

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

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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

over 10 years (Thompson et al., 2006; Triantafyllou et al., 2016). Indeed, the dynamics of IPV in the context of an intimate relationship are usually cyclic and defined by recurrent episodes of different types of violence. We propose that this characteristic is key to unravelling the neurobiological intermediaries between IPV and disease.

In the present review we approach IPV from the perspective of the neurobiological framework of chronic stress. We revise the literature that addresses this topic from diverse but complementary perspectives. Firstly, we present the model of chronic stress that is typically used in neurobiological research. Secondly, we describe the behavioural dynamics involved in coping with IPV and how they can be aligned with the neurobiological model of chronic stress. Thirdly, we resume data from large population-based surveys and datasets that describe the extent of the association between IPV and non-communicable diseases. Finally, we offer a detailed description of the published results on experimental data which focus on the stress-response system of IPV survivors and their link to disease. We propose that chronic activation of this system underlies the association between IPV and non-communicable diseases, particularly mental health disorders.

## **2. The neurobiological model of chronic stress**

Stress is experienced in situations in which persons are actually threatened, they perceive a threat, or the situation exceeds their ability to cope (Lazarus and Folkman, 1984). In its broadest sense, stress includes the environmental insult (stressor), the person's appraisal of that insult (stress processing and associated emotions), and the bio-behavioural response. *This stress response is orchestrated by the brain and involves central and peripheral functions, acting in concert (Charmandari et al., 2005). Emotional stressful situations are processed by cortico-limbic circuits, with signals eventually converging in the paraventricular nucleus of the hypothalamus (PVN) and brainstem noradrenergic nuclei (Chrousos and Gold, 1992; Ulrich-Lai*

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).

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

### 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

distinct (Fingerhut and Saltzman, 2000). Also, the term “domestic violence” is used either to refer exclusively to IPV or to include violence against children and men (European Agency for Fundamental Rights, 2014). Topographical similarities exist between physical and psychological abuse, as they tend to be serial and ongoing, and can occur during and after the termination of the romantic relationship. Given this background, whenever the reviewed data refer to forms of violence different from physical and sexual abuse, we explicitly acknowledge this information.

Term	Description
<b>Intimate partner violence (IPV)</b>	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.
<b>Physical violence</b>	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.
<b>Sexual violence</b>	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.
<b>Psychological abuse</b>	The woman is subjected to insults, belittling, constant humiliation, intimidation (e.g. destroying things), threats of harm, threats to take away her children.
<b>Controlling behaviour</b>	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.

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

#### 4. Psychological and behavioural coping of IPV

The complex dynamics involved in the behavioural response of women to IPV was first highlighted from the perspective of “learned helplessness” (Walker, 1984, 1979) and the complementary “survivor’s theory” (Gondolf, 1988). **These initial proposals present an evidence-based scheme of the wide range of behaviours that women survivors use to cope with the violence and their associations with IPV’s long-term repercussions** (Rizo et al., 2017; Waldrop and Resick, 2004). **Following**, we will describe results from studies aimed at exploring the associations between these coping strategies and health outcomes.

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



PTSD was also found, that was not moderated by coping strategies. In contrast to these results, a second investigation (Kocot and Goodman, 2003), reported a main effect of higher frequency of problem-focused coping on increased PTSD. A similar study (Lilly and Graham-Bermann, 2010) reported that more frequent emotion-focused coping was associated with higher violence exposure and PTSD symptoms. These data suggest that the impact of an emotion-focusing coping style could be markedly dependent on the intensity of IPV, **but** leave ample room for discussion owing to the lack of replication and the cross-sectional nature of the data. Only one longitudinal study has focused on coping strategies and PTSD (Krause et al., 2008). Avoidant coping was significantly and positively associated with PTSD symptomatology at inclusion and at the one-year follow-up, as was the severity of IPV. No interaction effects were found between IPV and coping.

As for studies where the primary outcome was depression, results showed a similar trend. An initial report (Mitchell and Hodson, 1983) **found that** frequency and level of violence were associated with depression, but the type of coping was important, in that active coping was associated with reduced levels of depression, whereas avoidant coping was associated with increased levels. The results were in line with those from the study mentioned above, which centred on problem-focused coping and also found main effect increased frequency of use of this strategy and increased levels of depression (Kocot and Goodman, 2003).

Several models of the potential mediating and moderating effects of coping on both depression and anxiety have been explored in one particular study **based on a sample of 113 women** (Calvete et al., 2008). IPV was associated with both anxiety and depression. There was no evidence for moderation, implying that the effect of IPV on health does not vary as a function of coping strategy. Zero-order correlations showed that disengagement and secondary control response were associated with anxiety symptoms, while only disengagement was associated with depression. Interestingly, results showed evidence of mediation effects to the extent that

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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10 Some factors that relate to coping and mental health may help understand the  
11 mechanisms involved in their relationships. Importantly, a history of childhood abuse appears  
12 to be relevant **and may moderate the effect of adult emotional abuse**. The results showed a  
13 greater effect of childhood emotional abuse than adult emotional abuse on depressive  
14 symptomatology, whereas the number of episodes of physical battering in adulthood was  
15 unrelated to depression (Lewis et al., 2006). There are two possible explanations for these  
16 results: (i) high levels of childhood abuse among these participants could shape a less reactive  
17 response to physical violence in adulthood; or (ii) the high levels of physical violence in IPV  
18 situations experienced by these participants during adulthood, might result in a ceiling effect.  
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#### 32 **4.2. Reflections from qualitative and mixed-model research**

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36 The adaptive capacity of any given coping strategy is heavily dependent on context,  
37 including the nature of the violence, the woman's perception of the situation, and her resources  
38 to address it. Most importantly, these factors vary during the course of IPV, and what may be  
39 perceived as adaptive behaviour at one point of the relationship may be seen as maladaptive at  
40 another. These dynamics follow stages of change that have been explored through different  
41 models (Brown, 1997; Reisenhofer et al., 2019). Hence, it is highly recommended that the coping  
42 strategies used by women are recognized in light of their complex and changing interpersonal  
43 intimate relationship.  
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56 The vast majority of studies that explore the relationship between IPV, coping and mental  
57 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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51 *In sum, women use a large number of coping strategies to deal with repetitive violence and*  
52 *threat. There is a high frequency of use of avoidant strategies that aim to provide immediate*  
53 *release from threat (e.g. avoidance) but have been associated with problematic mental health*  
54 *outcomes. This reality builds a context for chronic stress.*  
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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.**

The first study of this kind was the WHO multi-country study (Ellsberg et al., 2008). The prevalence of IPV varied widely between countries, from 15% to 71%. This cross-sectional study focused on physical and mental health symptoms during the four weeks preceding the interview (difficulties with walking, pain, memory loss, dizziness, along with suicidal thoughts and acts), reporting statistically significant results for all measures. The results of this initial work were later confirmed in the systematic review by WHO (García-Moreno et al., 2013). *More recent multi-country efforts were led by the European Union (European Agency for Fundamental Rights, 2014). The prevalence of physical IPV was 24%, while that of sexual IPV was 9%. Measuring health impact was not the main objective of the study, and the published results do not provide*

estimates of risk that could have been included in Table 1. However, some information can be retrieved, particularly regarding psychological consequences. For example, among all survivors of physical IPV, 32% showed anxiety, 12% panic attacks, 20% depression and 23% difficulty sleeping. The frequencies among survivors of sexual IPV were higher: 45% showed anxiety, 21% panic attacks, 35% depression and 41% difficulty sleeping. The high prevalence of mental health disorders and symptoms among these women in Europe coincides with the reported frequencies of symptoms of PTSD among American survivors of IPV. Indeed, a reported 51.8% of women who experienced contact sexual violence, physical violence and/or stalking by an intimate partner in their lifetime in the USA present symptoms of PTSD (Smith et al., 2017).

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.

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

(HR=1.18; 95%CI=1.00-1.39), **and** severe psychological IPV, as opposed to none or moderate exposure (HR=1.78, 95%CI=1.21-2.61).

A study based on a cross-sectional large sample of women between 15 and 49 years of age in the Indian National Family Health Survey explored the association between IPV and malnutrition (Ackerson and Subramanian, 2008). The authors propose that domestic violence in the country commonly takes the form of withholding food, which in turns leads to malnutrition and associated disorders. Prevalence of IPV was 9% in this sample, which is relatively low compared to other studies. Only physical abuse was considered, although the authors discuss the potential effect of other forms of abuse in these households. The authors measured two aspects of nutritional status: anaemia (assessed by means of blood test for haemoglobin) and being underweight (body mass index). Results showed a statistically significant relationship (OR) between anaemia and exposure to IPV when women were exposed to IPV more than once in the past year, as opposed to only once in the past year, more than one year ago or never. Similar results were reported for being severely underweight. Being underweight (any type, as opposed to being severely underweight) was evident among women reporting IPV in the last year or more than once in the last year, but not among those reporting IPV more than one year ago. Hence, time passing since IPV might have a mitigating effect on anaemia and being underweight. It is important to note that being underweight was the consequence of restricting food access in this study.

To our knowledge, only one study has used electronic records to explore the relationship between IPV and health (Chandan et al., 2019). **IRR estimates indicated increased risk of** anxiety, depression and serious mental illness after exposure after adjustment for relevant covariates. **The researchers also found** a significant association of IPV with a general measure of cardiovascular disease, and more specifically with ischemic heart disease, stroke/transient ischemic attack, and type II diabetes (Chandan et al., 2020). No associations

1 were found after adjustment for the presence of heart failure, hypertension and peripheral  
2 vascular diseases.  
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5 *Summing up, there is a significant relationship between exposure to IPV and non-*  
6 *communicable diseases. The most striking results are related to mental health. Prevalence of*  
7 *cardiovascular (including diabetes), respiratory, and musculoskeletal disorders have all been*  
8 *found to increase among IPV survivors. More research is warranted to understand the impact of*  
9 *IPV on cancer.*  
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**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 Supplementary Table 2 for more details.

Categories of health impact	Type of consequence	Results (95% CI) - unadjusted	Results (95% CI) - adjusted	Sample size	Study period	Country
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)
Cardiovascular	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)
	Heart disease	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)
	Heart failure	IRR 1.15 (0.75-1.77)	aIRR 1.06 (0.69-1.63)	91,778	1995-2017	United Kingdom (3)
	Heart attack	N/R	aOR 1.4 (1.1-1.7)	42,566	2005	United States of America (4)
	Hypertension	IRR 1.02 (0.90-1.15)	aIRR 0.99 (0.88-1.12)	91,778	1995-2017	United Kingdom (3)
		OR 1.25 (1.12-1.40)	aOR 1.03 (0.89-1.18)	14,100	1996	Australia (1)
	High blood pressure	N/R	aOR 1.1 (1.0-1.2)	42,566	2005	United States of America (4)
	High blood cholesterol	N/R	aOR 1.3 (1.1-1.4)	42,566	2005	United States of America (4)
	Ischaemic heart disease	IRR 1.45 (1.13-1.85)	aIRR 1.40 (1.09-1.79)	91,778	1995-2017	United Kingdom (3)
	Thrombosis	OR 1.52 (1.25-1.85)	aOR 1.10 (0.86-1.41)	14,100	1996	Australia (1)
	Peripheral vascular disease	IRR 1.27 (0.81-1.99)	aIRR 1.18 (0.75-1.86)	91,778	1995-2017	United Kingdom (3)
	Stroke	N/R	aOR 1.8 (1.4-2.2)	42,566	2005	United States of America (4)
Diabetes		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)
	Type II diabetes	HR 1.34 (1.14-1.58)	aHR 1.18 (1.00-1.39)	68,376	2001 to 2007	United States of America (5)
		HR 1.25 (1.01-1.55)	aHR 1.08 (0.86-1.35)	68,376	2001 to 2007	United States of America (5)
		IRR 1.55 (1.33-1.81)	aIRR 1.51 (1.30-1.76)	91,778	1995-2017	United Kingdom (3)
	Diabetes (nongestational)	N/R	aOR 1.1 (0.9-1.3)	42,566	2005	United States of America (4)
Musculoskeletal	Diabetes (unspecified)	OR 1.46 (1.15-1.86)	OR 1.11 (0.82-1.52)	14,100	1996	Australia (1)
	Pain	OR 1.8 (1.7-2.0)	aOR 1.6 (1.5-1.7)	24,097	2000-2003	Multi-country (6)
	Pain/fatigue	OR 1.95 (1.77-2.15)	aOR 1.28 (1.13-1.45)	14,100	1996	Australia (1)
	Chronic fatigue syndrome	IRR 1.71 (1.01-2.89)	aIRR 1.92 (1.11- 3.33)	92,735	1995-2017	United Kingdom (7)
	Fibromyalgia	IRR 1.95 (1.54-2.47)	aIRR 1.73 (1.36-2.22)	92,735	1995-2017	United Kingdom (7)
	Arthritis/rheumatoid arthritis/gout/lupus/fibromyalgia	N/R	aOR 1.7 (1.6-1.9)	42,566	2005	United States of America (4)
	Osteoporosis	OR 1.77 (1.45-2.16)	aOR 1.10 (0.86-1.42)	14,100	1996	Australia (1)
	Problems with walking	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)	N/R	14,739	2001	Australia (2)
		OR 2.21 (2.12-2.31)	aOR 1.91 (1.82-2.01)	92,735	1995-2017	United Kingdom (7)
		IRR 2.19 (1.98-2.38)	aIRR 1.99 (1.80-2.20)	92,735	1995-2017	United Kingdom (7)
	Depression	RR 1.96 (1.59-2.42)	N/R	14,739	2001	Australia (2)
		OR 3.15 (3.04-3.26)	aOR 2.61(2.51-2.71)	92,735	1995-2017	United Kingdom (7)
		IRR 3.40 (3.16-3.67)	aIRR 3.05 (2.81-3.31)	92,735	1995-2017	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)	aOR 2.13 (1.86-2.43)	92,735	1995-2017	United Kingdom (7)
		IRR 3.60 (2.63-4.92)	aIRR 3.08 (2.19-4.32)	92,735	1995-2017	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)
Respiratory	Asthma	OR 1.83 (1.64-2.05)	aOR 1.21 (1.04-1.41)	14,100	1996	Australia (1)
		N/R	aOR 1.6 (1.4-1.8)	42,566	2005	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 & Breiding, 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).

## 5.1. Influence of risk behaviours and other risk factors

**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*

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

## 19 **5.2. Methodological considerations**

22 Because the estimates used in the different studies are conceptually different (OR, RR,  
23 IRR, HR), direct comparisons are discouraged. Also, different studies have included several  
24 covariates in an effort to adjust the results for factors that have been linked to either IPV or to  
25 the particular health outcome. Age is adjusted for in most, although not all, studies, as is  
26 education and different indices of income or deprivation. Variations on the prevalence of IPV,  
27 health disorders and their associations according to age, education and income level should be  
28 further explored in health impact assessments. Globally, it has been estimated that 30% of all  
29 women suffer IPV at some point in their lives (García-Moreno et al., 2013). This prevalence is  
30 slightly higher in the USA, rising to 36.4% (Smith et al., 2018), and lower in the European Union,  
31 with a reported 22% (European Agency for Fundamental Rights, 2014). In some low- and middle-  
32 income countries the prevalence of current violence against women rises to 46% and that of  
33 lifetime IPV to 71% (Coll et al., 2020; Garcia-Moreno et al., 2006). Despite a trend towards a  
34 higher prevalence of IPV associated with income status between and within the countries, IPV is  
35 also highly prevalent in high-income countries with gender-equality policies, such as Denmark  
36 (32%), Finland (30%) and Sweden (28%) (Gracia and Merlo, 2016). These rates are indicative of  
37 the underlying complexity of IPV, which is reflected in the results of the association between IPV  
38 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*  
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4                   *possible that the estimates of risk reflect a role of previous health conditions as potential risk*  
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6                   *factors for IPV. This could be the case for mental health in particular, as people living with mental*  
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8                   *health disorders are a vulnerable group who habitually experience physical and sexual*  
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10                  *victimization, including IPV (Funk et al., 2010). However, it is also expected that these patients*  
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12                  *have been exposed to multiple focuses of violence throughout their adult lives and during*  
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14                  *childhood, which could have shaped their mental health outcome (Copeland et al., 2018).*  
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19                   *When models of future development of cardiovascular diseases are used, there is sound*  
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21                  *agreement that IPV predicts the development of pathology in the following 2.5 to 30 years (Clark*  
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23                  *et al., 2016; Pantell et al., 2019; Renner et al., 2021; Scott-Storey, 2013; Scott-Storey et al., 2019;*  
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25                  *Wright et al., 2021). In general, although the effects on cardiovascular diseases are consistent,*  
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27                  *the impact on hypertension is usually not significant, particularly when adjusting for other health*  
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29                  *variables (Breiding et al., 2008). Nevertheless, the risk of being prescribed antihypertensive drugs*  
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31                  *is increased (Stene et al., 2013) and a direct impact on hypertension might be possible under the*  
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33                  *most severe IPV conditions (Mason et al., 2012). Interestingly, a recent longitudinal study*  
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35                  *supports a role for depression as an intermediary between exposure to IPV and cardiovascular*  
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37                  *risk scores (Wright et al., 2019). To better understand these relationships, it is highly*  
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39                  *recommended that future research includes longitudinal follow-ups of cohorts of IPV women in*  
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41                  *which physical and mental health status can be explored, including a biological sample collection*  
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43                  *and a digital follow-up to test for pathways of associations.*  
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## 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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5 In contrast to the above reports describing hypocortisolemia, Pico-Alfonso et al. (Pico-  
6 Alfonso et al., 2004) did not observe differences in morning salivary cortisol, but did report  
7 higher evening cortisol levels in IPV (both physical and psychological) than non-abused women.  
8 This was accompanied by more symptoms of depression, anxiety and PTSD. The same laboratory  
9 again showed higher evening but not morning saliva cortisol levels in IPV women suffering major  
10 depressive disorder (MDD), compared to non-abused controls, but no differences from controls  
11 in IPV without symptoms or in those with MDD and PTSD (Blasco-Ros et al., 2014).  
12 Unfortunately, abused women having only PTSD were not included. **This was explored in**  
13 **another study in which** higher saliva cortisol levels across the day were reported in IPV victims  
14 that developed PTSD versus those without diagnosis, although the effect was particularly  
15 evident in remitted subjects (Inslicht et al., 2006). In a study of extant couples, women suffering  
16 from IPV showed a slightly altered circadian pattern of saliva cortisol, mainly characterized by a  
17 flattened slope, with similar morning levels but less decline over the day (Kim et al., 2015).  
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21 **Cortisol awakening response:** The way to evaluate CAR has been rapidly changing over the last  
22 decade, the present consensus including four time points on two different days: the first one  
23 just after awakening and again 30, 45 and 60 min later (Stalder et al., 2016). Recent data  
24 highlight the importance of following the cortisol response after awakening for 120 min, to catch  
25 both the slope of the response and its disappearance (Benz et al., 2019). Unfortunately, most of  
26 the few studies exploring CAR in IPV women were completed before the consensus was  
27 achieved.  
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31 Basu and colleagues (Basu et al., 2013) observed no differences between controls and  
32 IPV (physical and sexual) women and no influence of diagnosis (no symptoms, MDD, PTSD), but  
33 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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26 **Hair cortisol:** In recent years, the incorporation of hair cortisol concentration is allowing an  
27 overall picture of the changes in the HPA axis under chronic stress or in psychiatric patients to  
28 be seen. This measure has the advantage of evaluating free cortisol fraction and is an integrated  
29 measure of the cortisol released over a period of months (Stalder et al., 2017; Stalder and  
30 Kirschbaum, 2012). In pregnant women exposed to IPV during the last 12 months, higher hair  
31 cortisol levels have been observed compared to controls (Boeckel et al., 2017). This suggests  
32 that the chronic IPV stress is reflected in high overall HPA activity, in accordance with what is  
33 found in animal models of severe chronic stress (Scorrano et al., 2015). However, in another  
34 study using a small sample (IPV n=12; controls n=15) of non-pregnant women that investigated  
35 how an incident of physical and/or sexual assault in the past three months affected hair cortisol,  
36 no group differences in hair cortisol were found, despite levels of stress exposure being higher  
37 in IPV than in controls (Morris et al., 2017). It is possible that the level of stress was not as high  
38 as in the previous report.  
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57 **A very recent report studied hair cortisol in a sample of women in which IPV scores in the**  
58 **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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11 *In all, there are few studies of the impact of IPV on HPA activity and the results are*  
12 *controversial. This is not surprising as the HPA axis is highly sensitive to changes in activity, sleep*  
13 *pattern, drug consumption and anticipation of events which generate anxiety. More and better*  
14 *controlled studies are needed, including how IPV women respond to novel superimposed*  
15 *stressors.*  
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## 23 24 25 26 27 **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  $\alpha$  or  $\beta$ , IL-6, tumour necrosis factor (TNF)- $\alpha$  or interferon (IFN)- $\gamma$ . 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**  
8 **mediated** the increase in IFN- $\gamma$  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 Changes in CRP **appear to be** long-lasting, as women with a past traumatic IPV experience of  
40 being stalked on average 10 years before, still showed higher CRP levels versus non-stalked  
41 women (Newton et al., 2011). Although plasma IL-6 levels were not affected, the *in vitro* IL-6  
42 response to a mitogen was also enhanced, suggesting a functional hyper-responsiveness of the  
43 inflammatory system.  
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*Taken together, the above results suggest that IPV might impair the immune response to pathogens and induce a pro-inflammatory phenotype that can be observed even without overt psychiatric pathology and be long-lasting.*

### 6.3. Neurocognition

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).

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.

**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

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

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41 More recent data from another laboratory has focused on the specific impact of  
42 psychological *versus* physical and psychological IPV on women (Daugherty et al., 2019). The  
43 authors compared the neurocognitive performance in three groups: women exclusively  
44 suffering psychological abuse, women with a history of both physical and psychological abuse  
45 and control women. Women with a history of TBI and those with a diagnosis of mental health  
46 disorders were excluded from this study. Of note, women were included regardless of the  
47 duration of exposure to IPV. Attention, planning activities, inhibition and visuomotor abilities  
48 were significantly lower in the physical and psychological IPV, in contrast to the only  
49 psychological IPV and control groups. Importantly, attentional concentration and decision  
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making, the latter measured with the Iowa Gambling Task (Bechara et al., 1994), were significantly lower in the group of women that have been exposed exclusively to psychological IPV. This highlights the relevance of psychological abuse and its potential impact on the cognitive performance of women.

One study has investigated emotionally laden attentional bias specifically in IPV. This refers to the selective attention to potential threats, thus predisposing a person to enhanced vigilance (Robinson, 1998), a feature commonly found among patients with different mental health conditions, primarily PTSD, depression and anxiety (Bar-Haim et al., 2007; Buckley et al., 2000; Klawohn et al., 2020; Peckham et al., 2010). The study evaluated the recognition of emotional faces and the attention bias to the different emotional expressions in women currently suffering from IPV and controls (Clauss and Clements, 2021). They reported specific impairment in the recognition of happy faces in IPV women, bias attention towards fearful faces and bias attention away from sad faces. No bias with respect to angry faces was observed. No obvious explanation was offered for the avoidance of sad faces, although this might contribute to buffer negative affect as a protective mechanism.

*To sum up, very few studies are available that focus on the cognitive profile of IPV survivors not associated with TBI. Among those we were able to detect, attention, memory and processing speed were the cognitive domains most consistently found to be affected. The alterations reported for executive functions may be secondary to these changes.*

#### **6.4. Brain structure and function**

The study of the structure and function of the human brain is mostly based on magnetic resonance imaging (MRI) technology (Yousaf et al., 2018). Structural MRI **mainly measures brain volume through the detection of minor changes in the concentration of protons (i.e. water)**. A special application is diffusion tensor imaging (DTI), **which** allows the study of the integrity of

axonal tracts by **exploring** functional anisotropy (FA). In addition, functional MRI (fMRI) is based on the detection of the different magnetic properties of hemoglobin versus deoxyhemoglobin (BOLD signal). The fMRI approach allows for the comparison of brain activation when subjects are exposed to a stimulus. Functional connectivity can be inferred from the analysis of the temporal synchronization in the activation (or deactivation) of the areas of interest, either during resting conditions or in response to stimuli (Rubinov and Sporns, 2010). Finally, magnetic resonance spectroscopy (MRS) research enables the assessment of regional brain neurochemistry and, therefore, the *in vivo* identification of abnormalities in brain metabolites.

The areas that have attracted particular attention in the context of stress studies are those which participate in high order cognition (dorsolateral prefrontal cortex, DLPFC) and emotional processing (insula, anterior cingulate cortex, hippocampus and amygdala). The DLPFC is considered fundamental for executive functions, whereas the ventromedial and orbital prefrontal cortex are critical for the top-down regulation of emotions, acting directly on limbic areas, such as the hippocampus and the amygdala (which play a role in memory and emotional processing (Fanselow and Dong, 2010)), or indirectly through the anterior cingulate and insular cortices (which integrate various inputs to engage cognitive resources (Bush et al., 2000), influence inhibitory control (Cieslik et al., 2015) and guide motivational actions (Craig, 2009; Namkung et al., 2017). Importantly, relatively stable functional brain circuits among have been identified that include the mentioned regions. The most widely known is the default mode network (DMN), which is active while subjects are at rest (Raichle, 2015). Conversely, among the brain systems that highlight the correlation between regions during goal-directed paradigms, the salience network is highly relevant for attention to novel stimuli, response inhibition and engagement of voluntary cognitive control (Peters et al., 2016; Seeley et al., 2007)

**(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

cranial volume as well as frontal and occipital grey matter volumes, with cranial volume negatively correlating to childhood physical abuse rather than IPV (Fennema-Notestine et al., 2002). However, no evidence for a reduced hippocampus volume was observed in either IPV PTSD- or IPV PTSD+. Two other studies in IPV women without PTSD supported a lack of effect of IPV on the hippocampus (Flegar et al., 2011; Roos et al., 2017). Interestingly, in **one study using DTI** (Flegar et al., 2011), FA values were reduced in the body of the corpus callosum, suggesting a specific impact of IPV on this brain structure.

A further study used a structural covariance approach to describe brain connectivity in IPV survivors with no history of traumatic brain injury (Roos et al., 2017). Authors observed an altered connectivity suggestive of greater influence of caudal anterior cingulate/precuneus, middle temporal lobe and ventral diencephalon (that includes the thalamus) in IPV women versus non-IPV women, whereas in the latter the influence of frontal areas was predominate. These results suggest that posterior regions have a relevant influence over the global network in IPV women when compared to controls, while the influence of more frontal/anterior regions is relatively reduced. Finally, one study using MR spectroscopy reported unaltered anterior cingulate cortex integrity (assessed by the ratio N-acetyl-aspartate/creatine) **in IPV exposed women, with and without PTSD** (Seedat et al., 2005). There was evidence for higher choline/creatine and myo-inositol/creatine ratios in IPV PTSD+ compared to IPV PTSD- women. These ratios represent enhanced glial content that might reflect reduced neuronal arborisation.

**Alterations in resting state activity and stimulus-evoked activation.** To our knowledge, only one study has assessed resting state data among IPV survivors (Satterthwaite et al., 2016). The researchers compared women with a diagnosis of PTSD associated with IPV with those with MDD or healthy controls. Amygdala connectivity with DLPFC, anterior cingulate cortex and insula was reduced in IPV PTSD+ participants when compared to non-traumatized controls. This result might suggest an impaired cognitive control of PFC over the amygdala associated with PTSD.

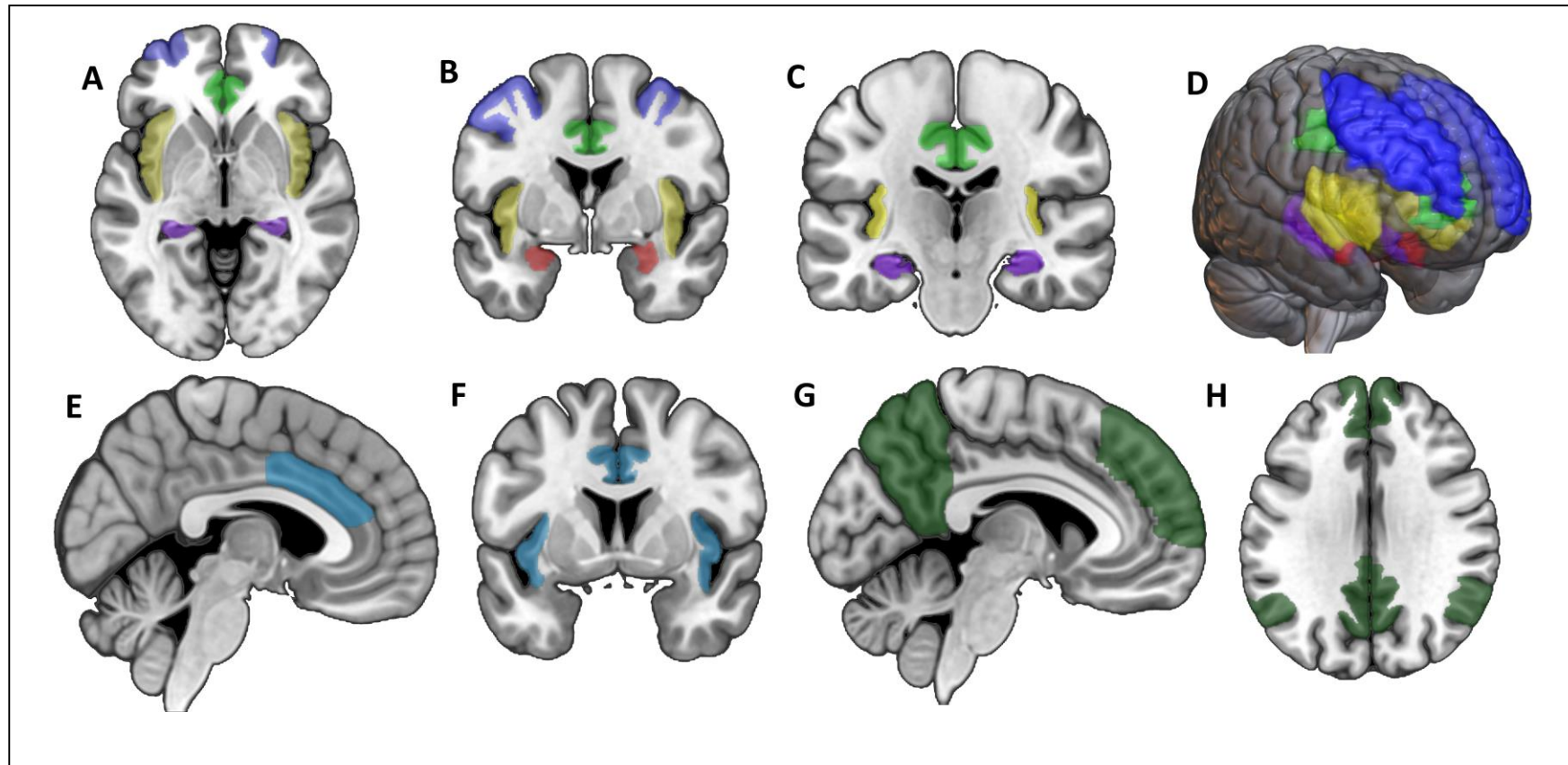
1 The effect of IPV on brain response to different categories of stimuli has been analysed  
2 in relatively small samples (10-37 women per group). One study explored cognitive response  
3 inhibition in a sample of IPV PTSD+ women and controls **using a stop-signal task** (Aupperle et  
4 al., 2016). The IPV PTSD+ group showed a greater contrast of stop vs non-stop, compared to  
5 non-traumatized women in DLPFC and insula activation, whereas the opposite pattern was  
6 found in the precuneus, posterior cingulate and the medial PFC. In the latter case, this was  
7 mainly driven by a greater activation during the non-stop trials in IPV PTSD+ subjects, resulting  
8 in less differential activation between conditions. Other studies have explored these activations  
9 relative to emotional content stimuli. A first article of IPV PTSD+ and non-traumatized women  
10 presented the participants with a continuous performance task with intercalated affective  
11 images, some of them reflecting traumatic events (Simmons et al., 2008). A greater activation in  
12 anticipation of negative versus positive images was found in the right anterior and middle insula  
13 of IPV PTSD+ women as compared to controls, together with reduced connectivity between the  
14 insula and the amygdala. Similar hyper-responsiveness of the right insula was observed in  
15 another study using the same approach, together with higher precuneus, inferior frontal and  
16 middle temporal and lower left dorsolateral and ventrolateral PFC activation (Aupperle et al.,  
17 2012) **and in a study using angry and fearful versus neutral faces** (Fonzo et al., 2010).

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



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

**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 to those areas that are mainly affected by IPV: dorsolateral prefrontal cortex (dark blue), anterior cingulate cortex (light green), insula (yellow), hippocampus (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 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 Supplementary Figures S1 and S2 for more details on the default mode network and salience network.



## 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  
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4 (Funk et al., 2012; Trevillion et al., 2012). From this perspective, mental and physical health  
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6 disorders may present irregularly and overlap throughout the lives of the survivors; they are a  
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8 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  
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14 morphological and functional changes in neurons of the prefrontal cortex, hippocampal  
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16 formation and amygdala that are likely to be involved in stress-induced cognitive and emotional  
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18 changes (McEwen, 2007; McEwen and Morrison, 2013; Roozendaal et al., 2009). These results  
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20 are in line with the already discussed impact of IPV in cognition, emotional processing and brain  
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22 structure and function. Hyperarousal and avoidant coping were associated with an increased  
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24 insula activation presented among IPV survivors in response to intense/negative stimuli. This  
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26 association is also present in PTSD patients, and suggests a close correlation between the  
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28 experience of threat, avoidant coping and neural adaptation. Moreover, disruption of “top-  
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30 down” cognitive-appraisal and attentional control in DLPFC, and dorsal anterior cingulate cortex  
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32 together with amygdala hyperactivation, were suggested to be present in IPV, consistent with  
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34 non-IPV trauma exposed samples (White et al., 2015; Zhai et al., 2019). When considering these  
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36 data in light of the temporal dynamics that define IPV and the extremely common use of  
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38 avoidance to cope with violence, it is possible to assume that the insular hyperactivation and  
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40 disruption of the cortical circuitry are neurobiological correlates of interpersonal violence in the  
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42 context of IPV.  
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51 According to this framework, exposure to IPV initially impacts the brain with changes  
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53 that are primarily expressed as mental health symptoms and signs. These changes, together with  
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55 learned strategies, modify the appraisal and coping strategies to face IPV violence and other  
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57 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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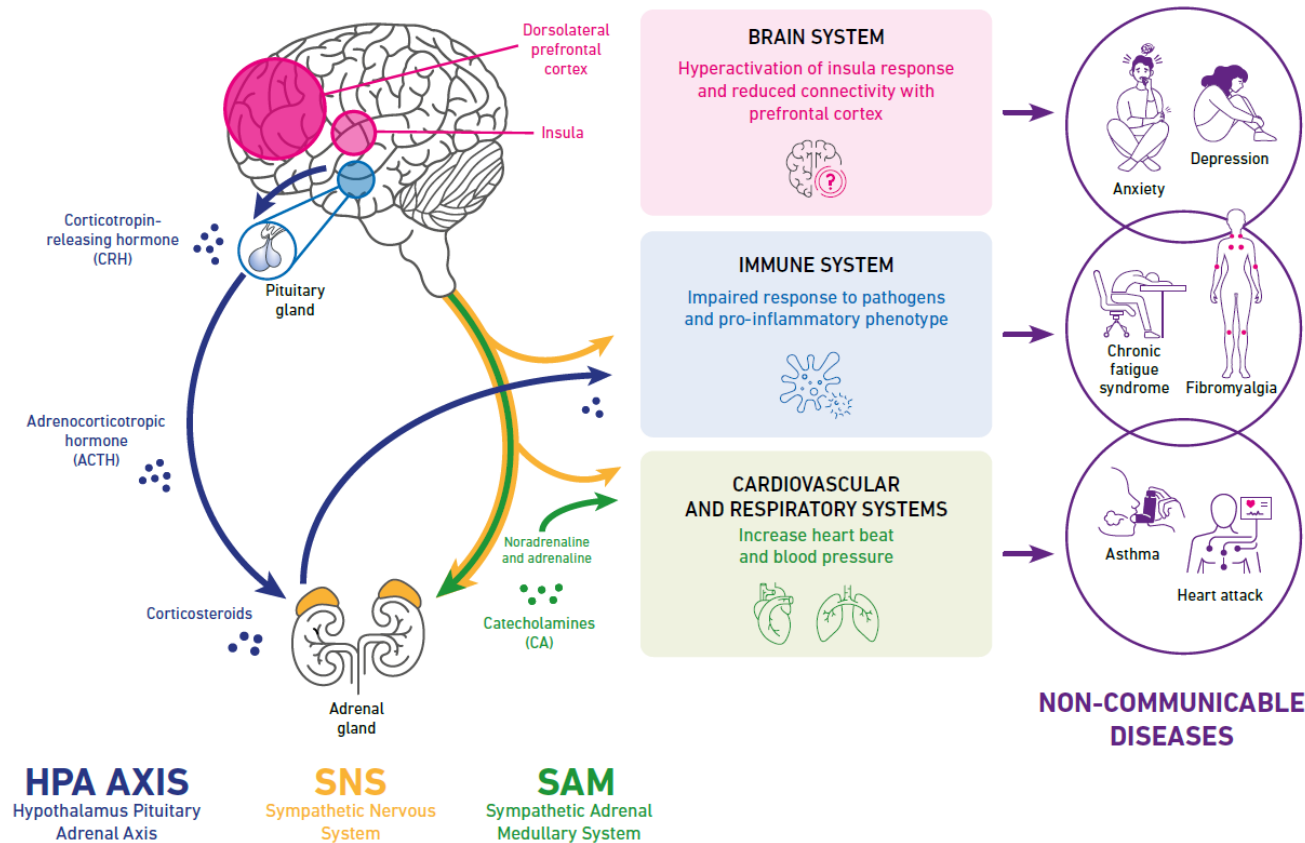
54 To the best of our knowledge, this is the first review on the impact of IPV on non-  
55 communicable diseases outcomes that includes large population-based studies, experimental  
56 data and several biological domains. It is apparent that we need a more in-depth  
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1 characterization of the short-term and long-term changes associated with IPV. Despite its  
2 tremendous social impact, the number of studies is far lower compared to other chronic  
3 stressful conditions. Nevertheless, epidemiological studies strongly suggest an important impact  
4 on the cardiovascular systems, particularly regarding heart disease and stroke, with less evident  
5 effects on blood pressure. More evidence has been gathered which supports it having an impact  
6 on the immune system, with enhanced susceptibility to infection and inflammation-related  
7 diseases, although the precise mechanisms involved is still to be explored. Current research  
8 exploring IPV effects on the brain suffer from several important limitation. In particular, factors  
9 presented prior to (child abuse), during (TBI) and after (PTSD and substance abuse) the  
10 victimization have an impact on brain functioning, hindering the capability to identify changes  
11 strictly related to IPV. Nonetheless, these aspects are too closely linked to the phenomenon of  
12 IPV, that characterizing a subsample of IPV without history of child abuse, TBI or PTSD would be  
13 untrue to the way IPV is observed. Also, the description of the experience of IPV has to include  
14 key variables such as the frequency of exposure to violent events, the type of violence exerted  
15 (including a clear depiction of psychological abuse), the duration of IPV, and the time between  
16 the first experience of IPV and the onset of the disease (incubation time). Moreover, the field  
17 clearly lacks studies exploring how women respond to acute stress challenges that exceed the  
18 context of IPV and could offer the opportunity to unmask alterations in the HPA axis that are not  
19 observable under resting conditions (Belda et al., 2015; Goldberg et al., 2020).

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21 Remarkably, health alterations among survivors are the norm, while the absence of any  
22 symptoms after years of systematic exposure to violence should be recognized as an indicator  
23 of outstanding resilience. The health consequences reflect the need for medical assistance  
24 related to IPV, even years after ceasing the violent relationship (Kruse et al., 2011). This  
25 translates into a tremendous burden for healthcare services. Complementary, clinical research  
26 would benefit from including IPV as a potential confounder or relevant variable in the  
27 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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20 Understanding the neurobiological impact of IPV and its relationship with health can  
21 help develop more precise treatments to reduce the prevalence of disease among women. Most  
22 relevantly, it offers a clear evidenced-based description of the damaging effects of IPV on long-  
23 term women's health, and provides support for the eradication of violence against women as a  
24 crucial target for settling the basis of sustainable development globally.  
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**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 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 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, which appear at different moments during the lifespan and may overlap.



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**SUPPLEMENTARY MATERIAL TO THE MANUSCRIPT**

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

- Supplementary Table S1: Details of the scales reported in the studies focused on coping strategies used among IPV-exposed women and mental health (pp 2-4)
- Supplementary Table S2: Details of the population-based studies focused on the 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)
- Supplementary Figure S2: Visualization of the salience network (p 10)
- References used in Supplementary Material (pp 11-15)

## Supplementary Table S1

Details of the scales reported in the studies focused on coping strategies used among IPV-exposed women and mental health

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

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

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



## Supplementary Table S2

Details of the population-based studies focused on the association between IPV and non-communicable diseases based on N>10,000

Reference(s)	Study	Details
Ellsberg, et. al., 2008 <sup>29</sup>	World Health Organization Multi-country study	This study was promoted after an international expert consultation of violence against women that recommended international research to explore the health consequences and risk factors of violence against women. Sample of 24,097 women aged 15 to 49 years old, from 10 countries and 15 sites between 2000 and 2003. The countries included in the study were Bangladesh, Brazil, Ethiopia, Japan, Namibia, Peru, Samoa, Serbia and Montenegro, Thailand and the United Republic of Tanzania. Exposures and outcomes were measured using a standardized questionnaire translated into 14 languages, along with a common definition of physical and sexual intimate partner violence.
Loxton, et. al., 2006 <sup>30</sup> Vos, et. al., 2006 <sup>31</sup>	Australian Longitudinal Study on Women's Health	Representative cohort of 40,000 randomly recruited Australian women followed up since 1996. The National Health Insurance Database was used as the sampling frame with systematic oversampling of participants living in rural and remote areas. The primary objective was to understand factors that affect women's health and well-being to inform national health policies. Data is collected longitudinally through surveys of the self-reported health and well-being of three cohorts of women who were classified by age groups at the time of start of the Study. Intimate Partner Violence was defined as having a violent relationship with an intimate partner.

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Reference(s)	Study	Details
Black & Breiding, 2008 <sup>32</sup>	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.</p> <p>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.</p> <p>IPV was identify 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 <sup>33</sup>	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.</p> <p>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”)</p> <p>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>

Reference(s)	Study	Details
Chandan, et. al., 2020 <sup>34</sup> Chandan, et. al., 2019 <sup>35</sup>	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 <sup>36</sup>	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>

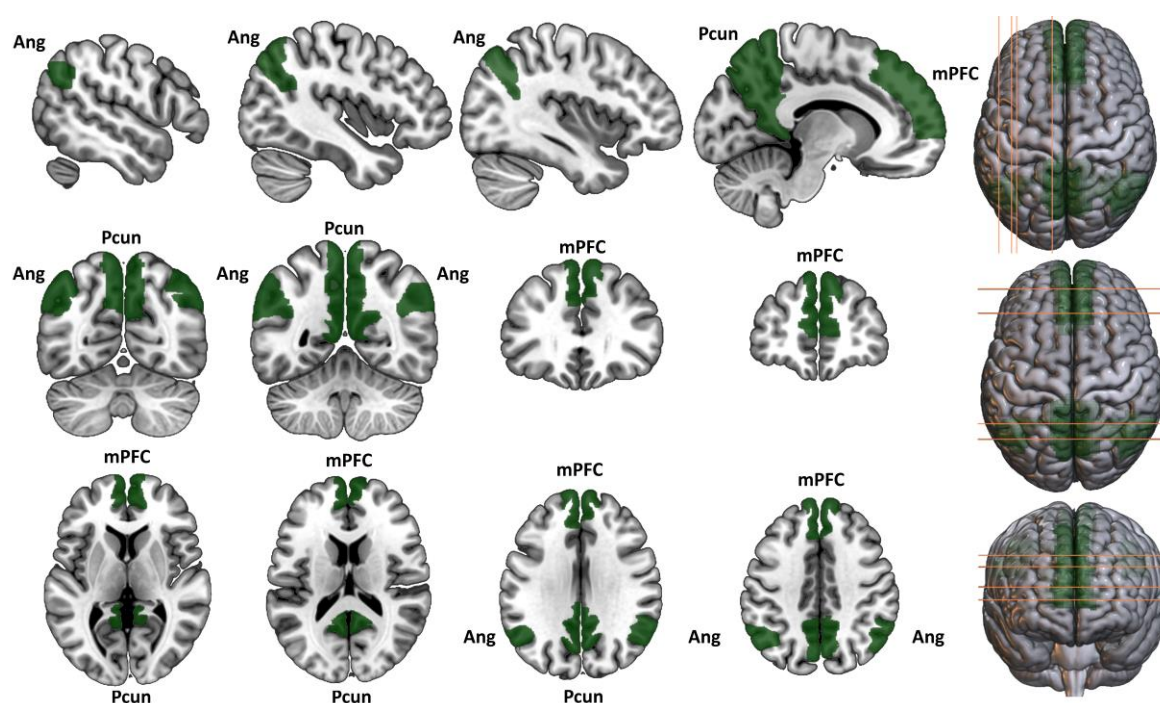
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Reference(s)	Study	Details
European Agency for Fundamental Rights, 2014 <sup>37</sup>	FRA EU-wide survey on violence against women	<p>This is the first European Union (EU)-wide survey to collect comparable data on women’s experiences of gender-based 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>

## 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.

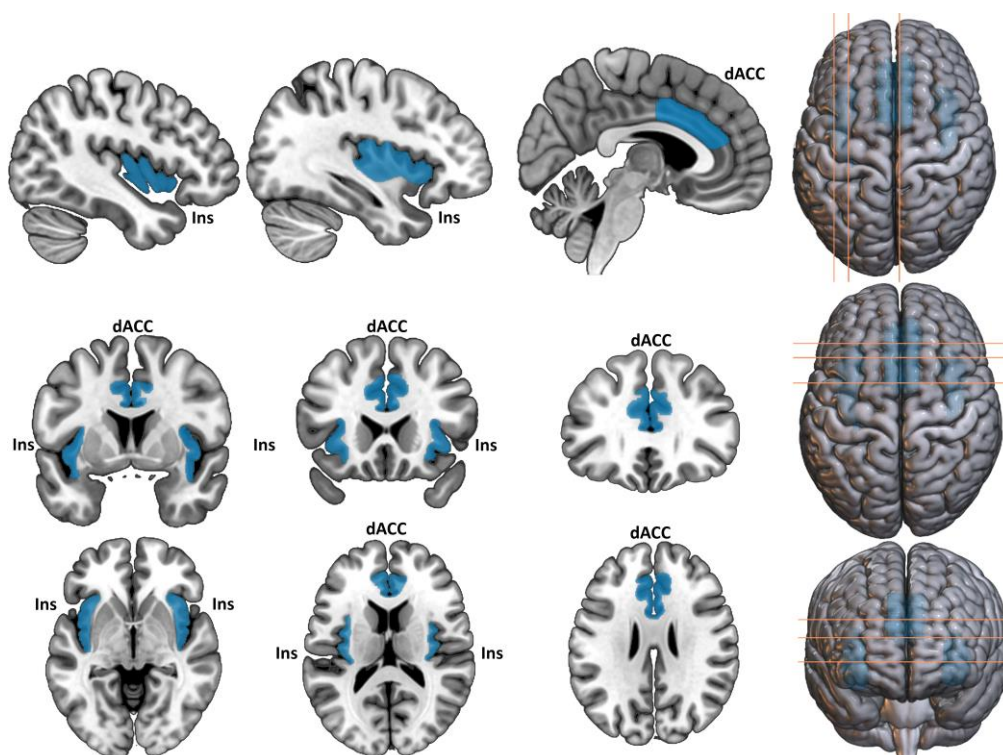


Findings in IPV (See Figure 1 in main document): Consistent with previous research indicating an influence of the insula over the DMN functioning<sup>38,39</sup>, alterations in the DMN are also observed in IPV, suggesting IPV survivors might have difficulties switching away from the DMN. These results 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.

## 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 <sup>40</sup>.

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