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10 **Non-communicable diseases among women survivors of intimate
11 partner violence: Critical review from a chronic stress framework**

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15 Ximena Goldberg^{1*}, Carme Espelt¹, Daniel Porta-Casteràs¹, Diego Palao¹, Roser Nadal², Antonio
16
17 Armario³

18
19 ¹Mental Health Department, Neuroscience and Mental Health Research Area, Institut d'Investigació i Innovació Parc
20
21 Taulí I3PT, Universitat Autònoma de Barcelona, CIBERSAM, Sabadell, Spain

22
23 ² Psychobiology Unit (School of Psychology), Institut de Neurociències, Universitat Autònoma de Barcelona,
24
25 CIBERSAM, Cerdanyola del Vallès, Spain

26
27
28 ³ Animal Physiology Unit (School of Biosciences), Institut de Neurociències, Universitat Autònoma de Barcelona,
29
30 CIBERSAM, Cerdanyola del Vallès, Spain

31
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43
44 (*) Correspondence concerning this article should be addressed to

45
46 Ximena Goldberg

47
48 Parc Taulí 1, Edifici Santa Fe 2º planta, 08208, Sabadell, Barcelona, Spain

49
50
51 xlgoldberg@tauli.cat

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1. Introduction

Violence against women is now recognized as a public health problem of epidemic proportions.

Not only is it consistently found to be extremely common on a global level, but also the prevalence of health problems among women survivors of violence is double or triple that of women who have not experienced any violence (García-Moreno et al., 2013). These findings have been a turning point for the inclusion of violence against women as a central matter within international health systems and policies (UN, 2015).

The most common and severe form of violence against women and girls worldwide is intimate partner violence (IPV). The lifetime prevalence of IPV has been reported to be as high as 71% in some settings (Garcia-Moreno et al., 2005). Evident health consequences of IPV are those associated with direct physical violence, which can involve a range of injuries, and sexual and reproductive health problems (García-Moreno et al., 2013). Traumatic brain injuries (TBI) are of central importance to the health of IPV-exposed women and further research is warranted to establish the prevalence of this problem (Campbell et al., 2018). In parallel with these noticeable conditions, women exposed to IPV present other less apparent health problems that are not directly observable, but which have a deep impact on their daily functioning. These health problems can be grouped under the general term of non-communicable diseases, and include cardiovascular and respiratory disorders, diabetes, cancer, and musculoskeletal and mental health disorders (Black and Breiding, 2008; Chandan et al., 2020; Ellsberg et al., 2008).

Despite a solid background supporting an increased risk of non-communicable diseases among survivors of IPV, the neurobiological correlates of this relationship are still unclear. A possible explanation emerges from approaching IPV not only as a single act of violence with a direct impact on physical health, but also from a longitudinal perspective where women are repetitively exposed to frequent and diverse life-threatening experiences that generally last for

1 over 10 years (Thompson et al., 2006; Triantafyllou et al., 2016). Indeed, the dynamics of IPV in
2 the context of an intimate relationship are usually cyclic and defined by recurrent episodes of
3 different types of violence. We propose that this characteristic is key to unravelling the
4 neurobiological intermediaries between IPV and disease.
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7 In the present review we approach IPV from the perspective of the neurobiological
8 framework of chronic stress. We revise the literature that addresses this topic from diverse but
9 complementary perspectives. Firstly, we present the model of chronic stress that is typically
10 used in neurobiological research. Secondly, we describe the behavioural dynamics involved in
11 coping with IPV and how they can be aligned with the neurobiological model of chronic stress.
12 Thirdly, we resume data from large population-based surveys and datasets that describe the
13 extent of the association between IPV and non-communicable diseases. Finally, we offer a
14 detailed description of the published results on experimental data which focus on the stress-
15 response system of IPV survivors and their link to disease. We propose that chronic activation
16 of this system underlies the association between IPV and non-communicable diseases,
17 particularly mental health disorders.
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20 2. The neurobiological model of chronic stress

21 Stress is experienced in situations in which persons are actually threatened, they
22 perceive a threat, or the situation exceeds their ability to cope (Lazarus and Folkman, 1984). In
23 its broadest sense, stress includes the environmental insult (stressor), the person's appraisal of
24 that insult (stress processing and associated emotions), and the bio-behavioural response. *This*
25 *stress response is orchestrated by the brain and involves central and peripheral functions, acting*
26 *in concert (Charmandari et al., 2005). Emotional stressful situations are processed by cortico-*
27 *limbic circuits, with signals eventually converging in the paraventricular nucleus of the*
28 *hypothalamus (PVN) and brainstem noradrenergic nuclei (Chrousos and Gold, 1992; Ulrich-Lai*
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1 and Herman, 2009). These nuclei in turn controls the activation of the sympathetic nervous
2 system (SNS) - principally responsible for the immediate cardiovascular and metabolic changes
3 observed during stress – and of the hypothalamic-pituitary-adrenal (HPA) axis. A main aspect of
4 the regulation of the HPA axis is the negative feedback exerted by glucocorticoids at the level of
5 the corticotrope cells, but also within the PVN and some extra-hypothalamic areas, such as the
6 hippocampal formation and the prefrontal cortex (Armario, 2006). These hormones are
7 important under conditions of relatively prolonged acute stress, to return altered functions to
8 pre-stress conditions, or to prepare the organism for future responses (Munck et al., 1984;
9 Sapolsky et al., 2000). Most of these actions of glucocorticoids are exerted within the brain and
10 encompass emotional and cognitive aspects (McEwen, 2000).

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24 While the overall response to acute stressors is considered to be predominantly
25 adaptive, chronic exposure to severe stressors, particularly if they are uncontrollable and
26 unpredictable, can cause detrimental effects (Chrousos, 2009). Unfortunately, this is the case
27 with IPV, where the victim is exposed to a stressful situation that presents itself frequently or
28 persists over an extended period. The classical view derived from animal models is that severe
29 chronic stress increases the potential capability of the HPA axis to respond to further stressors
30 by enhancing CRH expression in the PVN, ACTH response to CRH and adrenocortical response to
31 ACTH, while impairing negative glucocorticoid feedback (Armario, 2015). However, a meta-
32 analysis of the impact of chronic stress in humans suggests that this model is appropriate for
33 explaining the short-term consequences of chronic stress, but lower HPA activity is often found
34 in the long term (Miller et al., 2007). Moreover, regarding the interaction of glucocorticoids with
35 the immune system, there is evidence that chronic stress induces an impaired sensitivity of
36 certain elements of the immune system to glucocorticoids, thus resulting in a pro-inflammatory
37 state, not directly linked to altered circulating levels of glucocorticoids, which is reflected in
38 enhanced cytokine release (Miller et al., 2008; Rohleder, 2012). This altered sensitivity of
39 glucocorticoids after chronic stress might affect other biological systems.

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3 **3. Definition and scope of intimate partner violence**
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3. Definition and scope of intimate partner violence

For reasons of consistency throughout the review we use the definition of IPV as proposed by the World Health Organization, which refers to “any behaviour within an intimate relationship that causes physical, psychological or sexual harm to those in the relationship” (Krug et al., 2002). The types of behaviours are described in Box 1. In the present review, we only focus on IPV against women. The reason for this decision is threefold. Firstly, serious injuries and consequences of IPV are more prevalent among women than among men (Curry et al., 2018), which translates into an enormous burden on women’s health. Secondly, the human neuroendocrine system and associated biological mechanisms differ between sexes, which lately has promoted sex-specific literature and the disaggregation of results (Kudielka and Kirschbaum, 2005). Thirdly, there are important sex differences in the prevalence of non-communicable diseases, most significantly stress-related psychiatric disorders, with women being overrepresented among patients (Bangasser and Valentino, 2014).

Following the rationale represented by the neurobiological model of chronic stress, we have only included research that presents data from women who had suffered repeated violence in the context of IPV and who were not in the violent relationship at the time of inclusion in the studies. It is noteworthy that the vast majority of research only considers physical and/or sexual violence. Psychological abuse and controlling behaviours are recognized throughout studies as relevant factors that impact the health of women, but there is a lack of agreement on standard measures for these types of partner violence and the threshold at which acts that can be considered unkind or insulting cross the line and become emotional abuse (García-Moreno et al., 2013; Heise et al., 2019). Some researchers include stalking by a current or former intimate partner (Smith et al., 2017) and there is disagreement as to whether stalking should be included within the category of psychological abuse or whether it is conceptually

1 distinct (Fingerhut and Saltzman, 2000). Also, the term “domestic violence” is used either to
2 refer exclusively to IPV or to include violence against children and men (European Agency for
3 Fundamental Rights, 2014). Topographical similarities exist between physical and psychological
4 abuse, as they tend to be serial and ongoing, and can occur during and after the termination of
5 the romantic relationship. Given this background, whenever the reviewed data refer to forms of
6 violence different from physical and sexual abuse, we explicitly acknowledge this information.
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Term	Description
Intimate partner violence (IPV)	Any behaviour within an intimate relationship that causes physical, psychological or sexual harm to the woman in the relationship, since the age of 15. Only past and frequent IPV is considered in this review.
Physical violence	The woman is slapped, pushed or shoved, hit with a fist or something else that could hurt, is kicked, dragged or beaten up, is choked or burnt on purpose, and/or is threatened with, or actually, has a gun, knife or other weapon used on her.
Sexual violence	The woman is physically forced to have sexual intercourse when she does not want to, has sexual intercourse because she is afraid of what her partner might do, and/or is forced to do something sexual that she finds humiliating or degrading.
Psychological abuse	The woman is subjected to insults, belittling, constant humiliation, intimidation (e.g. destroying things), threats of harm, threats to take away her children.
Controlling behaviour	The woman is isolated from her family and friends; the woman is subjected to the monitoring of her movements and to restricting access to financial resources, employment, education or medical care.

35 **Box 1:** Definitions of IPV and types of violence used in this review (Krug, Dahlberg, Mercy, Zwi, & Loza,
36 2002; García-Moreno et al., 2013).
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43 4. Psychological and behavioural coping of IPV

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46 The complex dynamics involved in the behavioural response of women to IPV was first
47 highlighted from the perspective of “learned helplessness” (Walker, 1984, 1979) **and the**
48 **complementary “survivor’s theory”** (Gondolf, 1988). **These initial proposals present an**
49 **evidence-based scheme of the wide range of behaviours that women survivors use to cope**
50 **with the violence and their associations with IPV’s long-term repercussions** (Rizo et al., 2017;
51 Waldrop and Resick, 2004). **Following**, we will describe results from studies aimed at exploring
52 the associations between these coping strategies and health outcomes.
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The most popular categorization of strategies to cope with stress was first described by Lazarus and Folkman (Folkman et al., 1986), and distinguishes between (a) emotion-focused coping and (b) problem-focused coping. The first refers to strategies that are used to regulate the distress associated with specific problems, such as avoidance behaviour. The latter refers to strategies that are used to manage specific problems, and includes problem-solving thinking. A second categorization distinguishes between public and private attempts to deal with violence. Examples of private attempts are hiding or not putting up a fight, which aim to manage an ongoing emotional state. Public strategies involve talking to family and friends or seeking legal assistance, which aim to solve the conflict. Both categorizations largely converge; **however**, the selective use of the terms in the different reports of coping strategies among IPV survivors is relevant. The problem-focused *versus* emotion-focused categorization aims to identify those strategies that provide a better adjustment to the context. Therefore, this categorization is most commonly used in studies that emphasize the identification and prevention interventions of maladaptive behaviours, so far as they are considered to be causally linked to disease. In contrast, the public *versus* private approach largely focuses on identifying strategies that more effectively lead towards ceasing the violence within the context of the relationship. This categorization is more frequently used in qualitative studies which aim to describe the inner dynamics of the violent relationship.

4.1. Coping strategies and health

The main focus of the studies on the health impact of coping strategies is mental health, with PTSD, depression and anxiety being the most common pathologies (**Supplementary Table S1**). Regarding PTSD, a first study (Arias and Pape, 1999) showed a significant association between a higher frequency of use of emotion-focused coping strategies, such as hiding and avoiding, and an increased frequency of PTSD symptoms, while no association was found with problem-focused coping. A direct effect of frequency of psychological abuse on symptoms of

1 PTSD was also found, that was not moderated by coping strategies. In contrast to these results,
2 a second investigation (Kocot and Goodman, 2003), reported a main effect of higher frequency
3 of problem-focused coping on increased PTSD. A similar study (Lilly and Graham-Bermann, 2010)
4 reported that more frequent emotion-focused coping was associated with higher violence
5 exposure and PTSD symptoms. These data suggest that the impact of an emotion-focusing
6 coping style could be markedly dependent on the intensity of IPV, **but** leave ample room for
7 discussion owing to the lack of replication and the cross-sectional nature of the data. Only one
8 longitudinal study has focused on coping strategies and PTSD (Krause et al., 2008). Avoidant
9 coping was significantly and positively associated with PTSD symptomatology at inclusion and at
10 the one-year follow-up, as was the severity of IPV. No interaction effects were found between
11 IPV and coping.
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14 As for studies where the primary outcome was depression, results showed a similar
15 trend. An initial report (Mitchell and Hodson, 1983) **found that** frequency and level of violence
16 were associated with depression, but the type of coping was important, in that active coping
17 was associated with reduced levels of depression, whereas avoidant coping was associated with
18 increased levels. The results were in line with those from the study mentioned above, which
19 centred on problem-focused coping and also found main effect increased frequency of use of
20 this strategy and increased levels of depression (Kocot and Goodman, 2003).
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23 Several models of the potential mediating and moderating effects of coping on both
24 depression and anxiety have been explored in one particular study **based on a sample of 113**
25 **women** (Calvete et al., 2008). IPV was associated with both anxiety and depression. There was
26 no evidence for moderation, implying that the effect of IPV on health does not vary as a function
27 of coping strategy. Zero-order correlations showed that disengagement and secondary control
28 response were associated with anxiety symptoms, while only disengagement was associated
29 with depression. Interestingly, results showed evidence of mediation effects to the extent that
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1 disengagement was influenced by the experience of violence, and the increased use of
2 disengagement impacted mental health. It is worth noting, that although all the women in this
3 study had actually suffered physical abuse, these final results were specifically proven for
4 psychological abuse.
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8 Some factors that relate to coping and mental health may help understand the
9 mechanisms involved in their relationships. Importantly, a history of childhood abuse appears
10 to be relevant **and may moderate the effect of adult emotional abuse**. The results showed a
11 greater effect of childhood emotional abuse than adult emotional abuse on depressive
12 symptomatology, whereas the number of episodes of physical battering in adulthood was
13 unrelated to depression (Lewis et al., 2006). There are two possible explanations for these
14 results: (i) high levels of childhood abuse among these participants could shape a less reactive
15 response to physical violence in adulthood; or (ii) the high levels of physical violence in IPV
16 situations experienced by these participants during adulthood, might result in a ceiling effect.
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20 **4.2. Reflections from qualitative and mixed-model research**
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24 The adaptive capacity of any given coping strategy is heavily dependent on context,
25 including the nature of the violence, the woman's perception of the situation, and her resources
26 to address it. Most importantly, these factors vary during the course of IPV, and what may be
27 perceived as adaptive behaviour at one point of the relationship may be seen as maladaptive at
28 another. These dynamics follow stages of change that have been explored through different
29 models (Brown, 1997; Reisenhofer et al., 2019). Hence, it is highly recommended that the coping
30 strategies used by women are recognized in light of their complex and changing interpersonal
31 intimate relationship.
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35 The vast majority of studies that explore the relationship between IPV, coping and mental
36 health are based on samples of women that at the time of inclusion are seeking formal help
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1 from public shelters or legal entities. This should be carefully considered when interpreting the
2 findings, because women who are in the earlier stages of the process of change during IPV or in
3 different socioeconomic conditions might use a diverse set of coping strategies. The aim of
4 leaving the relationship may seem hard to achieve and stressful for the victims, and may not be
5 seen as a realistic possibility for many of them (Reisenhofer et al., 2019). During this time, coping
6 through avoidance may seem useful for women in a violent relationship, while the experience
7 of lack of agency when attempting to control the threat during a long period of time may be
8 accompanied by feelings of despair and hopelessness. This emotional context is present even
9 when women show active help seeking behaviour and eventually succeed in ceasing the violent
10 relationship.

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24 Interestingly, private strategies including avoidant behaviour are among the most
25 commonly reported by IPV survivors, but they are also largely regarded as ineffective by the
26 women themselves. A proposed explanation is that private coping offers immediate relief from
27 the threat and temporary safety, which is perceived as basic survival behaviour (Brabeck and
28 Guzman, 2008). These private strategies are actually adaptive, as women are able to cease the
29 violence in the short term. In contrast, the decision to move towards the use of strategies that
30 involve formal public networks generally comes at the advanced stages of change, and seem to
31 coincide with the women's perception that their own actions are not sufficient to overcome the
32 violent relationship (Bauman et al., 2008; Goodman et al., 2003). In this sense, being successful
33 in their aim to stop the violence does not necessarily indicate a better health outcome, as
34 symptoms of mental health disorders may already be present at this point.

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48 In sum, women use a large number of coping strategies to deal with repetitive violence and
49 threat. There is a high frequency of use of avoidant strategies that aim to provide immediate
50 release from threat (e.g. avoidance) but have been associated with problematic mental health
51 outcomes. This reality builds a context for chronic stress.

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3 **5. Impact of IPV on health outcomes**
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5. Impact of IPV on health outcomes

IPV in general, and different types of violence in particular, have been linked to long-term health outcomes that affect both physical and mental health. In Table 1 we resume data from large (N>10,000) population-based studies that have been carried out in an effort to provide a measure of the effect of such association. Following the rationale of this review, we are only including here data which address non-communicable diseases and symptoms, excluding injuries and reproductive health. We are also only reporting studies that address lifetime IPV after the age of 15 or 18, excluding results relative to ongoing IPV or IPV occurring less than 12 months ago. The effect sizes that are presented in Table 1 correspond to the comparison of frequency of health problems among women who have ever experienced physical or sexual violence from an intimate partner, relative to those among women who have not experienced such violence. Effect sizes are reported using Odds Ratios (OR), Hazard Risks (HR) and Incidence Rate Ratios (IRR) in line with the design of each study. Most studies presented adjusted measures of these estimates that are specified in Table 1. **The details of each study are presented in Supplementary Table S2.**

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39 The first study of this kind was the WHO multi-country study (Ellsberg et al., 2008). The
40 prevalence of IPV varied widely between countries, from 15% to 71%. This cross-sectional study
41 focused on physical and mental health symptoms during the four weeks preceding the interview
42 (difficulties with walking, pain, memory loss, dizziness, along with suicidal thoughts and acts),
43 reporting statistically significant results for all measures. The results of this initial work were
44 later confirmed in the systematic review by WHO (García-Moreno et al., 2013). **More recent**
45 *multi-country efforts were led by the European Union (European Agency for Fundamental Rights,*
46 *2014). The prevalence of physical IPV was 24%, while that of sexual IPV was 9%. Measuring*
47 *health impact was not the main objective of the study, and the published results do not provide*
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1 estimates of risk that could have been included in Table 1. However, some information can be
2 retrieved, particularly regarding psychological consequences. For example, among all survivors
3 of physical IPV, 32% showed anxiety, 12% panic attacks, 20% depression and 23% difficulty
4 sleeping. The frequencies among survivors of sexual IPV were higher: 45% showed anxiety, 21%
5 panic attacks, 35% depression and 41% difficulty sleeping. The high prevalence of mental health
6 disorders and symptoms among these women in Europe coincides with the reported frequencies
7 of symptoms of PTSD among American survivors of IPV. Indeed, a reported 51.8% of women who
8 experienced contact sexual violence, physical violence and/or stalking by an intimate partner in
9 their lifetime in the USA present symptoms of PTSD (Smith et al., 2017).

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Aside from these global estimates, some countries have published local population-based results, either using surveys or large datasets. The Australian Longitudinal Study on Women's Health (Loxton et al., 2006; Vos et al., 2006) reported associations between IPV and cervical cancer, pain, osteoporosis, respiratory disorders (including asthma), bronchitis and allergies; and health problems such as low iron, and bowel and skin alterations. The prevalence of IPV ranged between 15.4 and 17%. The associations between IPV and other forms of cancer or cardiovascular disorders were not significant after adjustment for confounders.

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Using cross-sectional random survey data from the Behavioural Risk Factor Surveillance System (BRFSS), researchers reported 23.8% prevalence of IPV (physical and sexual) **in the adult population of the United States of America**, and statistically significant results for an increased OR of stroke, heart disease, heart attack, high blood pressure and high blood cholesterol (but not diabetes), as well as arthritis and asthma (Black and Breiding, 2008). Complementarily, data from the Nurses' Health Study II (NHSII) reported an association between IPV and diabetes (Mason et al., 2013). In this cohort of USA female registered nurses, 23% of women reported lifetime physical IPV, 11% lifetime sexual IPV, 8% moderate psychological IPV and less than 2% severe psychological IPV. The results were statistically significant for the association between **diabetes and** repeated exposure to physical IPV, as opposed to never or only once exposure

1 (HR=1.18; 95%CI=1.00-1.39), **and** severe psychological IPV, as opposed to none or moderate
2 exposure (HR=1.78, 95%CI=1.21-2.61).
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5 A study based on a cross-sectional large sample of women between 15 and 49 years of
6 age in the Indian National Family Health Survey explored the association between IPV and
7 malnutrition (Ackerson and Subramanian, 2008). The authors propose that domestic violence in
8 the country commonly takes the form of withholding food, which in turns leads to malnutrition
9 and associated disorders. Prevalence of IPV was 9% in this sample, which is relatively low
10 compared to other studies. Only physical abuse was considered, although the authors discuss
11 the potential effect of other forms of abuse in these households. The authors measured two
12 aspects of nutritional status: anaemia (assessed by means of blood test for haemoglobin) and
13 being underweight (body mass index). Results showed a statistically significant relationship (OR)
14 between anaemia and exposure to IPV when women were exposed to IPV more than once in
15 the past year, as opposed to only once in the past year, more than one year ago or never. Similar
16 results were reported for being severely underweight. Being underweight (any type, as opposed
17 to being severely underweight) was evident among women reporting IPV in the last year or more
18 than once in the last year, but not among those reporting IPV more than one year ago. Hence,
19 time passing since IPV might have a mitigating effect on anaemia and being underweight. It is
20 important to note that being underweight was the consequence of restricting food access in this
21 study.
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24 To our knowledge, only one study has used electronic records to explore the
25 relationship between IPV and health (Chandan et al., 2019). **IRR estimates indicated increased**
26 **risk of** anxiety, depression and serious mental illness after exposure after adjustment for
27 relevant covariates. **The researchers also found** a significant association of IPV with a general
28 measure of cardiovascular disease, and more specifically with ischemic heart disease,
29 stroke/transient ischemic attack, and type II diabetes (Chandan et al., 2020). No associations
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were found after adjustment for the presence of heart failure, hypertension and peripheral
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vascular diseases.

Summing up, there is a significant relationship between exposure to IPV and non-communicable diseases. The most striking results are related to mental health. Prevalence of cardiovascular (including diabetes), respiratory, and musculoskeletal disorders have all been found to increase among IPV survivors. More research is warranted to understand the impact of IPV on cancer.

23 **Table 1.** Association between past and frequent exposure to physical and sexual IPV and non-communicable diseases based on results from published studies with N>10,000. See
 24 Supplementary Table 2 for more details.

26 Categories of health 27 impact	28 Type of consequence	29 Results (95% CI) - 30 unadjusted	31 Results (95% CI) - 32 adjusted	33 Sample size	34 Study period	35 Country
28 Cancer	Breast cancer	OR 0.91 (0.67-1.26)	N/R	14,100	1996	Australia (1)
	Lung cancer	OR 2.19 (0.89-5.40)	N/R	14,100	1996	Australia (1)
	Skin cancer	OR 1.10 (0.95-3.18)	N/R	14,100	1996	Australia (1)
	Bowel cancer	OR 1.84 (1.06-3.18)	aOR 0.66 (0.31-1.40)	14,100	1996	Australia (1)
	Cervical cancer	OR 2.31 (1.88-2.84)	aOR 1.34 (1.02-1.75)	14,100	1996	Australia (1)
		RR 1.46 (1.22-1.75)	N/R	14,739	2001	Australia (2)
34 Cardiovascular	35 Cardiovascular Disease (composite score*)	IRR 1.33 (1.13-1.57)	aIRR 1.31 (1.11-1.55)	91,778	1995-2017	United Kingdom (3)
	36 Heart disease	37 OR 1.98 (1.52-2.57)	aOR 1.32 (0.95-1.82)	14,100	1996	Australia (1)
		N/R	aOR 1.7 (1.4-2.1)	42,566	2005	United States of America (4)
	38 Heart failure	IRR 1.15 (0.75-1.77)	aIRR 1.06 (0.69-1.63)	91,778	1995-2017	United Kingdom (3)
	39 Heart attack	N/R	aOR 1.4 (1.1-1.7)	42,566	2005	United States of America (4)
	40 Hypertension	IRR 1.02 (0.90-1.15)	aIRR 0.99 (0.88-1.12)	91,778	1995-2017	United Kingdom (3)
		41 OR 1.25 (1.12-1.40)	aOR 1.03 (0.89-1.18)	14,100	1996	Australia (1)
	42 High blood pressure	N/R	aOR 1.1 (1.0-1.2)	42,566	2005	United States of America (4)
	43 High blood cholesterol	N/R	aOR 1.3 (1.1-1.4)	42,566	2005	United States of America (4)
	44 Ischaemic heart disease	IRR 1.45 (1.13-1.85)	aIRR 1.40 (1.09-1.79)	91,778	1995-2017	United Kingdom (3)
	45 Thrombosis	OR 1.52 (1.25-1.85)	aOR 1.10 (0.86-1.41)	14,100	1996	Australia (1)
	46 Peripheral vascular disease	IRR 1.27 (0.81-1.99)	aIRR 1.18 (0.75-1.86)	91,778	1995-2017	United Kingdom (3)
	47 Stroke	N/R	aOR 1.8 (1.4-2.2)	42,566	2005	United States of America (4)
		OR 2.92 (1.96-4.35)	aOR 1.44 (0.86-2.41)	14,100	1996	Australia (1)
	Stroke/transient Ischaemic attack	IRR 1.33 (1.05-1.68)	aIRR 1.29 (1.02-1.63)	91,778	1995-2017	United Kingdom (3)
48 Diabetes	49 Type II diabetes	50 HR 1.34 (1.14-1.58)	aHR 1.18 (1.00-1.39)	68,376	2001 to 2007	United States of America (5)
		51 HR 1.25 (1.01-1.55)	aHR 1.08 (0.86-1.35)	68,376	2001 to 2007	United States of America (5)
		52 IRR 1.55 (1.33-1.81)	aIRR 1.51 (1.30-1.76)	91,778	1995-2017	United Kingdom (3)
	53 Diabetes (nongestational)	N/R	aOR 1.1 (0.9-1.3)	42,566	2005	United States of America (4)
	54 Diabetes (unspecified)	OR 1.46 (1.15-1.86)	OR 1.11 (0.82-1.52)	14,100	1996	Australia (1)
55 Musculoskeletal	56 Pain	57 OR 1.8 (1.7-2.0)	aOR 1.6 (1.5-1.7)	24,097	2000-2003	Multi-country (6)
	58 Pain/fatigue	59 OR 1.95 (1.77-2.15)	aOR 1.28 (1.13-1.45)	14,100	1996	Australia (1)
	60 Chronic fatigue syndrome	IRR 1.71 (1.01-2.89)	aIRR 1.92 (1.11-3.33)	92,735	1995-2017	United Kingdom (7)
	61 Fibromyalgia	IRR 1.95 (1.54-2.47)	aIRR 1.73 (1.36-2.22)	92,735	1995-2017	United Kingdom (7)
	62 Arthritis/rheumatoid	N/R	aOR 1.7 (1.6-1.9)	42,566	2005	United States of America (4)
	63 arthritis/gout/lupus/fibromyalgia	OR 1.77 (1.45-2.16)	aOR 1.10 (0.86-1.42)	14,100	1996	Australia (1)
	64 Osteoporosis	OR 2.0 (1.8-2.1)	aOR 1.6 (1.5-1.8)	24,097	2000-2003	Multi-country (6)

Table 1 (cont.). Association between past and frequent exposure to physical and sexual IPV and non-communicable diseases based on results from published studies with N>10,000.

Categories of health impact	Type of consequence	Results (95% CI) - unadjusted	Results (95% CI) - adjusted	Sample size	Study period	Country
Mental Health	Anxiety	RR 1.83 (1.36-2.47) OR 2.21 (2.12-2.31) IRR 2.19 (1.98-2.38)	N/R aOR 1.91 (1.82-2.01) aIRR 1.99 (1.80-2.20)	14,739 92,735 92,735	2001 1995-2017 1995-2017	Australia (2) United Kingdom (7) United Kingdom (7)
	Depression	RR 1.96 (1.59-2.42) OR 3.15 (3.04-3.26) IRR 3.40 (3.16-3.67)	N/R aOR 2.61 (2.51-2.71) aIRR 3.05 (2.81-3.31)	14,739 92,735 92,735	2001 1995-2017 1995-2017	Australia (2) United Kingdom (7) United Kingdom (7)
	Eating disorders	RR 1.22 (1.04-1.43)	N/R	14,739	2001	Australia (2)
	Self-harm	RR 2.53 (1.81-3.56)	N/R	14,739	2001	Australia (2)
	Serious mental illness	OR 3.21 (2.84-3.62) IRR 3.60 (2.63-4.92)	aOR 2.13 (1.86-2.43) aIRR 3.08 (2.19-4.32)	92,735 92,735	1995-2017 1995-2017	United Kingdom (7) United Kingdom (7)
	Suicidal acts	OR 3.5 (3.0-4.1)	aOR 3.8 (3.3-4.5)	24,097	2000-2003	Multi-country (6)
	Suicidal thoughts	OR 2.4 (2.2-2.6)	aOR 2.9 (2.7-3.2)	24,097	2000-2003	Multi-country (6)
	Asthma	OR 1.83 (1.64-2.05) N/R	aOR 1.21 (1.04-1.41) aOR 1.6 (1.4-1.8)	14,100 42,566	1996 2005	Australia (1) United States of America (4)
	Bronchitis/emphysema	OR 1.87 (1.69-2.08)	aOR 1.23 (1.08-1.42)	14,100	1996	Australia (1)
	Allergies/breathing	OR 1.54 (1.40-1.69)	aOR 1.15 (1.02-1.30)	14,100	1996	Australia (1)
Other symptoms	Anaemia (any type)	OR 1.01 (0.95-1.07)	OR 0.97 (0.92-1.03)	69,072	1998-1999	India (8)
	Anaemia (severe)	OR 1.14 (0.92-1.42)	OR 1.01 (0.81-1.26)	69,072	1998-1999	India (8)
	Underweight (any type)	OR 1.12 (1.05-1.19)	OR 1.01 (0.95-1.07)	69,072	1998-1999	India (8)
	Underweight (severe)	OR 1.28 (1.14-1.44)	OR 1.10 (0.98-1.23)	69,072	1998-1999	India (8)
	Low iron	OR 1.43 (1.30-1.57)	aOR 1.27 (1.13-1.43)	14,100	1996	Australia (1)
	Bowel problems	OR 1.58 (1.44-1.74)	aOR 1.32 (1.17-1.49)	14,100	1996	Australia (1)
	Skin problems	OR 1.39 (1.27-1.52)	aOR 0.99 (0.88-1.11)	14,100	1996	Australia (1)
	Dizziness	OR 2.0 (1.9-2.2)	aOR 1.7 (1.6-1.8)	24,097	2000-2003	Multi-country (6)
	Memory loss	OR 2.0 (1.9-2.2)	aOR 1.8 (1.6-2.0)	24,097	2000-2003	Multi-country (6)

N/R= Not Reported. (a)OR=(adjusted) Odds Ratio; (a)IRR=(adjusted) Incidence Rate Ratio; (a)HR= adjusted Hazard Risk, RR=Relative Risk

(*) Cardiovascular disease composite score in this study was composed of the risk of developing ischemic heart disease, stroke or transient ischemic attack, heart failure, and peripheral vascular disease

(1) Loxton, Schofield, Hussain, & Mishra, 2006. OR were adjusted for other health variables (all illnesses explored in the study), demographics (marital status, education, income, area of residence) and lifestyle (smoking, alcohol use, binge drinking, physical activity).

(2) Vos et al., 2006. OR were adjusted for demographics (marital status, education, employment status, occupation, language spoken, indigenous status, place of residence) and lifestyle (smoking, drinking).

(3) Chandan et al., 2020. IRR were adjusted for health variables (use of lipid-lowering medications, comorbidities), demographics (age, socioeconomic status), and lifestyle (smoking status, alcohol excess, body mass index).

(4) Black & Breidig, 2008. OR were adjusted for demographics (age, education, annual household income race/ethnicity).

(5) Mason et al., 2013. HR were adjusted either only for age (presented here as unadjusted OR), or for age, race and child and adolescence confounders (child physical abuse, child sexual abuse, race, mother's educational attainment, father's educational attainment, somatogram score at age 5, body mass index at age 18, parental history of diabetes (presented here as adjusted aOR).

(6) Ellsberg et al., 2008. OR were adjusted for demographics (age, current marital status, education).

(7) Chandan et al., 2019. IRR were adjusted for demographics (age, socioeconomic status) and lifestyle (drinking status, smoking status, body mass index).

(8) Ackerson & Subramanian, 2008. OR were adjusted for health variables (affliction with recent major illness, recent birth, current breastfeeding, number of children born), demographics (age, education, employment, living standard, decision-making autonomy, rural/urban location, religion, caste).

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4 **5.1. Influence of risk behaviours and other risk factors**
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The study of risk behaviour and habits is particularly pertinent in the context of health outcomes because they may act as mediators between IPV and disease. The most relevant risk behaviours associated with health were smoking and heavy drinking, which were found to be more frequent among the exposed groups in all reporting studies. Increased adjusted odd ratios for current smoking ($aOR=2.3$, 95% CI=2.1-2.6) and heavy or binge drinking ($aOR=1.7$, 95% CI=1.5-2.0) were found in the USA study (Black and Breiding, 2008). Increased risks were reported in the Australian cohort for alcohol abuse ($RR=1.47$, 95% CI=1.03-2.10), illicit drug use ($RR=1.23$, 95% CI=1.02-1.48) and smoking ($RR=2.98$, 95% CI=2.09-4.25) (Vos et al., 2006). Similar results were reported for the UK study in terms of excessive drinking (10.1% in the exposed group versus 3.5% in the unexposed group) (Chandan et al., 2020). This latter study did not find differences in smoking behaviours, although the authors mention that both groups presented a high prevalence of smoking (44.7%). Recent longitudinal research has also suggested that there may be a causal relationship between IPV and substance use disorders among women (Ahmadabadi et al., 2019), and may compel further future research to include the assessment of risk behaviour in the analyses.

Studies differ in the inclusion of other variables depending on the outcome of interest, the theoretical model that is being tested, and the results of univariate analysis. For example, among the studies presented in Table 1, only four included race/ethnicity in the adjustment (Ackerson and Subramanian, 2008; Black and Breiding, 2008; Mason et al., 2013; Vos et al., 2006). Marital status was only found to be of interest in three studies (Ellsberg et al., 2008; Loxton et al., 2006; Vos et al., 2006) and only one study included child abuse as a potential confounder (Mason et al., 2013), acknowledging the potential impact of childhood maltreatment that is increasingly being recognized in health research. Body mass index was adjusted for in three analyses, two of them from the same population (Chandan et al., 2020, 2019; Mason et

al., 2013). Discussion has been raised regarding the possibility that IPV survivors may be overweight and show signs of metabolic syndrome. A longitudinal study of 5,593 women observed higher IRR for the effects of lifetime experience of physical/sexual abuse than for psychological abuse on cardiovascular diseases, and this was associated with metabolic alterations in lipid metabolism, although body mass index was not affected (Stene et al., 2013). Similarly, no differences were found in another large study (Chandan et al., 2019). In contrast, underweight can be a direct consequence of IPV, as shown in the study on Indian population mentioned above (Ackerson and Subramanian, 2008).

5.2. Methodological considerations

Because the estimates used in the different studies are conceptually different (OR, RR, IRR, HR), direct comparisons are discouraged. Also, different studies have included several covariates in an effort to adjust the results for factors that have been linked to either IPV or to the particular health outcome. Age is adjusted for in most, although not all, studies, as is education and different indices of income or deprivation. Variations on the prevalence of IPV, health disorders and their associations according to age, education and income level should be further explored in health impact assessments. Globally, it has been estimated that 30% of all women suffer IPV at some point in their lives (García-Moreno et al., 2013). This prevalence is slightly higher in the USA, rising to 36.4% (Smith et al., 2018), and lower in the European Union, with a reported 22% (European Agency for Fundamental Rights, 2014). In some low- and middle-income countries the prevalence of current violence against women rises to 46% and that of lifetime IPV to 71% (Coll et al., 2020; Garcia-Moreno et al., 2006). Despite a trend towards a higher prevalence of IPV associated with income status between and within the countries, IPV is also highly prevalent in high-income countries with gender-equality policies, such as Denmark (32%), Finland (30%) and Sweden (28%) (Gracia and Merlo, 2016). These rates are indicative of the underlying complexity of IPV, which is reflected in the results of the association between IPV and health outcomes in different contexts.

1 *Regardless of the sample size, results are commonly based on cross-sectional data, which*
2 *raises the discussion on the potential causal path between IPV and the presence of disease. It is*
3 *possible that the estimates of risk reflect a role of previous health conditions as potential risk*
4 *factors for IPV. This could be the case for mental health in particular, as people living with mental*
5 *health disorders are a vulnerable group who habitually experience physical and sexual*
6 *victimization, including IPV (Funk et al., 2010). However, it is also expected that these patients*
7 *have been exposed to multiple focuses of violence throughout their adult lives and during*
8 *childhood, which could have shaped their mental health outcome (Copeland et al., 2018).*

19 *When models of future development of cardiovascular diseases are used, there is sound*
20 *agreement that IPV predicts the development of pathology in the following 2.5 to 30 years (Clark*
21 *et al., 2016; Pantell et al., 2019; Renner et al., 2021; Scott-Storey, 2013; Scott-Storey et al., 2019;*
22 *Wright et al., 2021). In general, although the effects on cardiovascular diseases are consistent,*
23 *the impact on hypertension is usually not significant, particularly when adjusting for other health*
24 *variables (Breiding et al., 2008). Nevertheless, the risk of being prescribed antihypertensive drugs*
25 *is increased (Stene et al., 2013) and a direct impact on hypertension might be possible under the*
26 *most severe IPV conditions (Mason et al., 2012). Interestingly, a recent longitudinal study*
27 *supports a role for depression as an intermediary between exposure to IPV and cardiovascular*
28 *risk scores (Wright et al., 2019). To better understand these relationships, it is highly*
29 *recommended that future research includes longitudinal follow-ups of cohorts of IPV women in*
30 *which physical and mental health status can be explored, including a biological sample collection*
31 *and a digital follow-up to test for pathways of associations.*

6. Neurobiological intermediaries between IPV and health

6.1. The HPA axis

The activity of the HPA axis has been typically evaluated measuring plasma levels of ACTH or total cortisol. This includes the cortisol bound with high affinity to the corticosteroid-binding globulin (CBG) and the free fraction, which is considered the active biological signal. In the last two decades, salivary cortisol is the most reported measure, **as it is non-invasive** and shows a very good correlation with free plasma cortisol levels (Vining et al., 1983). *Changes in circulating levels of cortisol do not always reflect changes in ACTH because factors other than ACTH, including sympathetic innervation of the adrenal gland, might participate in its secretion and release (Bornstein et al., 2008)*. Unfortunately, ACTH levels cannot be reliably measured in saliva.

The activity of the HPA axis is characterized by a strong **activity-driven** circadian rhythm in all mammals, **including humans** (Krieger and Allen, 1975). Cortisol levels start rising before awakening and show an additional increase in the hour following awakening. This is the cortisol awakening response (CAR) (Pruessner et al., 1997), which has attracted considerable interest in recent years (Law et al., 2013; Stalder et al., 2016). After CAR, cortisol levels rapidly decline during the first hours of the morning and continue decreasing over the day to reach the lowest levels before bedtime.

Resting HPA Activity among IPV survivors: How IPV affects circulating cortisol levels is not clear. Morning plasma basal cortisol levels (4-24 months after violence) were reported to be lower in IPV exposed women than in control non-exposed women, regardless of PTSD symptoms (Seedat et al., 2003). However, PTSD symptoms did appear to be important in another study where IPV PTSD+ women, regardless of comorbid depression, have lower morning plasma cortisol levels in comparison to controls and IPV without psychiatric diagnosis (Griffin et al., 2005). Interestingly,

1 in the latter study cortisol suppression by dexamethasone did not reveal altered negative
2 feedback sensitivity in any IPV group.
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6 In contrast to the above reports describing hypocortisolemia, Pico-Alfonso et al. (Pico-
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8 Alfonso et al., 2004) did not observe differences in morning salivary cortisol, but did report
9 higher evening cortisol levels in IPV (both physical and psychological) than non-abused women.
10 This was accompanied by more symptoms of depression, anxiety and PTSD. The same laboratory
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12 again showed higher evening but not morning saliva cortisol levels in IPV women suffering major
13 depressive disorder (MDD), compared to non-abused controls, but no differences from controls
14 in IPV without symptoms or in those with MDD and PTSD (Blasco-Ros et al., 2014).
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16 Unfortunately, abused women having only PTSD were not included. **This was explored in**
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18 **another study in which** higher saliva cortisol levels across the day were reported in IPV victims
19 that developed PTSD versus those without diagnosis, although the effect was particularly
20 evident in remitted subjects (Inslicht et al., 2006). In a study of extant couples, women suffering
21 from IPV showed a slightly altered circadian pattern of saliva cortisol, mainly characterized by a
22 flattened slope, with similar morning levels but less decline over the day (Kim et al., 2015).
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26 **Cortisol awakening response:** The way to evaluate CAR has been rapidly changing over the last
27 decade, the present consensus including four time points on two different days: the first one
28 just after awakening and again 30, 45 and 60 min later (Stalder et al., 2016). Recent data
29 highlight the importance of following the cortisol response after awakening for 120 min, to catch
30 both the slope of the response and its disappearance (Benz et al., 2019). Unfortunately, most of
31 the few studies exploring CAR in IPV women were completed before the consensus was
32 achieved.
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35 Basu and colleagues (Basu et al., 2013) observed no differences between controls and
36 IPV (physical and sexual) women and no influence of diagnosis (no symptoms, MDD, PTSD), but
37 dissociative symptoms were related to a blunted CAR. In IPV exposed women (who reported it
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1 to the authorities or who were living in shelters), those without the expected increase in CAR (at
2 30 min post-awakening) suffered from more intense and chronic violence, more psychological
3 distress and more PTSD symptoms (Pinto et al., 2016). In a population of highly traumatized IPV
4 victims with PTSD symptoms, a flatter CAR slope was found in women with higher hyper-arousal
5 symptoms in comparison to those with lower symptoms (Garcia et al., 2020). In striking contrast,
6 in recently abused women, Pinna and colleagues (Pinna et al., 2014) observed that IPV women
7 suffering from MDD or both PTSD and MDD showed an increase in CAR (30, 45 and 60 min),
8 whereas those without PTSD or MDD did not. Similarly, in the same laboratory, IPV women with
9 PTSD diagnosis did show an increase in CAR whereas IPV without PTSD diagnosis did not
10 (Johnson et al., 2008). Future studies are needed to assess CAR response in IPV exposed women
11 compared to non-exposed women, in conjunction with other markers of the HPA axis.
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14 **Hair cortisol:** In recent years, the incorporation of hair cortisol concentration is allowing an
15 overall picture of the changes in the HPA axis under chronic stress or in psychiatric patients to
16 be seen. This measure has the advantage of evaluating free cortisol fraction and is an integrated
17 measure of the cortisol released over a period of months (Stalder et al., 2017; Stalder and
18 Kirschbaum, 2012). In pregnant women exposed to IPV during the last 12 months, higher hair
19 cortisol levels have been observed compared to controls (Boeckel et al., 2017). This suggests
20 that the chronic IPV stress is reflected in high overall HPA activity, in accordance with what is
21 found in animal models of severe chronic stress (Scorrano et al., 2015). However, in another
22 study using a small sample (IPV n=12; controls n=15) of non-pregnant women that investigated
23 how an incident of physical and/or sexual assault in the past three months affected hair cortisol,
24 no group differences in hair cortisol were found, despite levels of stress exposure being higher
25 in IPV than in controls (Morris et al., 2017). It is possible that the level of stress was not as high
26 as in the previous report.
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29 **A very recent report studied hair cortisol in a sample of women in which IPV scores in the
30 last 6 months were obtained (Alhalal and Falatah, 2020). Those suffering IPV showed lower
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1 hair cortisol concentration. Unfortunately, interpretation of results is unclear for three main
2 reasons. First, the mean IPV score was relatively low. Second, data about the duration of IPV
3 was not obtained. Third, hair cortisol concentration was associated in multiple regression
4 analysis both with IPV severity, but also with resilience, while the influence of the two factors
5 would have been expected to show opposite directions.
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12 *In all, there are few studies of the impact of IPV on HPA activity and the results are*
13 *controversial. This is not surprising as the HPA axis is highly sensitive to changes in activity, sleep*
14 *pattern, drug consumption and anticipation of events which generate anxiety. More and better*
15 *controlled studies are needed, including how IPV women respond to novel superimposed*
16 *stressors.*
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6.2. The immune system

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30 **The main components of the immune system can briefly described through** its two
31 main branches: innate and specific (Mak and Saunders, 2006). Innate immunity mainly involves
32 circulating monocytes and tissue macrophages and natural killer (NK) cells that recognize and
33 react against a restricted set of molecules in damaged or foreign cells (pathogens). Specific
34 immunity involves various types of lymphocytes T: helpers (Th cells) that contribute to immunity
35 against intracellular (Th1) or extracellular (Th2) pathogens, other regulatory T cells and also
36 cytolytic T lymphocytes (CTL). Adaptive immune response against pathogens can be achieved by
37 the activation of lymphocytes B or by activation of CTL. Lymphocytes B generate different types
38 of antibodies (immunoglobulins, Ig). Immune cells display a repertoire of plasma surface
39 molecules (cluster differentiation): CD19+ identifies almost all B lymphocytes, CD4+ cells
40 correspond to Th cells, CD8+ to CTL and CD16+ and/or 56+ to NK. CD3 is expressed in both Th
41 cells and CTL.
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The different components of the immune system communicate by proteins released by cytokines and chemokines such as interleukin (IL)-1 α or β , IL-6, tumour necrosis factor (TNF)- α or interferon (IFN)- γ . Some of these cytokines are predominantly (not exclusively) pro-inflammatory, whereas others exert an opposite action (e.g. IL-10). In addition, the C reactive protein (CRP) is also useful as marker of inflammation. Studies frequently evaluate *in vitro* the proliferative capability of circulating T cells in response to standard compounds eliciting such proliferation, as well as the release of cytokines by immune cells also in response to particular stimuli. Circulating levels of some cytokines are difficult to detect under normal conditions.

Immunological response in IPV survivors: Chronic stress has pro-inflammatory effects, delays wound healing and increases vulnerability to infections (Glaser and Kiecolt-Glaser, 2005). The complex bidirectional interactions between the brain, the hormones and the immune system can contribute to explaining the relationship between stress and immunity (Glaser and Kiecolt-Glaser, 2005; Payne, 2014). **In fact**, the pro-inflammatory state appears to be related to resistance of immune cells to glucocorticoids (Miller et al., 2008). Several types of IPV have been associated with an increase in the risk of communicable diseases such as urinary infections (Campbell et al., 2002), human immunodeficiency virus (HIV) (Dunkle et al., 2004) and other sexually-transmitted disorders (Dillon et al., 2013). These associations are most probably explained by direct sexual violence and it is difficult to relate them to chronic stress. However, other infections, such as those affecting the respiratory system (Bonomi et al., 2009), as well as the presence of alterations in the immune response, are harder to link to direct contact with the perpetrator. For example, violence against women appears to increase the risk of cancer, especially cervical cancer (Reingle Gonzalez et al., 2018).

A first study demonstrated that IPV women seeking protection from abuse showed reduced *in vitro* response of circulating T cells to mitogens (Constantino et al., 2000), suggesting impaired adaptive immunity. Accordingly, Garcia-Linares et al. (Garcia-Linares et al., 2004)

1 observed that physical, but not psychological, IPV reduced the capability of the saliva to
2 neutralize the herpes simplex type 1 (HSV-1), which causes opportunistic infection in conditions
3 of impaired immunity. The effect was not mediated by mental health status. Although a
4 reduction of saliva IgA against the virus was observed, this was not correlated to the degree of
5 immune-neutralization. In the most extensive study about the immune consequences of IPV, a
6 higher number of circulating T cells (CD3+, CD4+, CD8+ and CD19+) was found in IPV women
7 that were mediated by clinical PTSD symptoms (Woods, 2005). Similarly, **PTSD symptoms**
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9 **mediated** the increase in IFN- γ observed in IPV women (Woods et al., 2005).

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20 **Findings in vulnerable groups.** In HIV negative high-risk women, after controlling for sexual IPV,
21 lifetime physical and psychological abuse was associated with an enhanced number of activated
22 CD4+ cells (Kalokhe et al., 2016) that is known to favour HIV attack to these cells. In agreement
23 with these data, in IPV HIV infected women the decline in CD4+ cells after 1.3 years was
24 significantly associated with emotional abuse by their current partner, whereas the decline in
25 CD8+ cells was associated with lifetime emotional IPV (Jewkes et al., 2015).

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35 In a healthy population of pregnant women, the frequency of IPV was associated with
36 increased plasma CRP levels (Heath et al., 2013). Similarly, in post-menopausal women without
37 current psychiatric disease with a past (not present) history of stressful couple relationship, IPV
38 was related to higher plasma CRP, **despite normal IL-6 levels** (Fernandez-Botran et al., 2011).
39
40 Changes in CRP **appear to be** long-lasting, as women with a past traumatic IPV experience of
41 being stalked on average 10 years before, still showed higher CRP levels versus non-stalked
42 women (Newton et al., 2011). Although plasma IL-6 levels were not affected, the *in vitro* IL-6
43 response to a mitogen was also enhanced, suggesting a functional hyper-responsiveness of the
44 inflammatory system.

1 *Taken together, the above results suggest that IPV might impair the immune response to*
2 *pathogens and induce a pro-inflammatory phenotype that can be observed even without overt*
3 *psychiatric pathology and be long-lasting.*

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11 **6.3. Neurocognition**

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The relationships between the different cognitive components of the human mind follow an organization that has been described as modular and hierarchical within domains (Botvinick, 2008). Subcortical regions contain functional groups (nuclei) that provide the cerebral cortex with the capacity to direct attention to stimuli, process sensory information at different speeds, associate this information with emotional states, store it as memory and initiate actions (Kandel et al., 2000). In contrast, cortical regions are involved in cognitive control, planning and inhibition, which are characterized under the domain of executive functions and include the ability to temporarily hold information in order to make decisions (working memory process).

35 Cognitive functioning and the different domains including attention, vigilance, memory and executive functions can be assessed using a varied set of measurements. Although some scales focus on the self-perception of cognitive functioning and therefore base the assessment on the subjective impression of the subjects, the most commonly used tests are objective measures of the constructs and rely on validated tasks. In most cases, cognitive assessment involves a battery of tests that provide an overview of cognitive function and a description of specific alterations that may be present in groups of individuals. Because cognitive domains are associated with brain correlates, assumptions can be made at the level of diverse nucleus and brain regions that comprise complex neural circuitries.

57 **Neurocognitive alterations in IPV survivors.** Research on the neurocognitive profile of IPV women survivors not associated with TBI is extremely rare, but of great interest. An initial study

evaluated self-perceived cognitive dysfunctions in IPV women, with or without a life history of
1 PTSD (IPV PTSD+; IPV PTSD-), and controls (Kennedy et al., 2001). IPV was defined as physical
2 and/or sexual abuse by an intimate partner having ended at least four weeks, but no longer than
3 two years, before enrolment in the study. Self-perceived impairments were reported in
4 attention/concentration, orientation, memory and praxis. In a further study from the same
5 laboratory, the researchers compared IPV-exposed women, without or with current PTSD, and
6 controls in several cognitive domains assessed with direct validated measures of cognition.
7 These included attention, working and verbal memory, visuomotor capabilities and executive
8 functions (Stein et al., 2002). The results showed no impact on verbal learning, but lower
9 performance in the IPV group on sustained attention, visuomotor tasks (that includes visual
10 memory), and executive functions, more particularly impaired cognitive flexibility and inhibition.
11 Differences between IPV PTSD- and IPV PTSD+ women were not found and were not related to
12 PTSD severity, although executive functions did appear to be more affected in IPV PTSD+ than
13 IPV PTSD-. In a further study from the same group that included only IPV PTSD+ women and
14 controls (Twamley et al., 2009), impaired visuomotor capabilities were not confirmed, and
15 deficits in executive functioning were particularly restricted to cognitive flexibility, sensorial and
16 motor processing speed.

More recent data from another laboratory has focused on the specific impact of
1 psychological *versus* physical and psychological IPV on women (Daugherty et al., 2019). The
2 authors compared the neurocognitive performance in three groups: women exclusively
3 suffering psychological abuse, women with a history of both physical and psychological abuse
4 and control women. Women with a history of TBI and those with a diagnosis of mental health
5 disorders were excluded from this study. Of note, women were included regardless of the
6 duration of exposure to IPV. Attention, planning activities, inhibition and visuomotor abilities
7 were significantly lower in the physical and psychological IPV, in contrast to the only
8 psychological IPV and control groups. Importantly, attentional concentration and decision
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1 making, the latter measured with the Iowa Gambling Task (Bechara et al., 1994), were
2 significantly lower in the group of women that have been exposed exclusively to psychological
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4 IPV. This highlights the relevance of psychological abuse and its potential impact on the cognitive
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6 performance of women.
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10 One study has investigated emotionally laden attentional bias specifically in IPV. This
11 refers to the selective attention to potential threats, thus predisposing a person to enhanced
12 vigilance (Robinson, 1998), a feature commonly found among patients with different mental
13 health conditions, primarily PTSD, depression and anxiety (Bar-Haim et al., 2007; Buckley et al.,
14 2000; Klawohn et al., 2020; Peckham et al., 2010). The study evaluated the recognition of
15 emotional faces and the attention bias to the different emotional expressions in women
16 currently suffering from IPV and controls (Clauss and Clements, 2021). They reported specific
17 impairment in the recognition of happy faces in IPV women, bias attention towards fearful faces
18 and bias attention away from sad faces. No bias with respect to angry faces was observed. No
19 obvious explanation was offered for the avoidance of sad faces, although this might contribute
20 to buffer negative affect as a protective mechanism.
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36 *To sum up, very few studies are available that focus on the cognitive profile of IPV survivors*
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38 *not associated with TBI. Among those we were able to detect, attention, memory and processing*
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40 *speed were the cognitive domains most consistently found to be affected. The alterations*
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42 *reported for executive functions may be secondary to these changes.*
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49 **6.4. Brain structure and function**
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52 The study of the structure and function of the human brain is mostly based on magnetic
53 resonance imaging (MRI) technology (Yousaf et al., 2018). Structural MRI **mainly measures brain**
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55 **volume through the detection of minor changes in the concentration of protons (i.e. water).** A
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57 special application is diffusion tensor imaging (DTI), **which** allows the study of the integrity of
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1 axonal tracts by **exploring** functional anisotropy (FA). In addition, functional MRI (fMRI) is based
2 on the detection of the different magnetic properties of hemoglobin versus deoxyhemoglobin
3 (BOLD signal). The fMRI approach allows for the comparison of brain activation when subjects
4 are exposed to a stimulus. Functional connectivity can be inferred from the analysis of the
5 temporal synchronization in the activation (or deactivation) of the areas of interest, either
6 during resting conditions or in response to stimuli (Rubinov and Sporns, 2010). Finally, magnetic
7 resonance spectroscopy (MRS) research enables the assessment of regional brain
8 neurochemistry and, therefore, the *in vivo* identification of abnormalities in brain metabolites.
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19 The areas that have attracted particular attention in the context of stress studies are
20 those which participate in high order cognition (dorsolateral prefrontal cortex, DLPFC) and
21 emotional processing (insula, anterior cingulate cortex, hippocampus and amygdala). The DLPFC
22 is considered fundamental for executive functions, whereas the ventromedial and orbital
23 prefrontal cortex are critical for the top-down regulation of emotions, acting directly on limbic
24 areas, such as the hippocampus and the amygdala (which play a role in memory and emotional
25 processing (Fanselow and Dong, 2010)), or indirectly through the anterior cingulate and insular
26 cortices (which integrate various inputs to engage cognitive resources (Bush et al., 2000),
27 influence inhibitory control (Cieslik et al., 2015) and guide motivational actions (Craig, 2009;
28 Namkung et al., 2017). Importantly, relatively stable functional brain circuits among have been
29 identified that include the mentioned regions. The most widely known is the default mode
30 network (DMN), which is active while subjects are at rest (Raichle, 2015). Conversely, among the
31 brain systems that highlight the correlation between regions during goal-directed paradigms,
32 the salience network is highly relevant for attention to novel stimuli, response inhibition and
33 engagement of voluntary cognitive control (Peters et al., 2016; Seeley et al., 2007)
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(Supplementary Figures S1 and S2)

Structural brain alterations and neurochemistry. Using conventional MRI, preliminary structural data **showed** that IPV women (50% diagnosed with current PTSD) presented reduced

1 cranial volume as well as frontal and occipital grey matter volumes, with cranial volume
2 negatively correlating to childhood physical abuse rather than IPV (Fennema-Notestine et al.,
3 2002). However, no evidence for a reduced hippocampus volume was observed in either IPV
4 PTSD- or IPV PTSD+. Two other studies in IPV women without PTSD supported a lack of effect of
5 IPV on the hippocampus (Flegar et al., 2011; Roos et al., 2017). Interestingly, in **one study using**
6 **DTI** (Flegar et al., 2011), FA values were reduced in the body of the corpus callosum, suggesting
7 a specific impact of IPV on this brain structure.
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10 A further study used a structural covariance approach to describe brain connectivity in
11 IPV survivors with no history of traumatic brain injury (Roos et al., 2017). Authors observed an
12 altered connectivity suggestive of greater influence of caudal anterior cingulate/precuneus,
13 middle temporal lobe and ventral diencephalon (that includes the thalamus) in IPV women
14 versus non-IPV women, whereas in the latter the influence of frontal areas was predominate.
15 These results suggest that posterior regions have a relevant influence over the global network
16 in IPV women when compared to controls, while the influence of more frontal/anterior regions
17 is relatively reduced. Finally, one study using MR spectroscopy reported unaltered anterior
18 cingulate cortex integrity (assessed by the ratio N-acetyl-aspartate/creatinine) in **IPV exposed**
19 **women, with and without PTSD** (Seedat et al., 2005). There was evidence for higher
20 choline/creatinine and myo-inositol/creatinine ratios in IPV PTSD+ compared to IPV PTSD- women.
21 These ratios represent enhanced glial content that might reflect reduced neuronal arborisation.
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24 **Alterations in resting state activity and stimulus-evoked activation.** To our knowledge, only
25 one study has assessed resting state data among IPV survivors (Satterthwaite et al., 2016). The
26 researchers compared women with a diagnosis of PTSD associated with IPV with those with
27 MDD or healthy controls. Amygdala connectivity with DLPFC, anterior cingulate cortex and insula
28 was reduced in IPV PTSD+ participants when compared to non-traumatized controls. This result
29 might suggest an impaired cognitive control of PFC over the amygdala associated with PTSD.
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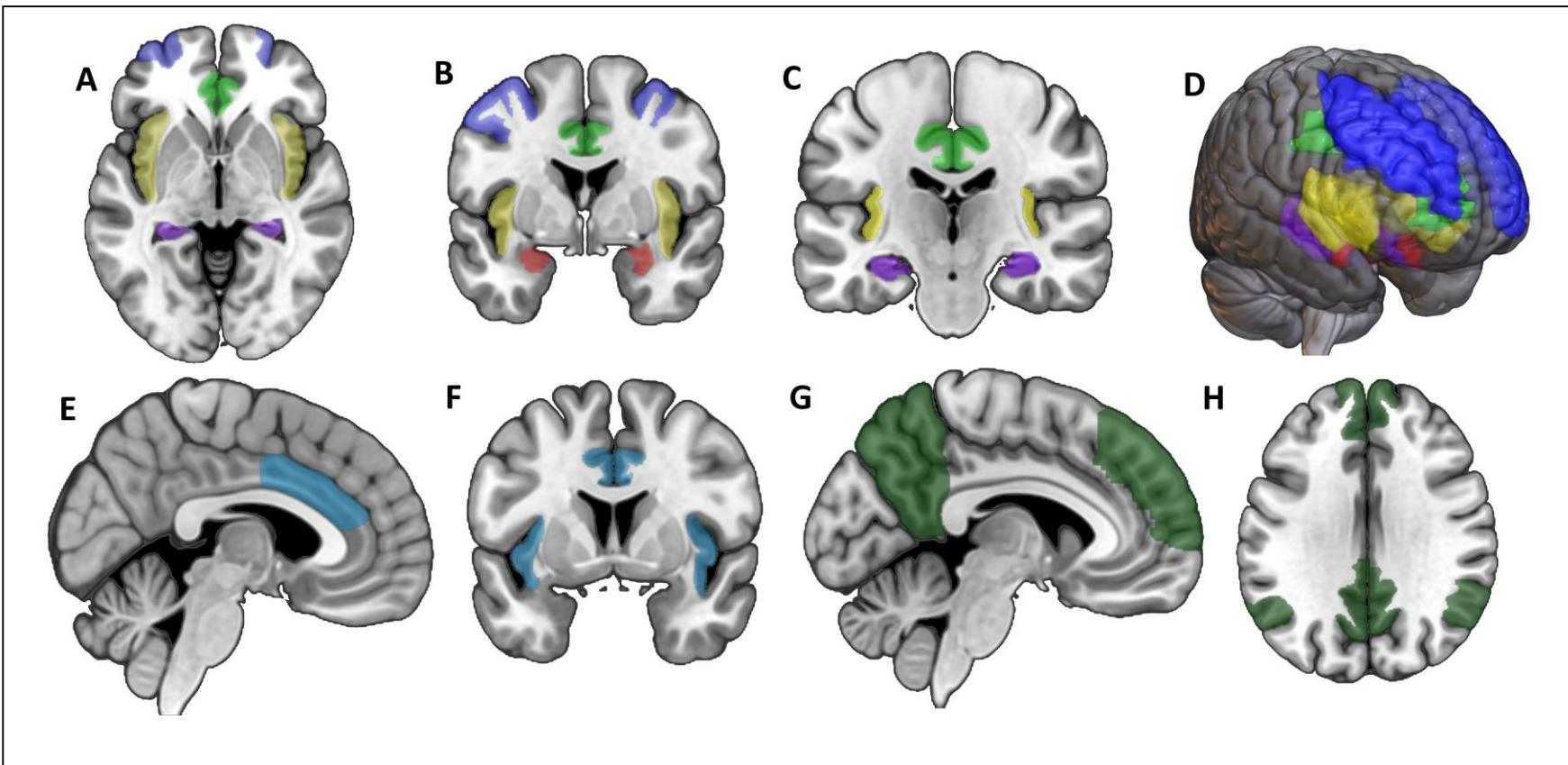
The effect of IPV on brain response to different categories of stimuli has been analysed in relatively small samples (10-37 women per group). One study explored cognitive response inhibition in a sample of IPV PTSD+ women and controls **using a stop-signal task** (Aupperle et al., 2016). The IPV PTSD+ group showed a greater contrast of stop vs non-stop, compared to non-traumatized women in DLPFC and insula activation, whereas the opposite pattern was found in the precuneus, posterior cingulate and the medial PFC. In the latter case, this was mainly driven by a greater activation during the non-stop trials in IPV PTSD+ subjects, resulting in less differential activation between conditions. Other studies have explored these activations relative to emotional content stimuli. A first article of IPV PTSD+ and non-traumatized women presented the participants with a continuous performance task with intercalated affective images, some of them reflecting traumatic events (Simmons et al., 2008). A greater activation in anticipation of negative versus positive images was found in the right anterior and middle insula of IPV PTSD+ women as compared to controls, together with reduced connectivity between the insula and the amygdala. Similar hyper-responsiveness of the right insula was observed in another study using the same approach, together with higher precuneus, inferior frontal and middle temporal and lower left dorsolateral and ventrolateral PFC activation (Aupperle et al., 2012) **and in a study using** angry and fearful versus neutral faces (Fonzo et al., 2010).

Finally, one study exploring pain sensitivity in IPV PTSD+ women (Strigo et al., 2010) **presented women with** thermal stimuli of three different intensities. IPV PTSD+ showed increased activation of the right DLPFC as well as in areas involved in executive and emotional processing (parietal cortex, middle anterior insula, cuneus/precuneus, temporal lobe). However, IPV PTSD+ participants showed a decrease in the right anterior insula activation from the first to the second exposure, whereas an increase was observed in controls. The anterior cingulate cortex followed the opposite pattern to the insula in both groups. Interestingly, avoidance symptoms of PTSD were negatively associated with subjective attenuation of pain and insula activation in IPV PTSD+ women.

1 *In brief, the limited research in IPV-related functional changes suggests the presence of*
2 *an hyperactivation of the insula, together with a reduced connectivity between this brain area*
3 *and both amygdala and PFC regions, in response to emotionally salient stimuli and in association*
4 *with hyperarousal and avoidance behaviour. Figure 1 characterizes the findings of functional*
5 *neuroimaging studies among IPV women and presents the activation networks that are of*
6 *interest for this discussion.*

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23 **Figure 1.** Visualization of the main regions of interest (ROIs) explored by reviewed research regarding neural changes linked to IPV. The upper part (A-D) refers
24 to those areas that are mainly affected by IPV: dorsolateral prefrontal cortex (dark blue), anterior cingulate cortex (light green), insula (yellow), hippocampus
25 (purple) and amygdala (red). The lower part (E-H) corresponds to networks of interest: the salience network (light blue) and the default mode network (dark
26 green). Images represent horizontal sections (A and H), coronal sections (B, C and F), sagittal sections by midline (E and G) and overall brain view (D). See
27 Supplementary Figures S1 and S2 for more details on the default mode network and salience network.
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7. Overall discussion

After decades of research in this area, it is now clear that chronic exposure to IPV has an enormous impact on women's health. There is consistent evidence for large increases in the risk of mental health problems among survivors, and also for other non-communicable diseases, particularly cardiovascular and respiratory disorders and musculoskeletal problems. A framework of chronic stress, largely based on data from basic biological research, proves to be a valuable tool in clarifying how IPV affects the health of women. The interpersonal dynamics that characterize IPV are depicted as repeated events of threat and avoidant coping. These processes highlight the longitudinal nature of IPV, as it builds a context for the consolidation of long-lasting neurobiological changes. Such changes are localized mainly at the level of the brain and HPA axis, but also affect the immune and other peripheral physiological systems; these alterations being implicated in the pathophysiology of non-communicable diseases that are common among women survivors of IPV. The health profile of survivors is most likely a result of individual-level physiological vulnerabilities, where the central nervous system acts as a main intermediary.

The dynamics of interpersonal relationships are subject to change over the years, and it is clear from the reviewed studies that this perspective of stages of change can help clarify the health impact of IPV on women survivors. Women use different strategies aimed at providing momentary relief – or even survival – from the violent situation. When life is under threat, all coping behaviours can be considered adaptive if they allow the women to stay alive. What seems to be most relevant for health is the use of certain strategies that can provide an immediate escape from IPV, but which do not prevent the repetition of violence in the middle and long term. As the threatening events are repeated over time, avoidant behaviour becomes progressively reinforced as a valid response to stress. This learning process is likely to be reflected in the stress-response system. Chronic exposure to stress elicits neurobiological

1 changes that in turn can alter the way IPV women perceive and process stressors, increase
2 vulnerability and risk of further suffering from IPV and other forms of interpersonal violence
3 (Funk et al., 2012; Trevillion et al., 2012). From this perspective, mental and physical health
4 disorders may present irregularly and overlap throughout the lives of the survivors; they are a
5 part of a dynamic process that changes along with experience and neurobiological adaptation.
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12 Experimental evidence strongly suggests that exposure to chronic stress can induce
13 morphological and functional changes in neurons of the prefrontal cortex, hippocampal
14 formation and amygdala that are likely to be involved in stress-induced cognitive and emotional
15 changes (McEwen, 2007; McEwen and Morrison, 2013; Roozendaal et al., 2009). These results
16 are in line with the already discussed impact of IPV in cognition, emotional processing and brain
17 structure and function. Hyperarousal and avoidant coping were associated with an increased
18 insula activation presented among IPV survivors in response to intense/negative stimuli. This
19 association is also present in PTSD patients, and suggests a close correlation between the
20 experience of threat, avoidant coping and neural adaptation. Moreover, disruption of “top-
21 down” cognitive-appraisal and attentional control in DLPFC, and dorsal anterior cingulate cortex
22 together with amygdala hyperactivation, were suggested to be present in IPV, consistent with
23 non-IPV trauma exposed samples (White et al., 2015; Zhai et al., 2019). When considering these
24 data in light of the temporal dynamics that define IPV and the extremely common use of
25 avoidance to cope with violence, it is possible to assume that the insular hyperactivation and
26 disruption of the cortical circuitry are neurobiological correlates of interpersonal violence in the
27 context of IPV.
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31 According to this framework, exposure to IPV initially impacts the brain with changes
32 that are primarily expressed as mental health symptoms and signs. These changes, together with
33 learned strategies, modify the appraisal and coping strategies to face IPV violence and other
34 stressful experiences. In addition to the IPV-induced changes in the way the brain processes
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1 stressors, this situation also results in alterations of peripheral physiological functions that are
2 the consequence of the chronic stress state IPV represents (e.g. HPA axis resting activity and
3 responsiveness, endocrine and immune resistance to glucocorticoids). Together they may foster
4 further health disorders including cardiovascular and respiratory diseases, along with other
5 health conditions that may be better explained by the impact of a dysregulation of the immune
6 response, such as cancer. We propose that these neurobiological processes underlie the
7 pathways from IPV to non-communicable diseases, as depicted in Figure 2.
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17 A key mechanism in the proposed pathway between IPV and non-communicable
18 diseases is HPA axis dysfunction. The literature showed IPV-related alterations in the circadian
19 cortisol pattern and the CAR, with important discrepancies regarding the direction of such
20 alterations. Given the low number of studies, it is difficult at present to speculate about the
21 reason for these discrepancies, but there are some possibilities. First, plasma cortisol measures
22 the total content of the steroid, whereas saliva cortisol reflects the free fraction; therefore,
23 altered levels of CBG in IPV can result in a change in the ratio of saliva/plasma cortisol. Second,
24 the effect of IPV may be modulated by the presence of different pathologies or lifestyles. For
25 example, there is evidence that PTSD from different causes could be associated with low hair
26 cortisol levels, whereas the opposite occurs in MDD (Herane Vives et al., 2015; Staufenbiel et
27 al., 2013). Thus, we are superimposing the putative impact of chronic stress suffered by IPV
28 women upon the changes in the HPA axis specifically associated with the appearance of certain
29 psychiatric symptoms/diseases. Although the exposure may be similar in many women (IPV), it
30 is possible that the phenotype associated with the exposure (i.e. specific disease) may differ as
31 a consequence of inter-individual differences, either of environmental or genetic origin.
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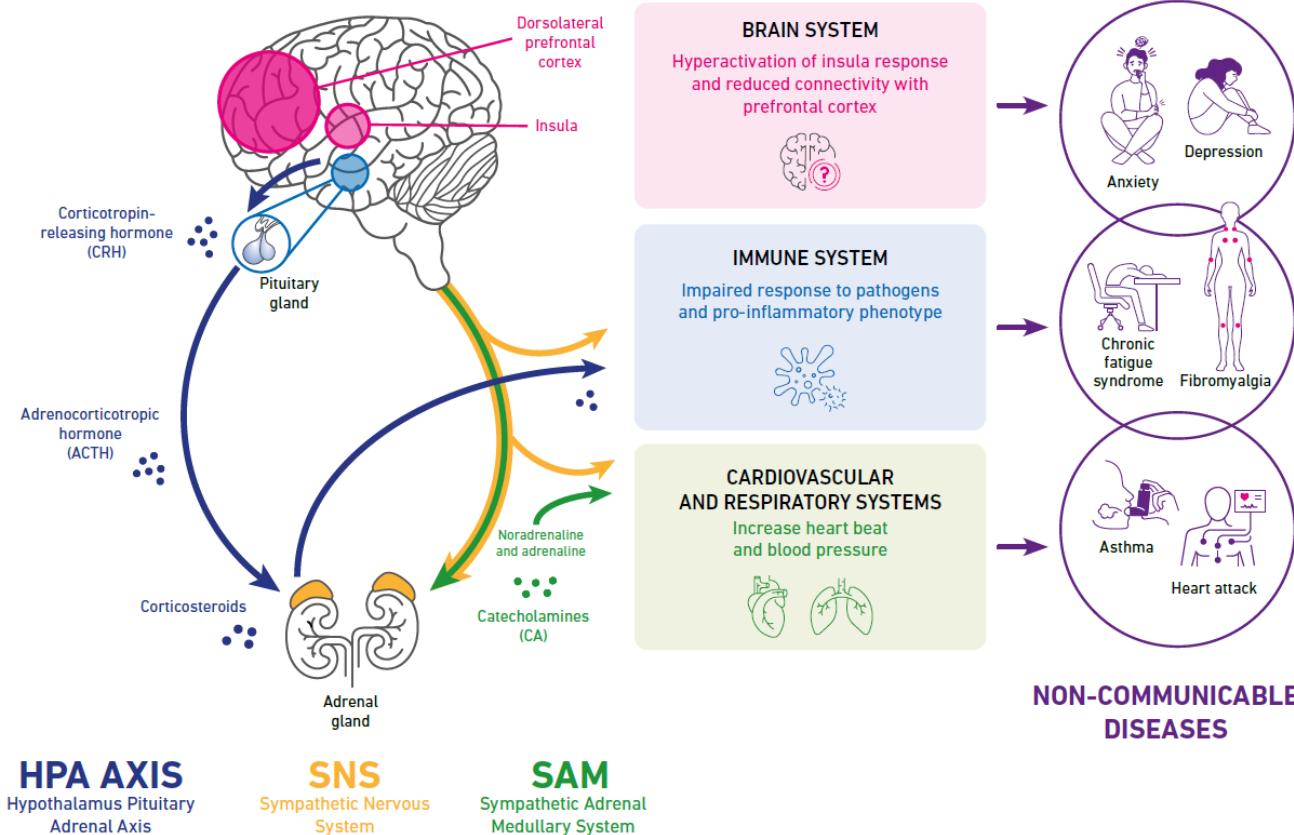
54 To the best of our knowledge, this is the first review on the impact of IPV on non-
55 communicable diseases outcomes that includes large population-based studies, experimental
56 data and several biological domains. It is apparent that we need a more in-depth
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characterization of the short-term and long-term changes associated with IPV. Despite its tremendous social impact, the number of studies is far lower compared to other chronic stressful conditions. Nevertheless, epidemiological studies strongly suggest an important impact on the cardiovascular systems, particularly regarding heart disease and stroke, with less evident effects on blood pressure. More evidence has been gathered which supports it having an impact on the immune system, with enhanced susceptibility to infection and inflammation-related diseases, although the precise mechanisms involved is still to be explored. Current research exploring IPV effects on the brain suffer from several important limitation. In particular, factors presented prior to (child abuse), during (TBI) and after (PTSD and substance abuse) the victimization have an impact on brain functioning, hindering the capability to identify changes strictly related to IPV. Nonetheless, these aspects are too closely linked to the phenomenon of IPV, that characterizing a subsample of IPV without history of child abuse, TBI or PTSD would be untrue to the way IPV is observed. Also, the description of the experience of IPV has to include key variables such as the frequency of exposure to violent events, the type of violence exerted (including a clear depiction of psychological abuse), the duration of IPV, and the time between the first experience of IPV and the onset of the disease (incubation time). Moreover, the field clearly lacks studies exploring how women respond to acute stress challenges that exceed the context of IPV and could offer the opportunity to unmask alterations in the HPA axis that are not observable under resting conditions (Belda et al., 2015; Goldberg et al., 2020).

Remarkably, health alterations among survivors are the norm, while the absence of any symptoms after years of systematic exposure to violence should be recognized as an indicator of outstanding resilience. The health consequences reflect the need for medical assistance related to IPV, even years after ceasing the violent relationship (Kruse et al., 2011). This translates into a tremendous burden for healthcare services. Complementary, clinical research would benefit from including IPV as a potential confounder or relevant variable in the interpretation of clinical data. Indeed, it is possible that the results of neuroimaging studies of

1 patients with MDD or anxiety could be associated with a history of chronic stress, specifically
2 IPV, rather than disease. Finally, prevention campaigns could benefit from focusing on tackling
3 IPV and other forms of interpersonal violence. In the case of depression, it has been estimated
4 that one million cases per year could be completely averted if no women were exposed to IPV
5 (Beydoun et al., 2012). When other health outcomes associated with IPV are considered, the
6 medical costs linked to IPV have been estimated at US \$2.1 trillion only in the United States of
7 America (Peterson et al., 2018). The estimated costs rise to US \$3.6 trillion when productivity
8 and criminal justice expenditures are included.
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Understanding the neurobiological impact of IPV and its relationship with health can help develop more precise treatments to reduce the prevalence of disease among women. Most relevantly, it offers a clear evidenced-based description of the damaging effects of IPV on long-term women's health, and provides support for the eradication of violence against women as a crucial target for settling the basis of sustainable development globally.



55 **Figure 2. Proposed model of chronic stress in the context of IPV.** The dynamics of IPV is cyclic and presents recurrent episodes of violence. A single event of intimate partner violence activates the HPA axis in the
 56 same way as an acute stressor, triggering central and peripheral responses mainly represented by brain and cardiorespiratory adaptive changes. As violent events are repeated over time, changes in the primary
 57 systems are consolidated and the immune response is intensified. These consolidated alterations are the neurobiological correlates of the non-communicable diseases most commonly found among IPV survivors,
 58 which appear at different moments during the lifespan and may overlap.

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4 **SUPPLEMENTARY MATERIAL TO THE MANUSCRIPT**
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12 **Non-communicable diseases among women survivors of intimate partner violence: Critical
13 review from a chronic stress framework**
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- Supplementary Table S1: Details of the scales reported in the studies focused on coping
25 strategies used among IPV-exposed women and mental health (pp 2-4)
- Supplementary Table S2: Details of the population-based studies focused on the
26 association between IPV and non-communicable diseases based on $N > 10,000$ (pp 6-8)
- Supplementary Figure S1: Visualization of the default mode network (p 9)
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- References used in Supplementary Material (pp 11-15)

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20 **Supplementary Table S1**
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28 Details of the scales reported in the studies focused on coping strategies used among IPV-exposed women and mental health
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Reference	Participants	Variables	Measurements
Mitchell & Hodson, 1983 ¹	60 battered women	Intimate Partner Violence	The Conflicts Tactics Scale (CTS) ²
		Depressive symptoms	Brief Symptom Inventory (BSI) ³
		Coping: active behavioral, active coping, avoidance. Social Support.	Coping scale developed by Billings & Moos ⁴ . Semi-structured interview of social support developed by the authors.
Arias & Pape, 1999 ⁵	68 battered women living in shelters	Intimate Partner Violence	The Conflict Tactics Scale-Form R (CTS-R) ⁶ ; Psychological Maltreatment of Women Inventory (PMWI) ⁷
		Post-Traumatic Stress Disorder Symptoms	Symptom Checklist-90-revised (SCL-90-R) ⁸
		Coping: Problem-focused, emotion-focused.	Ways of coping Checklist-Revised (WCCL-R) ⁹
Kocot & Goodman, 2003 ¹⁰	169 women at intake center for survivors of domestic violence	Intimate Partner Violence	The Revised Conflict Tactics Scale 2-Form A (CTS2) ¹¹ ; The Psychological Maltreatment of Women Inventory (PMWI) ¹²
		Depression and Post-Traumatic Stress Disorder Symptoms	Center for Epidemiological Studies Depression Scale (CES-D) ¹³ ; The PTSD Checklist (PCL) ¹⁴
		Coping: problem focused-coping. Social support	3 subscales of Problem-focused Coping Scale ¹⁵ : active coping, planning and seeking of instrumental support. Interpersonal Support Evaluation List (ISEL) ¹⁶

Reference	Participants	Variables	Measurements
Lewis, et. al., 2006 ¹⁷	102 battered women living in shelters	Intimate Partner Violence Depressive symptoms Coping: Engagement and disengagement	The Conflicts Tactics Scale (CTS) ² Center for Epidemiological Studies Depression Scale (CES-D) ¹³ Coping Strategies Inventory—Short Form (CSI) ¹⁸
Krause, Kaltman, Goodman & Dutton, 2008 ¹⁹	262 women exposed to IPV	Intimate Partner Violence Post-Traumatic Stress Disorder Symptoms Coping: cognitive avoidance and avoidance-escape behaviour. Social support	The Revised Conflict Tactics Scale 2-Form A (CTS2) ¹¹ PTSD Checklist - Civilian version (PCL) ¹⁴ Cognitive avoidance subscale of Coping Responses Inventory ²⁰ and the avoid-escape subscale of the Ways of Coping Questionnaire ⁹ . Interpersonal Support Evaluation List (ISEL) ¹⁶ . Formal network strategies subscale of IPV Strategies index (ISI) ²¹
Calvete, Corral & Estevez, 2008 ²²	298 women reporting physical IPV	Physical aggression and psychological abuse in the context of IPV Distress symptoms	Physical assault scale of The Revised Conflict Tactics Scale 2-Form A (CTS2) ¹¹ Psychological abuse inventory (PAI) ²³ Center for Epidemiological Studies Depression Scale (CES-D) ¹³ and Anxiety scale of the Symptom Checklist-90-revised (SCL-90-R) ²⁴

Reference	Participants	Variables	Measurements
		Coping: primary and secondary control engagement, disengagement including avoidance.	Responses to Stress Questionnaire (RSQ) ²⁵
Lilly & Graham-Bermann, 2010 ²⁶	97 participants with past-year IPV	Intimate Partner Violence	The Conflict Tactics Scale-Revised (CTS-R) ⁶
		Post-Traumatic Stress Disorder Symptoms	The Posttraumatic Stress Diagnostic Scale (PDS) ²⁷
		Coping: Problem-focused, emotion-focused	Ways of coping Checklist-Revised (WCCL-R) ²⁸

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20 **Supplementary Table S2**
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22 Details of the population-based studies focused on the association between IPV and non-communicable diseases based on N>10,000
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28 Reference(s)	29 Study	30 Details
31 Ellsberg, et. al., 2008 ²⁹	32 World Health Organization 33 Multi-country study	34 This study was promoted after an international expert 35 consultation of violence against women that recommended 36 international research to explore the health consequences 37 and risk factors of violence against women. 38 Sample of 24,097 women aged 15 to 49 years old, from 10 39 countries and 15 sites between 2000 and 2003. 40 The countries included in the study were Bangladesh, Brazil, 41 Ethiopia, Japan, Namibia, Peru, Samoa, Serbia and 42 Montenegro, Thailand and the United Republic of Tanzania. 43 Exposures and outcomes were measured using a 44 standardized questionnaire translated into 14 languages, along with a common definition of physical and sexual intimate partner violence.
45 Loxton, et. al., 2006 ³⁰	46 Australian Longitudinal Study on 47 Women's Health	48 Representative cohort of 40,000 randomly recruited 49 Australian women followed up since 1996. The National 50 Health Insurance Database was used as the sampling frame 51 with systematic oversampling of participants living in rural 52 and remote areas. The primary objective was to understand 53 factors that affect women's health and well-being to inform 54 national health policies. 55 Data is collected longitudinally through surveys of the self- 56 reported health and well-being of three cohorts of women 57 who were classified by age groups at the time of start of the 58 Study. 59 Intimate Partner Violence was defined as having a violent 60 relationship with an intimate partner.
61 Vos, et. al., 2006 ³¹	62	63

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Reference(s)	Study	Details
Black & Breiding, 2008 ³²	Behavioral Risk Factor Surveillance System (BRFSS)	<p>The BRFSS is an annual survey of the adult (aged ≥ 18 years) population of the United States of America (USA). Participants are contacted through a state-based, random-digit-dialed strategy. In 2005, a total of 70,156 respondents (42,566 women and 27,590 men) in 16 states completed the optional IPV module. The prevalence of each health condition and risk behavior was calculated by sex of the respondent and lifetime experience of IPV. IPV was identified when responders reported any of the following had occurred during their lifetimes: threatened, attempted, or completed physical violence or unwanted sex by a current or former intimate partner.</p>
Mason, et. al., 2013 ³³	Nurses' Health Study II (NHSII)	<p>The Nurses' Health Study was initially set in 1976 supported by the National Institute of Health of USA. The initial objective was to investigate the potential long-term effects of oral contraceptives, and nurses were selected as the study population due to their knowledge about health. Data is collected longitudinally regarding sociodemographic, behavioral and health data. Participants of the NHSII study (N=68,376) answered a Violence Questionnaire that was introduced in 2001. IPV assessment includes physical and sexual IPV ("ever been hit, slapped, kicked, or otherwise physically hurt by spouse or significant other"; "has your spouse/significant other ever forced you to have sexual activities") The researchers used hazard ratio estimates to explore the relationship between lifetime IPV as reported in 2001, and type II diabetes diagnosed over the 2001-2007 period.</p>

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Reference(s)	Study	Details
Chandan, et. al., 2020 ³⁴ Chandan, et. al., 2019 ³⁵	Health Improvement Network (THIN) database	<p>The THIN database consists of the electronic health registries from over 750 general practices comprising 3.6 million patients in the United Kingdom (UK) collected between 1995 and 2017. It is considered representative of the UK population.</p> <p>IPV was identified through the registries as reported by General Practitioners. A total of 18,547 exposed women were included and each woman was matched with up to four control (non-exposed to IPV) women based on age at index date.</p> <p>In their study of mental health outcomes, the authors report both OR and IRR, the latter providing an estimate of the new cases per 1,000-person years. The use of this estimate offers the opportunity to explore not only the cross-sectional association between IPV and health outcomes – which may reflect the likelihood of having an illness before IPV (OR) – but also the increased risk of disease after exposure (IRR).</p>
Ackerson & Subramanian, 2008 ³⁶	Indian National Family Health Survey	<p>This 1998-1999 Indian National Family Health Survey is a nationally representative cross-sectional study of 92,447 households. Face-to-face interviews were conducted with 90,303 ever-married women between 15 and 49 years of age. Information on domestic violence was collected during this survey.</p> <p>After dropping cases with missing information, 69,072 women located in 3,190 primary sampling units in 26 Indian states were finally included.</p> <p>Only physical abuse was considered, although the authors discuss the potential effect of other forms of abuse in these households.</p>

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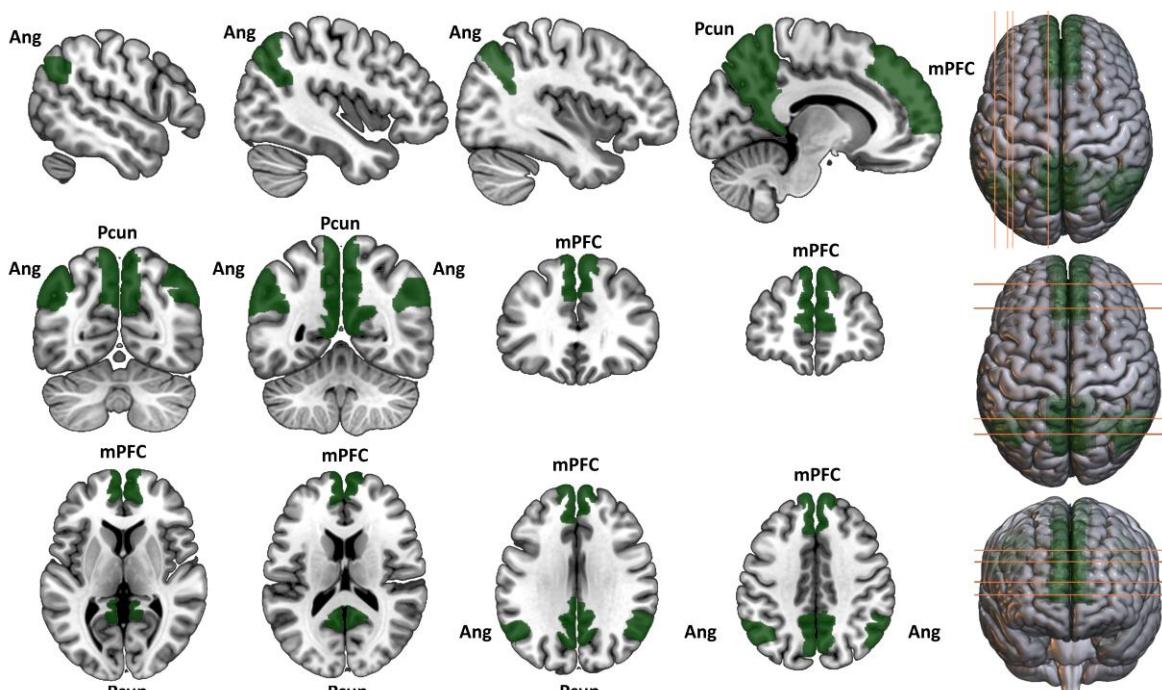
Reference(s)	Study	Details
European Agency for Fundamental Rights, 2014 ³⁷	FRA EU-wide survey on violence against women	<p>This is the first European Union (EU)-wide survey to collect comparable data on women's experiences of gender-based violence in all 28 EU Member States.</p> <p>This survey included over 40,000 adult (+18 years old) women from all 28 Member States of the European Union at the time: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovenia, Slovakia, Spain, Sweden and the United Kingdom</p>

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Supplementary Figure S1

Visualization of the default mode network (DMN)

The default mode network (DMN) involves the correlated activation of the medial prefrontal cortex (mPFC) the precuneus and posterior cingulate cortex (Pcun) and the angular gyrus (Ang). The DMN is normally engaged when subjects are at rest, mind-wandering or while performing tasks that require self-directed thought or introspection.



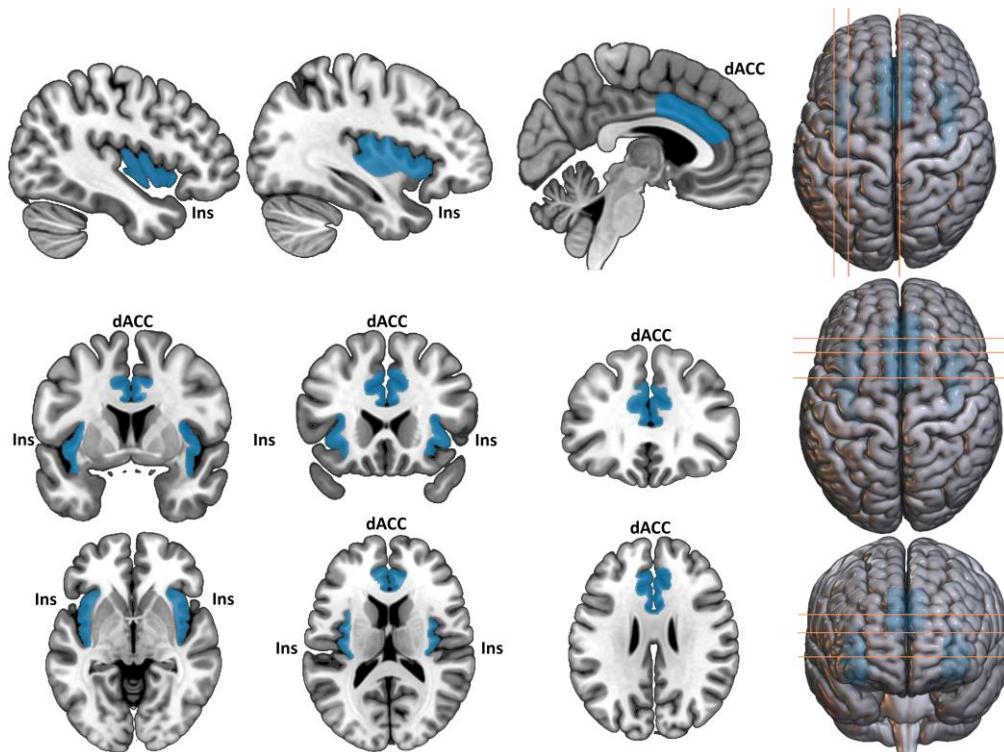
Findings in IPV (See Figure 1 in main document): Consistent with previous research indicating an influence of the insula over the DMN functioning^{38,39}, alterations in the DMN are also observed in IPV, suggesting IPV survivors might have difficulties switching away from the DMN. These results are supported by studies of the neurocognitive profile of IPV survivors, which show a significant contribution of altered attention and processing speed to their cognitive deficits.

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Supplementary Figure S2

Visualization of the salience network

The main nodes of the salience network are the dorsal anterior cingulate cortex (dACC) and the insula (mainly anterior). The salience network is active when subjects engage in goal-directed behaviors aimed at identifying relevant stimuli in the environment, and when the brain coordinates neural resources to respond to these stimuli.



Findings in IPV (See Figure 1 in main document): FMRI research on IPV provides evidence for neural alterations located in the DLPFC, anterior and posterior cingulate cortex, insula and medial temporal lobe (i.e. amygdala, hippocampus and parahippocampus). Hence, changes within the salience network can be observed, which could be related to the increased detection of threat and reactivity in IPV survivors, as previously observed in PTSD patients ⁴⁰.

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