEO PI-R): Reliability and Normative Data in Volunteers From the General Population. *Clinica y Salud* 2009;**20**:131–144.
Cognition	Semantic memory: Rey Auditory Verbal Learning Test (RAVLT)	Cronbach's α coefficient is 0.80. Reference for the original version: Rey, A (1964). *L'examen clinique en psychologie (The Clinical Psychological Examination).* Paris, FR: Presse Universitaires de France. Spanish adaptation: Valencia R. Prueba de Aprendizaje Auditivo-Verbal de Rey. *Hispanic Journal of Behavioral Sciences,* 1997;**19:**171-181.
	Intelligence quotient: Wechsler Adult Intelligence Scale, 4th version (WAIS-IV)	The internal consistency of the test is very high, reaching Cronbach's α coeffcients of 0.9. Reference for the original version: Wechsler D, Coalson D, Raiford S. *Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV)*; Administering and Scoring Manual. San Antonio, TX, USA: Pearson. 2008. Spanish adaptation: De la Guia E, Hernánde, A, Paradell E & Vallar F. *WAIS-IV (Escala de Inteligencia de Wechsler para adultos-IV).* España: Pearson Educación 2012.
	Executive function: Stroop Color and Word Test & Trail Making Test	The Stroop Color and Word Test presents a very high internal consistency, reaching Cronbach's α coefficient of 0.8. Reference for the original version: Golden CJ. Stroop Color and Word Test: A manual for clinical and experimental uses. *Chicago: Stoelting* 1978. Spanish adaptation: Golden, C. J. *Stroop test de colores y palabras, manual* (5° Ed.). Madrid, España: TEA Ediciones. 2007. The correlation of the Trail Making Test with other tests measuring similar constructs is between 0.36 and 0.48. Reference for the original version: Reitan RM. Validity of the Trail Making Test as and indicator of organic brain damage. *Percept Mot Skills* 1958;**8**:271–6. Spanish adaptation: Fernández AL, Marino JC & Alderete AM. Estandarización y validez conceptual del test de trazo en una muestra de adultos argentinos. *Revista de Neurología Argentina* 2002;**27**:83-88.