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Carrie Esopenko

Jessica Meyer

Elisabeth A. Wilde

Amy D. Marshall

David F. Tate

*See next page for additional authors*

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## Authors

Carrie Esopenko, Jessica Meyer, Elisabeth A. Wilde, Amy D. Marshall, David F. Tate, Alexander P. Lin, Inga K. Koerte, Kimberly B. Werner, Emily L. Dennis, Ashley L. Ware, Nicola L. de Souza, Deleene S. Menefee, Kristen Dams-O'Connor, Dan J. Stein, Erin D. Bigler, Martha E. Shenton, Kathy S. Chiou, Judy L. Postmus, Kathleen Monahan, Brenda Eagan-Johnson, Paul van Donkelaar, Tricia L. Merkley, Carmen Velez, Cooper B. Hodges, Hannah M. Lindsey, Paula Johnson, Andrei Irimia, Matthew Spruiell, Esther R. Bennett, Ashley Bridwell, Glynnis Zieman, and Frank G. Hillary

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Published in final edited form as:

*Brain Imaging Behav.* 2021 April ; 15(2): 475–503. doi:10.1007/s11682-020-00417-0.

## A global collaboration to study intimate partner violence-related head trauma: The ENIGMA consortium IPV working group

Carrie Esopenko<sup>1,2</sup>, Jessica Meyer<sup>3</sup>, Elisabeth A. Wilde<sup>4,5</sup>, Amy D. Marshall<sup>6</sup>, David F. Tate<sup>4,5</sup>, Alexander P. Lin<sup>7</sup>, Inga K. Koerte<sup>8,9</sup>, Kimberly B. Werner<sup>10</sup>, Emily L. Dennis<sup>4,5</sup>, Ashley L. Ware<sup>4,11</sup>, Nicola L. de Souza<sup>12</sup>, Deleene S. Menefee<sup>13</sup>, Kristen Dams-O'Connor<sup>14,15</sup>, Dan J. Stein<sup>16</sup>, Erin D. Bigler<sup>4,17</sup>, Martha E. Shenton<sup>10,18,19</sup>, Kathy S. Chiou<sup>20</sup>, Judy L. Postmus<sup>21</sup>, Kathleen Monahan<sup>22</sup>, Brenda Eagan-Johnson<sup>23</sup>, Paul van Donkelaar<sup>24</sup>, Tricia L. Merkley<sup>4,17,25</sup>, Carmen Velez<sup>4</sup>, Cooper B. Hodges<sup>4,5,17</sup>, Hannah M. Lindsey<sup>4,5,17</sup>, Paula Johnson<sup>4,5,26</sup>, Andrei Irimia<sup>27,28</sup>, Matthew Spruiell<sup>25</sup>, Esther R. Bennett<sup>29</sup>, Ashley Bridwell<sup>30</sup>, Glynnis Ziemann<sup>30</sup>, Frank G. Hillary<sup>6,31</sup>

<sup>1</sup>Department of Rehabilitation & Movement Sciences, School of Health Professions, Rutgers Biomedical and Health Sciences, Newark, NJ 07107, USA

<sup>2</sup>Department of Health Informatics, School of Health Professions, Rutgers Biomedical and Health Sciences, Newark, NJ 07107, USA

<sup>3</sup>Department of Psychiatry, Summa Health System, Akron, OH 44304, USA

<sup>4</sup>Traumatic Brain Injury and Concussion Center, Department of Neurology, University of Utah School of Medicine, Salt Lake City, UT 84132, USA

<sup>5</sup>George E. Wahlen Veterans Affairs Medical Center, Salt Lake City, UT 84148, USA

<sup>6</sup>Department of Psychology, Pennsylvania State University, University Park, PA 16802, USA

<sup>7</sup>Department of Clinical Spectroscopy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

<sup>8</sup>Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, Ludwig-Maximilians-Universität, 80336 Munich, Germany

<sup>9</sup>Psychiatry Neuroimaging Laboratory, Brigham & Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

<sup>10</sup>College of Nursing, University of Missouri, St. Louis, MO 63121, USA

<sup>11</sup>Department of Psychology, University of Calgary, Calgary, AB T2N 1N4, Canada

<sup>12</sup>School of Graduate Studies, Biomedical Sciences, Rutgers, The State University of New Jersey, Newark, NJ 07103, USA

<sup>13</sup>Michael E. DeBakey VA Medical Center, Houston, TX 77030, USA

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Carrie Esopenko, carrie.esopenko@rutgers.edu.

**Conflict of interest** AL co-founded the company BrainSpec and serves as a consultant to Moncton MRI. DJS has received research grants and/or honoraria from Lundbeck and Sun. IKK has received research funds and/or honoraria from Abbott and Expecisor. EDB receives royalties from Oxford University Press and provides forensic consultation. BEJ provides forensic consultation. DFT provides forensic consultation.

<sup>14</sup>Department of Rehabilitation Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

<sup>15</sup>Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

<sup>16</sup>Department of Psychiatry and Neuroscience Institute, South African Medical Research Council Unit on Risk & Resilience in Mental Disorders, University of Cape Town, Cape Town 7501, South Africa

<sup>17</sup>Department of Psychology, Brigham Young University, Provo, UT 84602, USA

<sup>18</sup>Departments of Psychiatry and Radiology, Brigham & Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

<sup>19</sup>Veterans Affairs, Boston Healthcare System, Boston, MA 02130, USA

<sup>20</sup>Department of Psychology, University of Nebraska-Lincoln, Lincoln, NE 68588, USA

<sup>21</sup>School of Social Work, University of Maryland, Baltimore, USA

<sup>22</sup>School of Social Welfare, Stony Brook University, Stony Brook, NY 11794-8231, USA

<sup>23</sup>Traumatic Brain Injury Educational Consulting, New Castle, PA 16101, USA

<sup>24</sup>School of Health and Exercise Sciences, University of British Columbia, Kelowna, BC V1V 1V7, Canada

<sup>25</sup>Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, TX 77030, USA

<sup>26</sup>Neuroscience Center, Brigham Young University, Provo, UT 84602, USA

<sup>27</sup>Ethel Percy Andrus Gerontology Center, Leonard Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA

<sup>28</sup>Denney Research Center Department of Biomedical Engineering, University of Southern California, Los Angeles, CA 90089, USA

<sup>29</sup>Rutgers University School of Social Work, New Brunswick, NJ 08901, USA

<sup>30</sup>Barrow Concussion and Brain Injury Center, Barrow Neurological Institute, Phoenix, AZ, USA

<sup>31</sup>Social Life and Engineering Sciences Imaging Center, University Park, PA 16802, USA

## Abstract

Intimate partner violence includes psychological aggression, physical violence, sexual violence, and stalking from a current or former intimate partner. Past research suggests that exposure to intimate partner violence can impact cognitive and psychological functioning, as well as neurological outcomes. These seem to be compounded in those who suffer a brain injury as a result of trauma to the head, neck or body due to physical and/or sexual violence. However, our understanding of the neurobehavioral and neurobiological effects of head trauma in this population is limited due to factors including difficulty in accessing/recruiting participants, heterogeneity of samples, and premorbid and comorbid factors that impact outcomes. Thus, the goal of the *Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium*

*Intimate Partner Violence Working Group* is to develop a global collaboration that includes researchers, clinicians, and other key community stakeholders. Participation in the working group can include collecting harmonized data, providing data for meta- and mega-analysis across sites, or stakeholder insight on key clinical research questions, promoting safety, participant recruitment and referral to support services. Further, to facilitate the mega-analysis of data across sites within the working group, we provide suggestions for behavioral surveys, cognitive tests, neuroimaging parameters, and genetics that could be used by investigators in the early stages of study design. We anticipate that the harmonization of measures across sites within the working group prior to data collection could increase the statistical power in characterizing how intimate partner violence-related head trauma impacts long-term physical, cognitive, and psychological health.

## Keywords

Brain injury; Neuroimaging; Neuropsychological function; Psychosocial function; Intimate partner violence

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## Introduction

According to the Centers for Disease Control (CDC) National Center for Injury Prevention and Control, intimate partner violence (IPV) includes physical violence, sexual violence, psychological aggression, and stalking by a current or former intimate partner (Breiding et al. 2014), and it affects millions of people in the United States each year (Black et al. 2011). A more broadly defined concept of IPV is offered by organizations like The National Coalition Against Domestic Violence, indicating domestic violence is not physical violence alone, but rather any behavior where the purpose is to gain power and control over a spouse, partner, or intimate family member (National Coalition Against Domestic Violence 2015). This can include physical abuse, sexual abuse, emotional abuse and intimidation, isolation, financial abuse and verbal abuse (e.g., coercion, threats and blame). Global estimates suggest that approximately 30% of women over 15 years of age will have experienced physical or sexual IPV over their lifetimes (Devries et al. 2013). Similarly, a recent report from the CDC estimates that 32.9% of women and 28.1% of men report physical aggression from an intimate partner in their lifetimes. Moreover, roughly 24% of women and 14% of men report experiencing severe physical aggression (Breiding et al. 2014). IPV prevalence is typically highest in the 18–24 year old age group (Breiding et al. 2014), although older women also experience IPV, with aging victims facing unique barriers to obtaining help (Pathak et al. 2019).

Although both men and women experience IPV, violence against women tends to result in more severe and chronic injuries relative to violence against men (Brush 1990; Dobash and Dobash 2004; Tjaden and Thoennes 2000), with the majority of research to date focused on outcomes in women who have experienced IPV. This may be particularly true with regard to the prevalence and severity of IPV-related traumatic brain injury (TBI) and strangulation or intentional impeded breathing leading to hypoxic/anoxic brain injury. Regardless, IPV most commonly results in injuries to the head, neck, and face (George et al. 2019; Ochs et al. 1996; Sheridan and Nash 2007; Wu et al. 2010), putting individuals exposed to IPV at a high

risk for brain injury. Based on current estimates from the CDC of the number of women who experience IPV in their lifetimes, coupled with past reports suggesting that 60–92% of women with a history of IPV experience IPV-related head and facial injuries, St Ivany and Schminkey (2016) approximate that 23 million women are living with IPV-related head trauma in the United States. Thus, IPV-related TBI is a significant public health concern. Further, studies suggest that between 50% and 75% of women who experience physical trauma report multiple hits to the head or occasions of violence/abuse resulting in repetitive exposure to head trauma (Valera and Berenbaum 2003; Valera and Kucyi 2017), and some individuals report they have suffered too many hits to the head to provide an accurate account of frequency (Valera 2018).

The Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium is a framework for global collaborative meta- and mega-analysis and has led to some of the largest neuroimaging studies to date, with working groups dedicated to various psychiatric, neurological, and developmental disorders (Hibar et al. 2018; Hoogman et al. 2017; Schmaal et al. 2017). The ENIGMA Brain Injury group was recently created with subgroups based on population type and injury mechanism (Dennis et al. 2020). TBI in the general population is an extremely heterogeneous injury, making it difficult to diagnose, manage, and treat (Millis et al. 2001; Saatman et al. 2008). This is compounded in those exposed to IPV, as TBI may co-occur with both a range of physical traumas and mental disorders, increasing the complexity of these injuries. The mission of the ENIGMA Brain Injury IPV working group is to develop a global collaboration to examine the effects of IPV-related head trauma on neuronal, cognitive, psychosocial, and mental health outcomes in men and women through the mega- and meta-analysis of data collected across studies. We are a newly-developed group who is actively recruiting new members across IPV and TBI disciplines, and we have outlined potential opportunities of collaboration within the working group.

The aim of our paper is to review the current literature on IPV-related head trauma, including its effects on neurocognitive outcomes, mental health and psychological functioning, and neural processes. Based on previous literature, we identified specific domains the ENIGMA IPV Working Group seeks to assess when examining the impact of IPV-related head trauma: neuroimaging, neurocognitive, psychosocial, mental health, TBI history, IPV-specific measures, and genetics. Suggested measures to assess each domain are based on common data elements (CDEs) that have been identified in the TBI and PTSD literature. Use of CDEs has the potential to facilitate a collaborative approach across studies, but we realize that CDEs have not been developed specifically for the IPV field and suggested measures are likely to evolve with the group's work in this area. We also realize that the measures used in studies are heavily dependent on investigator expertise, study funding, and time constraints of participants, and that not all investigators will be able to complete all measures described below. However, by providing a number of suggestions for each assessment domain (e.g., cognitive and psychological functioning), investigators can choose the measures they can access or have the expertise to administer. In using at least some of these measures, investigators will still be able to contribute data for large-scale mega-analysis across working group study sites.

Furthermore, through the development of a multidisciplinary collaboration that includes researchers, clinicians (e.g., psychologists, social workers, physicians, nurses), first responders, and community stakeholders (e.g., domestic violence organizations, shelters, support groups, and policy makers), we aim to optimize the feasibility of data collection and ecological validity of studies within the working group, including strategies to facilitate participation of those exposed to IPV and the knowledge translation of study outcomes to first responders, healthcare providers, community stakeholders, and survivors of IPV and their families. We also invite investigators who have already been examining IPV-related TBI to contribute data to the working group to facilitate meta-analysis of data across studies and samples, as well as inform the growth of the working group by helping to identify and prioritize opportunities for research on IPV-related TBI. Lastly, we provide suggestions for behavioral surveys, cognitive and psychological measures, and neuroimaging parameters that can be collected by sites within the working group to promote data sharing, cross-study comparisons, and mega-analysis of data across studies.

Individuals exposed to IPV face a number of unique and complex problems that merit their own research focus, such as unique injury dynamics, multi-determined symptom profiles, and special considerations for safety and privacy in this population. However, the potential harmonization of measures and study procedures across sites will increase the power of analyses to address these complex questions safely. For example, from a mechanism of injury perspective, how the brain may be injured in IPV likely differs from other causes. Common causes of head injury, including falls and motor vehicle accidents, lead to blunt force, impact trauma to the head. In IPV, however, injuries can also be caused due to violent shaking and slapping or forceful falls (i.e., thrown down or pushed). Each different mechanism of injury involves unique biomechanical movement vectors and brain deformation, creating highly individualized patterns of pathology in each victim (Bayly et al. 2012; Ommaya et al. 2002). Gunshot wounds, stabbings and strangulation/impeded breathing likewise have their own etiological mechanisms resulting in acquired brain injuries and potential TBI. Therefore, just as each instance of IPV has its own unique circumstances (Sugg 2015), brain injuries from IPV vary greatly. Furthermore, given individual differences associated with personal and medical histories, age at injury, social, cultural, developmental and life span issues along with genetics, each of these factors have the potential to influence the effects of IPV on neurocognitive and neurobehavioral functioning. Taken together, these factors make the study of IPV daunting and complex. In addition, a recent report from the Government Accountability Office found that data on IPV-related TBI prevalence and outcomes is limited and the importance of more research on the topic is needed to inform public health (U.S. Government Accountability Office 2020). As such, using “big data” techniques through multidisciplinary collaboration may provide a useful approach to comprehensively address the complex questions associated with IPV (Fillinger et al. 2019), which is embodied by the ENIGMA Collaboration initiative (Thompson et al. 2014; Thompson et al. 2020).

In the following sections, to justify the suggested measures for each assessment domain, we describe the latest research for each domain as well as how future studies using the large-scale meta-analytic techniques of the ENIGMA Consortium can contribute to this growing body of literature.

## TBI HISTORY: Head trauma in individuals who have experienced IPV

Due to the high degree of physical aggression associated with IPV, individuals are at a significant risk for TBI (Corrigan et al. 2003; Valera 2018; Valera and Berenbaum 2003). IPV-related TBIs can be caused by blunt force trauma, being violently shaken or pushed (Sheridan and Nash 2007; Valera and Berenbaum 2003). Additional brain injury is often inflicted via strangulation or an attempt to impede normal breathing by different mechanisms. The prevalence of head injuries in female victims of IPV is estimated to be between 30% and 92%, with a high proportion of these women reporting injuries as a result of strangulation (Campbell et al. 2017; Roberts and Kim 2008; St Ivany and Schminkey 2016; Valera and Berenbaum 2003). Adverse outcome from TBI is enhanced in the presence of hypoxic/anoxic injury (Bramlett et al. 1999; Davies et al. 2018), so some with IPV have multiple sources of potential brain injury. Trauma to the head producing TBI followed by strangulation or other forms of oxygen restriction (e.g., near drowning, smothering) may significantly increase the morbidity of IPV. Neck injury can result in stroke (Long et al. 2019) or vascular dissection, as can strangulation (De Boos 2019), particularly in older victims with cerebrovascular risk factors. Bodily injuries that result in internal hemorrhaging have the potential to result in secondary brain injury (Fox et al. 2017). Also, long-bone fractures can result in what is referred to as “fat embolism syndrome” that may also result in stroke, but more often affect the pulmonary system (DeFroda and Klinge 2016). This could contribute to cerebral hypoxia when abuse results in bone fractures.

A Valera and Berenbaum 2003 study found that 68% of those who have experienced IPV reported sustaining at least one mild TBI, and 10% reported sustaining at least one moderate or severe TBI (Valera and Berenbaum 2003). Recent reports from the CDC demonstrate that approximately 14% of individuals who experience IPV have at least one instance of loss of consciousness from sustaining impacts to their head and/or strangulation (Breiding et al. 2014). Past work also suggests that a significant proportion of victims of IPV report strangulation, with estimates ranging from 36% to 68% in victims of physical violence (Campbell et al. 2017; McQuown et al. 2016; Wilbur et al. 2001), and 7% to 22.5% in victims of sexual assault by an intimate partner (McQuown et al. 2016; Zilkens et al. 2016). Of further note, blunt trauma to the head can cause focal lesions and diffuse axonal injury, while being pushed or shaken violently can result in diffuse axonal injury due to acceleration and deceleration forces (Bigler and Maxwell 2011). Brain injury caused by strangulation or manipulation of oxygen sources, however, results in hypoxic/anoxic brain injuries due to decreased oxygen to the brain (Valera and Berenbaum 2003; Valera et al. 2018; Valera and Kucyi 2017). Interestingly, both TBI and anoxic brain injury at the moderate-to-severe levels of injury share some common neurocognitive impairments, especially in the domains of memory, executive functioning and speed of processing based on neuropsychological testing (Hopkins et al. 2005). Partly due to premorbid cerebrovascular disease, and similar to older adults with TBI, older IPV victims who sustain head trauma may also be at higher risk for breakdown of the blood-brain barrier, resulting in cerebral microbleeds, arteriolosclerosis and cerebral amyloid angiopathy, all of which increase the risk for mild cognitive impairment and dementia—including Alzheimer’s disease (Irimia et al. 2018).



In addition, those who experience IPV are also at increased risk for repetitive brain trauma. It is estimated that approximately 50–70% of women exposed to IPV suffer multiple brain injuries due to abuse-related head trauma (Valera 2018; Valera and Berenbaum 2003). Another study of individuals experiencing IPV reported on average > 200 assaults with blows to the head per individual (Deering et al. 2001). However, this number only captures the incidents with at least one blow to the head and does not reflect the frequency of hits during a single assault, which is likely higher (Deering et al. 2001). Thus, future research needs to account for the high likelihood of exposure to repetitive head trauma in this population. Additionally, research in this population must also consider lifetime prevalence of head trauma, given the high prevalence of childhood abuse in individuals who have experienced IPV (Whitfield et al. 2003; Widom et al. 2014) and the fact that milder forms of head trauma, including subconcussive injuries and mild TBI, often go unreported, medically evaluated or treated (Zieman et al. 2017).

Since IPV survivors may not seek medical care until the violence has reached some critical level, diagnosis of TBI is an important challenge. Due to the absence of past medical documentation, as well as the repetitive nature of injuries, survivors may not be able to provide full details of their injuries. Thus, it is sometimes impossible to quantify and qualify TBI in this population. Further, doing so also requires special considerations when conducting IPV research (see section on “Considerations for Recruitment, Study Participation, and Attrition”).

Criteria for the classification of TBI severity have evolved over the years. Currently, TBI is classified as mild, complicated mild, moderate and severe, as recommended by a collaborative workshop hosted by the National Institute of Neurological Disorders and Stroke (Saatman et al. 2008). In sports concussion, the standards promulgated by the 5th International Conference on Concussion in Sport may also be particularly useful in IPV (McCrory et al. 2017). However, all of these definitional statements have limitations in addressing retrospective diagnostic issues of whether or not a TBI has occurred in the past. The Department of Defense in association with the Veterans Administration (Defense and Veterans Brain Injury Center 2020; U.S. Department of Veteran Affairs & U.S. Department of Defense, 2016) have provided guidelines on retrospective methods for assessing patient histories compatible with having sustained a TBI. These guidelines may be particularly useful in IPV studies where prior injuries were never medically documented. In this special issue of ENIGMA Brain Injury, other TBI/concussion populations are specifically addressed (Wilde et al. 2019).

## **NEUROCOGNITIVE OUTCOMES: Cognitive impairment in IPV, IPV-related head trauma, and hypoxic/anoxic brain injuries**

Cognitive dysfunction including impaired reaction time, response inhibition, working memory, attention, visuoconstruction, visual memory, as well as executive dysfunction have been reported in individuals exposed to IPV (Stein et al. 2002; Twamley et al. 2009). The etiology of this cognitive impairment is likely multifactorial, and may reflect the effects of mood disorders, chronic stress responses, and prolonged self-protective hypervigilance, as

well as the cumulative effects of repetitive exposure to brain trauma. Studies evaluating self-report of cognitive functioning have found increased endorsement of memory problems and attention problems in victims of IPV with an additional history of head trauma (Campbell et al. 2017; Jackson et al. 2002; Monahan and O’Leary, 1999; Smirl et al. 2019). In a study of the effects of brain injury on cognitive functioning in individuals who experienced IPV, significant correlations between brain injury and aspects of verbal learning and memory were observed even when controlling for abuse severity, anxious arousal, and post-traumatic stress disorder (PTSD) symptom severity (Valera and Berenbaum 2003).

Research on hypoxic/anoxic brain injury associated with strangulation in IPV is growing, and evidence from past work in cardiac arrest, non-fatal drowning, and sleep apnea indicate that anoxic/hypoxic injuries are associated with impaired memory, processing speed, attention, as well as executive dysfunction (Anderson and Arciniegas 2010; Bichard et al. 2020; Caine and Watson 2000; Monahan et al. 2019; Peskine et al. 2010; Wright et al. 2017). In addition, studies of self-reported symptoms after strangulation show a high frequency of neurological symptoms such as dizziness, loss of consciousness, loss of sensation, and memory problems (Smith et al. 2001; Wilbur et al. 2001), with some evidence that the frequency of symptoms increases with the instances of strangulation (Smith et al. 2001). Thus, strangulation in this population may result in anoxic or hypoxic brain injury, and associated symptoms, and is an area of work requiring attention in IPV.

## **MENTAL HEALTH and PSYCHOSOCIAL FACTORS: Mental health outcomes associated with IPV and IPV-related head trauma**

Individuals who experience IPV often report a high degree of mental health disorders, such as depression, anxiety, substance use disorders, suicidal ideation, and PTSD (Afifi et al. 2009; Brignone et al. 2018; Carbone-López et al. 2006; Fletcher 2010; Iovine-Wong et al. 2019; Jones et al. 2001; Monahan 2019; Okuda et al. 2011; Zlotnick et al. 2006). Furthermore, the traumatic nature of IPV, coupled with the interpersonal betrayal of experiencing IPV, confers a high risk for PTSD specifically (Temple et al. 2007). According to the WHO World Mental Health Surveys (Kessler et al. 2017), the highest conditional risk for PTSD is associated with IPV (specifically, sexual violence), compared to exposure to other types of traumas (e.g., war-related trauma, accident, unexpected death of a loved one). Past research has also demonstrated a 2.3- to 3.74-fold increased risk of PTSD in individuals exposed to IPV (Fedovskiy et al. 2008; Golding 1999; O’Campo et al. 2006), and that increased severity of IPV is associated with increased PTSD symptom severity (Chandra et al. 2009). Those who experience IPV who also have comorbid PTSD demonstrate impairments in neuropsychological function including attention, memory, and executive functioning (Twamley et al. 2009). Furthermore, the observed neuropsychological deficits in PTSD overlap with those observed in individuals who sustained a mild TBI. Of note, PTSD and mild TBI are highly comorbid in military populations (Bryant 2008; Dolan et al. 2012; Hoge et al. 2008; Iovine-Wong et al. 2019; Iverson et al. 2017; Kaplan et al. 2010) and research suggests a potential for greater severity of cognitive symptoms in co-occurring PTSD and mild TBI (Campbell et al. 2009b; Nelson et al. 2009). Heightened symptoms of PTSD have also been shown in women with a history of IPV and TBI

(Valera and Berenbaum 2003; Valera and Kucyi 2017). Similar results have been shown in female Veterans where IPV-related TBI has been associated with increased depression and PTSD symptom severity (Iverson et al. 2019; Iverson and Pogoda 2015). Additionally, because TBI and PTSD share many of the same symptoms and have various cognitive deficits in common (Iverson et al. 2017; Monahan 2019), distinguishing between the two can be difficult and undiagnosed TBI may contribute to treatment nonresponse among PTSD patients (Rosen and Ayers 2020). However, it remains unclear if premorbid mental disorder severity, possibly associated with prior trauma or abuse, increases the risk of IPV, or rather, occurs as a result of experiencing IPV. What further complicates this picture is the role of head trauma, and specifically whether exposure to head trauma exacerbates mental health problems (e.g., Kessler et al. 2018). Inclusion of measures to assess the chronology of events (e.g., TBI, IPV, mental health issues) and in some cases age of first exposure (e.g., childhood abuse, IPV, and/or TBI), will help determine if experiencing TBI and IPV individually result in mental illness, or whether mental illness is a risk factor and/or predisposes an individual to ongoing abuse including head trauma. Assessing the impact of comorbid mental disorders, and in particular PTSD, in individuals exposed to IPV is extremely important, as mental illness is associated with higher rates of revictimization (Iverson et al. 2013). Additionally, psychopathology is a significant predictor of poor outcomes from mild TBI and the development of persistent post-concussion symptoms (e.g., Broshek et al. 2015; McCauley et al. 2013; Ponsford et al. 2012; Silverberg and Iverson 2011). Knowing the factors that impact IPV-related psychopathology is important since they can inform treatment domains and increase the effectiveness of interventions, while also potentially limiting continued exposure to, and severity of, IPV.

## **NEUROIMAGING IN IPV: Neural changes in IPV and IPV-related head trauma**

There is evidence, which has emerged over the past decade, that exposure to IPV impacts neuronal structure and function. For example, women who experience IPV show reduced cortical thickness in both frontal and occipital brain regions (Fennema-Notestine et al. 2002), as well as reduced white matter integrity in the body of the corpus callosum compared to women with no history of IPV (Flegar et al. 2011). Furthermore, alterations in global and regional functional connectivity of regions involved in cognitive-emotional control have been shown in women who have experienced IPV (Roos, Fouche, & Stein, 2017). Differences in functional connectivity have additionally been shown in female survivors of IPV who are comorbid for PTSD compared to those without a comorbid history with PTSD (Aupperle et al. 2016; Neumeister et al. 2017; Simmons et al. 2008). Two neuroimaging studies to date have examined neuronal changes associated with exposure to head trauma in individuals with exposure to IPV. More specifically, Valera and colleagues noted that brain injury scores, which accounted for severity, frequency, and recency of head trauma, were negatively correlated with fractional anisotropy (FA) in the posterior and superior corona radiata in a sample of women who experienced IPV (Valera et al. 2018). Furthermore, the same group found that intrinsic functional connectivity from the right anterior insula to posterior cingulate and precuneus, regions within the default mode network, were negatively associated with TBI severity in women who experienced IPV and TBI (Valera and Kucyi 2017). Importantly, these effects were present even when

accounting for the potentially confounding effects of comorbidities such as PTSD, anxiety, depression, and history of child abuse. Since IPV may emerge within the context of major environmental and psychosocial stressors that have the potential to independently influence brain structure and function, the challenge is to understand how traumatic injury influences clinical outcome in an already vulnerable brain.

In the only published study investigating the neuropathological sequelae of IPV in postmortem brain tissue, the pattern and distribution of paired helical filament immunoreactive tangles and burden of diffuse cortical  $\beta$ -amyloid immunoreactive plaques was described as bearing a high resemblance to published cases of “dementia pugilistica” (Roberts et al. 1990). Due to a lack of brain tissue from individuals with well-characterized IPV exposure available for study, the progress in characterizing the pathological sequelae of IPV-related brain injury has been limited. Future post-mortem studies that include well-characterized, lifetime exposure to IPV and IPV-related head trauma, are needed to understand the effects of what is likely repetitive, multiple episodes of head trauma in IPV and its effects on microstructural changes in brain tissue and vasculature.

Likewise, given the limited number of neuroimaging studies in IPV, there are a number of other modalities that could be explored in future studies that could provide greater insight into pathophysiological changes. For example, magnetic resonance spectroscopy (MRS) can provide measures of brain metabolism that has been shown to increase choline levels reflective of membrane turnover in IPV (Seedat et al. 2005). In addition, MRS can be used to explore markers of hypoxia due to strangulation or inflammatory markers that have been shown to underlie repetitive concussive (Lin et al. 2015) and subconcussive injuries (Koerte et al. 2015).

## **GENETICS: Influence of genetic phenotypes in TBI risk and recovery**

There is evidence to suggest that genotype may be an important factor in the response to and recovery from TBI, and various genetically mediated responses are triggered during both the acute and chronic post-injury time periods (Bennett et al. 2016; McAllister 2010, 2015). Broadly, individual differences in genotype can influence outcome after brain injury by mitigating or exacerbating the extent of the injury sustained or by governing the neuroplasticity and repair processes that follow (Jordan 2007; Lipsky and Lin 2015; McAllister 2015). Furthermore, genes may hold important influence over preinjury traits, such as personality, cognitive capacity and reserve, and risk of injury, and genetic predispositions to neurobehavioral disorders may interact with the long-term effects of neurotrauma. There are a large number of potential mechanisms that may contribute to the influence genotype has on functional outcome in each of these contexts (for a review, see McAllister 2019); however, at this early stage in the research, sufficient proof of concept has only been provided for a few genotypes.

Evidence has suggested that *apolipoprotein e* (APOE) allele type (i.e.,  $\epsilon 2$ ,  $\epsilon 3$ ,  $\epsilon 4$ ) affects outcome, although the mechanism by which this occurs is not yet known. There is a growing literature demonstrating an association between the  $\epsilon 4$  allele and poor short- and long-term outcome following TBI (Alexander et al. 2007; Chiang et al. 2003; Isoniemi et al. 2006; Li

et al. 2015; Ponsford et al. 2011; Zeng et al. 2014; Zhou et al. 2008), and one study found a similar association between the T allele at the G-219 T site in the promoter region and poor outcome (Lendon et al. 2003). Additionally, poor outcome may be related to polymorphisms in brain-derived neurotrophic factor (BDNF; McAllister et al. 2008; McAllister et al. 2012) and potentially in pro-inflammatory cytokines, specifically interleukin-1 $\beta$  (IL-1 $\beta$ ; Uzan et al. 2005) and interleukin-6 (IL-6; Dalla Libera et al. 2011; Winter et al. 2004). Lastly, single-nucleotide polymorphisms (SNPs) in the *ankyrin repeat and kinase domain containing 1* (ANKK1) at the dopamine D2 receptor region may be associated with poor cognitive outcome 6-months post-injury (McAllister et al. 2008; Myrga et al. 2016; Nielson et al. 2017; Treble-Barna et al. 2017; Yue et al. 2015), and there may be a relation between the G/A SNP of *catechol o-methyltransferase* (COMT) and impaired frontal-executive cognitive functions following TBI (Lipsky et al. 2005; Myrga et al. 2016). For a thorough review of the influence of specific genetic polymorphisms in neurotrauma outcomes and candidate genes to be assessed, see (McAllister 2010, 2015, 2019).

## Summary

Millions of individuals worldwide experience IPV each year. Recent research suggests that between 30% and 90% of women exposed to IPV experience head trauma, with 50–75% reporting repetitive head trauma. Recent work demonstrates that individuals who experienced IPV show cognitive impairment and report symptoms of PTSD and other forms of psychopathology, which seem to be compounded in those victims who experience TBI. Moreover, there is evidence that IPV-related TBI alters brain function and structure. Furthermore, the majority of work has focused on women exposed to IPV, likely given women's higher exposure to severe physical trauma. There remain important challenges to understanding the interaction between IPV-related TBI and cognitive and psychosocial functioning, mental health, and neural outcomes. Of paramount importance is the identification and characterization of TBI in this population, which is commonly post-hoc, and due to the nature of the underlying cause of the injury, is often without corroborative witnesses as to the duration and severity of immediate behavioral consequences. Finally, the study of IPV-related TBI as a function of age at injury should be examined, such as in the case of older victims, who are very vulnerable—both psychiatrically and neurologically—to its sequelae (Calvillo and Irimia 2020).

By forming a global collaboration across disciplines, we will be able to combine large scale datasets to answer these difficult questions and facilitate further translation of research outcomes to clinical care and community-based supports. To this end, in the following section we outline several decisions we have made as a working group to isolate the effects of IPV-related TBI for the domains of functioning described above. For groups that have already begun data collection, we hope to identify common measures that have been collected for sites within the working group to allow for meta-analysis within and across domains of interest. For investigators that have not begun data collection, or are in the process of study design, what we outline in the following might serve as a common framework to facilitate collaboration and, ideally, mega-analysis of data across working group sites. This harmonization of measures prior to data collection, may substantially increase the statistical power of studies within the working group to assess specific IPV-

related TBI mechanisms and their association with cognitive and psychosocial functioning, mental health, and neural outcomes from multiple datasets across studies. Further, mega- and meta-analytic analyses may offer unique opportunities to address challenging questions regarding the effect of sex, socioeconomic status, race or ethnicity, age at exposure, duration and severity of exposure, and comorbid psychiatric disorders on neuronal and functional outcomes.

### **Measuring the psychological and cognitive consequences of IPV-related head trauma: Establishing domains of study for the ENIGMA IPV working group**

In the following sections we outline the early suggestions from our working group in order to facilitate common data collection, collaboration and maximize potential for ideal data harmonization. We should make clear that what is outlined in the following is not meant to be prescriptive for investigators of IPV-related neurotrauma. Our goal is to present decisions from the working group to foster a research collaboration within the group and as a guide to investigators who have interest in participating in the ENIGMA IPV Working group. Working group decisions were based upon published CDEs for the study of TBI and PTSD, published studies on IPV, TBI, and mental health, as well as expertise from clinical neuropsychologists, social workers, and community stakeholders. The measures target the following domains: 1) collection of IPV and TBI specific demographic information, 2) TBI and physical injury variables, 3) neuroimaging measures, 4) neurocognitive and neurobehavioral measures, and 5) genetics. We also provide decisions from our working group regarding inclusion and exclusion criteria of participants, which may serve as guidelines for investigators seeking to contribute to the ENIGMA IPV Working Group through meta-/mega-analyses. Finally, we include information for issues pertaining to participant safety during the recruitment process and study participation that should be considered. We also discuss the importance of including social determinants of health, adequate comparison participants, and engagement of, and knowledge translation to, community stakeholders. Our goal for this framework is to provide methods for standardization of data collected across studies in the working group resulting in increased power and sensitivity in identifying brain and behavioral phenotypes specific to IPV-related head trauma. The battery of measures described below was developed to assess the majority of domains found in past research and clinical expertise within our working group has determined are impacted by IPV. Given the difficulty with obtaining research funding and accounting for potential participant fatigue, we do not anticipate that any individual study will maintain comprehensive coverage of all tests; instead, we offer the domains of functioning being assessed that emerged as vital to the ongoing studies for the working group and consistency across current (or future) sites will facilitate data harmonization and analysis. We recognize that there is redundancy in some domains, thus investigators should select the measure(s) that best fit their research question and psychometric expertise.

#### **Demographic measures**

For collection of demographic information, we suggest the use of a version of demographics included in the National Institute of Neurological Disorders and Stroke (NINDS) TBI common data elements (CDEs; <https://www.commondataelements.ninds.nih.gov/>), modified to meet the needs of the particular study undertaken. Demographic data included in the

CDEs currently consist of: age, race/ethnicity, biological sex, gender identity, education, socioeconomic status, military service, primary language, and handedness. Additional IPV-specific demographic information to the CDEs are recommended, which include information relevant to: 1) whether the individual is still living in an abusive relationship, 2) previous abusive relationships, 3) when physical abuse first occurred and duration of occurrence(s), and 4) frequency and severity of physical abuse (e.g., number of abusive episodes, if had to seek treatment). This can further be accomplished via interview and supplemented with use of a number of standardized IPV measures: Revised Conflict Tactics Scale (Straus et al. 1996), the Abusive Behavior Inventory-Revised (Postmus et al. 2016), Women's Experience with Battering (Smith et al. 1995; otherwise known as the Relationship Assessment Tool), and Composite Abuse Scale (Hegarty et al. 1999) (see Table 1). We also suggest that investigators determine if Lethality Assessment Program or Danger Assessment outcomes were collected from first responders, healthcare providers, or women's shelter staff, respectively, as this would provide an additional measure of severity of IPV and risk of future IPV in study participants (Campbell 1986; Campbell et al. 2009b; Messing et al. 2015)(see Table 1). Head trauma related to childhood abuse could be assessed through the Adverse Childhood Experiences (ACE) questionnaire, Traumatic Life Events Questionnaire (TLEQ), and Childhood Trauma Questionnaire or other clinical interviews, in order to better identify onset and duration of abuse. It is also important to obtain relevant information to past health history including history of learning disability, attention deficit/hyperactivity disorder (ADHD), medication use, nonprescription drug use and current or past history of diagnosed mental illness, as well as account for this information in analytical models as either a covariate or effect of interest. Finally, a detailed history of all physical injuries sustained through IPV and non-IPV related injuries, including time of injury, injury type and mechanism, injury severity (hospitalization and treatments), and impact on functioning and quality of life should also be collected. Any information from hospitals including imaging findings should also be obtained.

### History and classification of injuries

As introduced and discussed above, given the nature of abuse (i.e., physical trauma with and without head trauma, strangulation, and sexual violence) in IPV, it is difficult to identify specific injuries and to quantify the severity of each specific injury in this population. Furthermore, there is limited consistency in measures used in past research to determine retrospective head trauma history, resulting in limited standardization of TBI diagnosis across studies (Haag, Jones, Joseph, & Colantonio, 2019), even with the TBI diagnostic guidelines given above. Assessment of TBI history is also challenging because it typically relies on self-reported recall of events, despite the potential that head trauma adversely impacts memory functioning both acutely and chronically. Several studies have identified the need for a specific tool to screen IPV-related TBI (Goldin et al. 2016; Haag et al. 2019; St Ivany et al. 2018b). In a 2016 review, two measures were deemed appropriate for use with individuals who have experienced IPV (Goldin et al. 2016). While Goldin and colleagues identified the Ohio State University TBI Identification Method (OSU TBI-ID) and the Brain Injury Screening Questionnaire (BISQ) as both meeting criteria for safe endorsement for the IPV event and ease of administration, enhanced screening of IPV is recommended by adding items related to blows to the face and near strangulation. The OSU TBI-ID is a standardized

procedure for eliciting a person's lifetime history of TBI via a structured interview (Corrigan and Bogner 2007) and has been effective in determining IPV-related TBI history/problems (Goldin et al. 2016). The OSU TBI-ID Interview allows for the determination of head trauma severity and frequency across a number of mechanisms, but also includes questions of specific interest to survivors of IPV, such as being hit and shaken violently, as well as quantifying exposure to repetitive head trauma. Given that the goal of the interview is to ascertain lifetime TBI exposure, other than loss of consciousness or post-traumatic amnesia (being dazed or experiencing a gap in memory), the interview does not probe for specific symptoms post-injury. Thus, we suggest also including an additional post-TBI symptom scale, such as the Rivermead Post-Concussion Symptom Questionnaire (King et al. 1995), to determine symptom complaints and severity when using the OSU TBI-ID. The BISQ, a structured self-report screening questionnaire to assess lifetime history of TBI (Dams-O'Connor et al. 2014), may also be used for ascertainment of IPV-related head trauma. The BISQ provides contextual recall cues to facilitate recall of remote head trauma, thereby characterizing the mechanism of TBI and, for each reported injury, the severity of the TBI. An optional module of the BISQ includes 7 additional contextual cues specific to IPV (e.g., hit in the head with an object, hand or fist, strangled or choked) as recommended by prior studies (Goldin et al. 2016; Iverson et al. 2017). The IPV module of the BISQ was extensively vetted by panels of stakeholders to ensure broad content coverage with inclusive and sensitive language; the instrument is available from the authors (visit [www.tbicentral.org](http://www.tbicentral.org) to request the BISQ). Both measures will also allow for the collection of TBI(s) not due to IPV (e.g., motor vehicle accidents, sports, and falls) which also need to be accounted for when determining the chronic effects of head trauma in this population. Additionally, the Brain Injury Severity Assessment (BISA) has been used in a number of studies to assess IPV-related TBI (Smirl et al. 2019; Valera and Berenbaum 2003; Valera et al. 2018; Valera and Kucyi 2017). The BISA is a semi-structured interview to determine a brain injury severity score based on how recent an injury is, the number of brain injuries reported, and if a moderate-to-severe brain injury has occurred (Valera and Berenbaum 2003). Recent work has compared TBI symptoms on the BISA with the SCAT5 and found that the total number of TBIs identified was higher when using the BISA as a screening measure compared to the SCAT5, but that the total number of injuries on the SCAT5 was correlated with the BISA severity score (Smirl et al. 2019). A detailed list of potential measures that can be used to assess IPV-related TBI are included in Table 2.

In addition, a current gap in this area of research is a lack of standard methodology for how to characterize exposure to repetitive IPV-related head trauma that does not lead to clinical concussion in this population (Bailes et al. 2013). In the context of contact sports, for example, longer duration and earlier exposure was significantly associated with increased odds of developing chronic traumatic encephalopathy (Adams et al. 2018; Alosco et al. 2018), and provides an adequate index of repetitive head trauma exposure as more refined methods are being developed. Quantifying head trauma exposure is made even more challenging by the multitude of different mechanisms of head trauma in IPV (violent shaking or pushing and/or strangulation). However, a reasonable approach is to use a semi-structured clinical interview that focuses on assessment of the duration and nature of violence in a relationship to obtain estimates of exposure to head trauma. Specifically, an



interview that probes or can estimate the number of abusive episodes that includes impacts to the head and nature of trauma (e.g., strangulation, pushing/shoving, being hit) would help determine potential exposure to repetitive head impacts, and furthermore, when violence including head impacts is noted, whether this included single or multiple (repetitive) hits to the head should be clarified. It should be noted, however, that although semi-structured interviews are beneficial for providing a wealth of participant specific information about IPV and head trauma exposure, their open-ended, free text-based responses can be difficult when meta-analyzing data across sites. Thus, developing methods of quantifying open-ended responses from semi-structured interviews (e.g., number of head impacts, time since last injury) will allow for use of interview data across sites, and limited missing data collected through interviews.

This can be achieved using the BISA or other comprehensive head trauma assessment tools that include IPV-specific items (e.g., BISQ), or by using well-validated TBI assessment tools (e.g., OSU-TBI-ID) alongside additional IPV-specific follow-up interview questions. Although the format of the interview should be dependent on the research question at each individual study site, the use of a timeline follow-back interview centered on lifetime exposure to violence may be most fruitful in this case. This methodology has previously been used in other studies to obtain retrospective reports of experiencing IPV (Marshall et al. 2017; Testa et al. 2003; Yoshihama and Bybee 2011) and IPV-related TBI (e.g., Valera and Berenbaum 2003; Valera and Kucyi 2017; Valera et al. 2018). We further suggest determining when in development abuse occurred and assessing exposure to childhood trauma (see Table 2), as abuse sustained during childhood may include impacts to the head (Keenan et al. 2003), and is also a risk factor for experiencing IPV in later life (Whitfield et al. 2003; Widom et al. 2014). Although TBIs sustained as a result of childhood abuse can be obtained through suggested measures of TBI history (e.g., OSU-TBI-ID), childhood abuse related head trauma could also be assessed through the ACE, TLEQ, and clinical interviews. Similar to the proxy of head trauma exposure above, it would be helpful to include questions about the duration and frequency of violence and typical nature of violence in this interview. The other advantage of using an assessment that provides an estimate of the extent of exposure to abusive episodes resulting in brain trauma is that it allows for within-group comparisons across injury load (e.g., Valera et al. 2018). By this means, one can infer the impact of different levels of IPV-related TBI without having to rely on comparisons to a control group that would be challenging to define given the multiple factors contributing to the lived experience of IPV survivors.

## Neurocognitive and neurobehavioral

**Cognitive assessment measures**—The heterogeneity of TBI coupled with the unique characteristics of individuals who have experienced IPV, including the potential of hypoxic/anoxic injuries, head trauma in the context of unresolved TBI, and a high prevalence of psychopathology, as well as variable time since injury, indicates the need for a broad assessment of functioning across cognitive domains, including processing speed, working memory, sustained attention, verbal learning and memory, auditory attention, and executive function, as well as measures of resilience and coping. As such, in Table 3 we provide a detailed list of neuropsychological assessments that target these domains for investigators

wanting to contribute data to the ENIGMA IPV Working Group. The measures we have suggested are part of the NINDS recommended neuropsychological tests for TBI. Consistent with the NIH CDEs, these domains can also be assessed using measures included in the NIH Toolbox Cognition Battery. By using the assessments included in the NINDS TBI CDEs, we will be able to compare outcomes associated with IPV-related TBI to other ENIGMA consortium working groups (e.g., sports-related brain injuries, military TBI and blast-related injuries) to determine the overlapping and unique effects of head trauma in IPV. In addition, to further promote study feasibility and generalizability of study outcomes, we also support the use of the Brief Test of Adult Cognition by Telephone (Alosco et al. 2017; Dams-O'Connor et al. 2018; Lee et al. 2019; Tun and Lachman 2006) for participants who cannot attend test sessions in-person. It should also be noted that there is a major movement in neurocognitive assessment to capitalize on virtual technologies (Parsons et al. 2018), where the potential may be to better customize the assessment tailored to the symptoms/problems being experienced by the examinee, using more real-world virtual assessment technologies (Foerster et al. 2019). Virtual technologies and telehealth assessment/treatment are particularly important for populations and events that make completing face-to-face research and support difficult (e.g., rural populations, pandemics, and natural disasters; Edwards 2015; Lanier and Maume 2009; Peek-Asa et al. 2011; Schneider et al. 2016; Schumacher et al. 2010). All of the standard CDE tests listed in Table 3 have a rich and well-established history in the field of clinical assessment, but most are so-called paper-and-pencil measures that may not fully capture subtle deficits associated with the mildest of injuries from IPV (Bigler 2017). Establishing reliable cognitive assessment methods with virtual techniques may be particularly important in functional neuroimaging studies where cognitive probes are used in real time while the IPV research participant is being scanned. For a systematic review of psychometric assessments of all cognitive domains and subdomains and their relationship to neuroimaging findings, the reader is referred elsewhere (Calvillo and Irimia 2020).

**Psychological, behavioral, and mental health measures**—The high prevalence of PTSD in those who have experienced IPV and evidence for synergistic negative effects of PTSD and TBI on cognitive functioning (Nelson et al. 2009) support the need for an in-depth assessment of PTSD symptoms. Further, given the high prevalence of general psychopathology, including substance use disorders (Afifi et al. 2009; Carbone-López et al. 2006; Okuda et al. 2011), major depression (Carbone-López et al. 2006; Fletcher 2010; Okuda et al. 2011; Zlotnick et al. 2006), and anxiety disorders (Afifi et al. 2009; Okuda et al. 2011) in individuals who have experienced IPV or have a history of TBI, we suggest assessing for psychopathology, as well as current and past substance use. In Table 4 we provide suggested measures that can be used by investigators within the working group to assess specific psychological and mood problems commonly experienced by individuals with exposure to IPV and/or TBI. In addition, components of the NIH Toolbox Emotion Battery can also be used to assess psychosocial, mood, and quality of life. Similar to the cognitive measures listed above, use of such measures to assess mood and psychological functioning will allow for mega- and meta-analysis of data across sites within the working group. Moreover, if investigators are interested in examining the lifetime history of substance use, then this should be included as part of the semi-structured

interview that probes age of first use, duration of use, and quantity and frequency of use of each substance reported. Additionally, collection of information pertaining to exposure to traumatic events across the lifespan using measures such as the TLEQ (Kubany et al. 2000) or ACE (Dube et al. 2003; Felitti et al. 1998) would also be beneficial to understanding the risk factors for psychopathology in this population. Further, given the focus on examining the effects of anoxic and/or hypoxic injuries in this population, it is important to collect lifetime history of tobacco use (e.g., Flicker et al. 2018). We also suggest the assessment of emotional dysregulation, aggression, and impulsivity as they often occur in individuals with psychopathology (e.g. PTSD) and/or following TBI (Arciniegas and Wortzel 2014; Miles et al. 2016; Stanford et al. 2003; Wood and Thomas 2013). Importantly, analytical techniques should be used that can accommodate the effect of these comorbidities, or inclusion as effects of interest, depending on the research question.

### Neuroimaging and genetics

**Brain imaging measures**—There is a growing structural and functional neuroimaging literature in the study of IPV. Women who experience IPV show alterations in brain volume (Fennema-Notestine et al. 2002), white matter microstructure (Flegar et al. 2011), and global and regional functional connectivity (Roos et al. 2017). Several studies have recommended including neuroimaging to better understand the effects of IPV-related TBI (Haag et al. 2019; Valera et al. 2018; Wong et al. 2014). The two studies published to date specifically examining the effect of IPV-related TBI show that higher brain injury severity scores (computed using the BISA) were related to reduced white matter microstructural integrity as assessed by fractional anisotropy (Valera et al. 2018), as well as alterations in intrinsic functional connectivity (Valera and Kucyi 2017). While not all investigators within the working group will be able to collect neuroimaging data, for those who can, we provide suggested sequences for structural, functional, and metabolic neuroimaging measures in Table 5. These sequences were based on existing ENIGMA protocols such as the DTI pipeline (Jahanshad et al. 2013) and common data elements from traumatic brain injury studies (Duhaime et al. 2010). For MRS studies, the methods used are based on ENIGMA recommendations in TBI (Bartnik-Olson et al. 2019) which recommended white matter and posterior cingulate brain regions as well as PTSD studies (Miller et al. 2018) where the anterior cingulate was shown to be sensitive to PTSD effects. The harmonization of neuroimaging measures across sites within the working group has the potential to vastly increase our available aggregated data and the opportunity to advance knowledge of how IPV-related head trauma impacts neuronal structure and function, and also how neural changes affect cognitive, psychosocial, and mental health outcomes. Moreover, given the risk of PTSD and anxiety in this population, study personnel should assess for claustrophobia prior to participants beginning the MRI scan. As is true for most clinical samples, motion mitigation protocols, including mock scanning, are essential for training participants how to recognize head motion during data acquisition and advanced post-processing protocols are vital to correct for motion effects (Murphy et al. 2009; Power et al. 2012, 2011, 2014; Saad et al. 2012).

**Neuropathology**—Major advances in the understanding of neurodegenerative disorders can be attributed to the postmortem study of brain tissue, often integrated with antemortem

neuroimaging. To date, investigations into the neuropathology associated with the exposure to repetitive head trauma (e.g., chronic traumatic encephalopathy – CTE) have been limited to mostly male contact sport athletes, and little is known about the pathology of IPV-related head trauma. Two published studies have screened for CTE in community-based autopsy cohorts (Bieniek et al. 2015,2020). One focused on male contact sport athletes (Bieniek et al. 2015) and the other found features of CTE in only 1 of 273 women (Bieniek et al. 2020). Repetitive head trauma exposure was ascertained through postmortem internet searches for obituaries and yearbook records, sources that are unlikely to mention IPV; as such, a link between IPV-related head trauma and neuropathological changes has not been investigated. Prospective studies of the cognitive, psychosocial, and neurological sequelae of IPV are ideally positioned to include the post-mortem collection of brain tissue from individuals with history of IPV as exposure will have been well-characterized during life. Consensus-based provisional criteria for the postmortem diagnosis of CTE (e.g., McKee et al. 2016) can and should be applied to the study of IPV-related head trauma. Further, advanced methods of image-guided tissue sectioning which permit histological characterization of lesions detected on in-vivo and/or ex-vivo MRI (Keene et al. 2018) can also be readily applied in this context.

**Genetics**—To date, the genetic contributions to impairments in cognitive, behavioral, and psychosocial functioning in individuals who experienced both IPV and TBI are not well understood. However, given the evidence genetic variations influence severity and long-term outcome following TBI and other neurological disorders, it will be a focus of our working group to extend analyses to IPV-related TBI. Thus, it would be beneficial for future studies to include collection of blood or saliva samples to assess polygenic risk, whenever feasible. CDE guidelines for the collection of blood samples have been suggested previously (Manley et al. 2010). Major advances in mild TBI biomarkers have occurred in recent years and this would be critical in differentiating TBI-specific issues versus those more associated with stress mediated factors (Zetterberg et al. 2013; Zetterberg and Blennow 2016). Based on the current literature on genetic influences on outcome after TBI, our current suggestions for genetic profiles to be collected are presented in Table 6.

### **Suggested inclusion and exclusion criteria for studies within the working group**

In the following section, we outline suggestions for inclusion and exclusion criteria for sites participating in the ENIGMA IPV working group. These are working suggestions, and will likely change as the focus and interests within the group evolve. Although the highest rates of IPV occur between the ages of 18 and 24 in women (Breiding et al. 2014), studies within the working group should consider including all age ranges as IPV occurs across the lifespan. Further, to be classified as part of the head trauma group, participants should have had at least one episode of physical and/or sexual trauma resulting in injury to the head or face and/or TBI, or strangulation, suffocation, or other method of oxygen restriction by an intimate partner. As study designs that focus on acute effects will naturally differ from those examining chronic effects, potential participants may be included or excluded based on time since injury and other demographic factors depending on the study question. Furthermore, as IPV occurs regardless of race/ethnicity, adult age, degree of education obtained, socioeconomic status, and sexual orientation we suggest studies participating in

the working group include broad recruitment methods that are not restrictive to specific groups to increase the generalizability of outcomes. Although the majority of existing data focuses on women, future studies need to include data for both males and females with history of IPV; both sex and gender identity should be collected for all studies.

In general, we recommend investigators contributing data to the working group exclude participants with a history of neurological illness other than TBI/concussion (e.g., Huntington's, Parkinson's, dementia, multiple sclerosis, etc.), history of seizure disorders, neurodevelopmental disorders with the exception of ADHD and/or learning disability (due to confounding effects on imaging and cognition), and current homicidal and/or suicidal ideation with intent requiring crisis intervention (due to management and safety issues). Given the range of potential mental health disorders associated with experiencing IPV, we suggest the inclusion of mental health diagnoses, particularly PTSD, major depression, and anxiety disorders (due to their high comorbidity), but suggest exclusion of participants with severe mental health disorders (e.g., schizophrenia spectrum disorders, (due to confounding effects on imaging and cognition). Finally, we suggest that studies exclude individuals who report moderate or greater substance dependence as outlined in the DSM-5 within 6 months of assessment, again, due to confounding effects on cognition and imaging. We realize that some studies may already include severe mental health disorders, as well as have different inclusion and exclusion criteria for recency and severity of substance dependence; in such cases detailed information should be provided to combine and compare datasets across studies.

**Comparison groups**—The choice of comparison group is key across patient groups but is especially important to consider with IPV-related TBI. Survivors of IPV often experience multiple types of trauma, including psychological and sexual abuse in addition to physical abuse. Frequent comorbidities include depression and other mood disorders (~48%), PTSD (~64%), and substance use disorders (~9–19% depending on substance; (Golding 1999; Lagdon et al. 2014; Mengo et al. 2020). The chronic, repetitive nature of TBI in IPV-related brain injury also differentiates it from many other patient groups. With these considerations in mind, individuals with a history of IPV who have not been exposed to TBI are the most appropriate comparison group but may be difficult to recruit given the challenges of accurately diagnosing TBI in this population. For this reason, samples with overlapping comorbidities, but without TBI, may serve as comparison groups, including women with PTSD, mood disorders, and/or history of abuse.

### **Considerations for recruitment, study participation, and attrition**

**Participant safety during the recruitment process and study participation**—Working with women exposed to IPV-related head trauma poses several unique challenges compared to traditional TBI populations (e.g., sports-related concussion, military, motor vehicle accidents) including potentially unique recruitment pathways and considerations for participant safety (Bogat et al. 2005; Dichter et al. 2019; Dutton et al. 2003; Goldin et al. 2016; Gondolf et al. 1997; World Health Organization 2001). Because of this, collaboration with local domestic violence organizations, as well as consultation and/or collaboration with healthcare personnel (e.g., social workers, nurses, clinical psychologists) who manage and

provide interventions to IPV victims can contribute practical guidelines when determining study safety, feasibility, and design (Campbell and Boyd 2000; Dutton et al. 2003; Gondolf et al. 1997; National Violence Against Women Prevention Research Center 2001). Of particular concern are safety issues with shelter residents, IPV victims residing in the community, or individuals who come to the attention of emergency departments and healthcare personnel. Consultation with domestic violence organization staff regarding safety planning can assist in research design, recruitment, and attrition (see Dutton et al. 2003; Logan et al. 2008, for recommendations on recruitment and retention in IPV research).

Recruitment and assessment of individuals who have experienced IPV requires that additional safety measures be in place in addition to what is standard practice in NIH-funded research projects. We provide some recommendations, although additional measures may be added to individual studies dependent on safety risk (e.g., ongoing abusive relationship, children in the home) to reduce the potential to trigger further abuse through study recruitment and participation (Dutton et al. 2003; St Ivany et al. 2018a, 2018b). Study names should be generalized and should not include reference to forms of violence or abuse (e.g., IPV, domestic violence, sexual violence, assault), mental illness, or health problems. This should include all hard copy and online materials referencing the study. In addition, it may not be safe for participants to have hard copies of informed consent documents or study information. Online information should, however, be provided so participants retain access to study personnel. Participants should be presented with the option to either decline or keep a copy of the signed consent. Participants choosing to keep their own copies of the consent who are currently involved in an abusive relationship should also be encouraged to keep study materials private or stored in a separate location. Researchers should consider only disclosing the non-specific study name, with no reference to IPV, if anyone other than the study participant answers the phone. However, study participants should be aware that study personnel are using non-specific study names so they know they are communicating with the correct person (Dutton et al. 2003). Study personnel should use an unblocked phone number, so participants recognize the caller (Dutton et al. 2003). Further, before disclosing study information and the reason for reaching out to participants, study personnel along with the participant, should determine whether it is safe for individuals to talk. If it is not safe, the call should be terminated and completed at another time. These safeguards can pose barriers to honoring an individual's participation in brain donation (for those including neuropathology as a study component), as some states require post-mortem consent from a legal next of kin. Whenever possible, prospective brain donor programs can seek consent during life (permitted in many states as with organ donor laws) and/or collect contact information for family members other than a known perpetrator.

Further, all study staff should be trained by senior study personnel with expertise in recruitment of at-risk populations before involvement in participant recruitment. These safety issues are of utmost importance in studies recruiting participants who are still involved in a violent relationship. This makes training particularly important for research study staff involved in recruitment and data collection. More specifically, prior to assessment of participants, all study personnel should be trained on safety risks and precautions for participants in the study, as well as on how to identify mental health problems that place

participants at risk (e.g., suicidality or homicidality) and determining participant safety if participants show signs of continued physical abuse (e.g., bruises, burns). Given the under-reporting of head trauma and mental illness in individuals who have experienced IPV, strategies should be in place for referral to treatment when significant problems associated with TBI and mental illness are identified (Murray et al. 2016). This is particularly important since these studies will be asking participants to describe past physical trauma or violence which could result in psychological distress through re-experiencing the event (Stein et al. 2000). In addition, the gender of research personnel collecting information should be considered. For example, if a woman has experienced abuse by a male perpetrator, she may feel more comfortable being assessed by female study personnel. Participants can also be asked whether they have a preference for the gender of study personnel assessing them (Dutton et al. 2003). The assessment of geriatric cases may require additional considerations for the physical condition of those with a history of IPV, as well as for their safety from additional abuse, depending on living arrangements (e.g., retirement home, hospice, nursing home, etc.).

Although we have provided reference for assessments within the working group, cognitive and psychological assessments that are culturally appropriate (Ackerman and Banks 2009) and with inclusive language (Dyar et al. 2019) should also be considered. Additionally, measures or tasks that require participants to be touched or restrict vision should be avoided. However, when such measures are necessary to assess particular aspects of brain function, the participant should be made aware that touching or restricting vision will take place during informed consent procedures and just prior to the procedure in question. They should also be provided with the opportunity to decline participating in such measures both prior to and during the assessment. If participants are expected to complete assessments at home or on their own electronic devices, an immediate termination button can be included to allow prompt exit from testing sessions if/when they pose safety risks in the home environment. Reporting requirements and ethical obligations based on psychologists' and physicians' colleges or licensure bodies should be followed. Further, participants should also be informed of the reporting requirements in situations of ongoing threats to safety (self-harm or harm to others including the potential for child abuse), and such reporting requirements vary by jurisdiction. Finally, we suggest that non-NIH funded studies occurring in the United States obtain a National Institutes of Health Certificate of Confidentiality for further protection of both study personnel and participants from being forced to disclose sensitive study information unless the participant provides consent or due to legal obligations for reporting (i.e., risk of suicide or harm to others including child abuse; <https://grants.nih.gov/policy/humansubjects/coc.htm>).

**Social determinants of health**—There are a number of studies documenting that IPV occurs in all populations of women; however, subpopulations experience social determinants of health that can impact the prevalence and severity of IPV, as well as access to care and support services for those exposed to IPV (Capaldi et al. 2012; Petrosky et al. 2017). These social determinants of health include access to health care and transportation (Wilson et al. 2007), food insecurity (Ricks et al. 2016), safe housing (Gilroy et al. 2016), level of education (Weitzman 2018), socioeconomic status (Cunradi et al. 2002; Rennison and

Planty 2003), and being part of a racial or ethnic minority (Cho 2012; Lipsky et al. 2006) or due to sexual orientation and gender identity (Ard and Makadon 2011; Edwards, et al. 2015). Further, geographic location also impacts IPV as risk and severity of IPV tends to be high in rural populations due to physical and social isolation, as well as limited access to healthcare and support services (Edwards 2015; Peek-Asa et al. 2011). Moreover, adding to this complex issue is the shortage of safe, accessible, affordable housing for survivors, thereby making this population, and particularly those accessing shelter services, transient. As such, not only is recruitment, attrition, and longitudinal data impacted by social determinants of health, but they may also affect assessment outcomes and should be accounted for by adopting an intersectional approach to data analyses.

**Engagement of stakeholders and clinicians in research studies**—Staff and advocates working at domestic violence organizations are sometimes hesitant to work with researchers for fear that their clients may be further victimized or traumatized in the process, or due to limitations in funding and already being strapped for resources. When planning on recruiting participants from domestic violence organizations, it is suggested to use community-based, participatory research (CBPR) principles to guide such recruitment (Hacker 2013). The framework for these principles focuses on the relationships between researchers and practitioners with a focus on societal transformation rather than a specific set of research methods or techniques. Such principles include building collaboration and partnership with community stakeholders, balancing knowledge generation and intervention, focusing on cyclical and iterative processes to inform the research, and emphasizing translatable knowledge dissemination. In essence, researchers should partner with staff from domestic violence organizations to share control of the study as much as possible. This could include: getting feedback on measures; involving staff in recruiting participants and developing IRB protocols to keep women safe; and collaboration in data sharing and research dissemination efforts.

Just as many community organizations implement trauma-responsive care in their service of survivors with IPV, researchers may find such an approach useful in guiding their interactions with survivors with IPV. Some of the common principles of trauma-responsive practices (Wilson et al. 2015), such as establishing safety, imparting trustworthiness, and restoring choice and control can easily be applied to working with survivors in a research context. First, care should be taken to ensure the personal safety and comfort of the participant. In addition to respecting the survivor's physical safety, the goals of the research and the voluntary nature of the survivor's participation should be emphasized during consenting to maximize personal control on the part of the participant including their right to discontinue research participation at any time. Imparting this autonomy and sense of personal control is critical in preventing the research experience itself from becoming a traumatic stressor.

As disclosure of trauma may arise during the research session, investigators should also be prepared to provide supportive and appropriate responses if study participation results in adverse reactions (Clements and Holtzworth-Munroe 2009). Notably, a meta-analysis of 70 unique samples found that reactions to trauma-related research present minimal risk of retraumatization to participants, as they are experientially different from reactions to actual



trauma (Jaffe, DiLillo, Hoffman, Haikalas, & Dykstra, 2015). While participants perceived engaging in trauma-related research to be a positive experience overall, reminders of trauma brought up in research did elicit greater levels of immediate distress for individuals with a history of trauma or PTSD compared to nonvictims (Jaffe et al. 2015). Thus, research protocols should be designed to address cases in which a survivor's distress escalates. Investigators should familiarize themselves and be able to implement grounding techniques, or initiate a referral for further clinical services, if necessary. Collaborating with other clinical and/or academic professionals with trauma expertise in the development of a comprehensive and appropriate response plan for re-traumatization or heightened affective response to research participation is essential.

Finally, trauma-responsive care seeks to understand each survivor in his or her own cultural context (Elliott et al. 2005). Indeed, this is highly relevant as women from ethnic minority groups are disproportionately affected by IPV (Stockman et al. 2015). To this end, researchers should be cognizant and intentional in adopting a culturally-sensitive approach in working with survivors from diverse backgrounds. This can include (but is not limited to) implementing necessary adaptations to data collection procedures that accommodate culturally specific needs (e.g., potential use of an interpreter to overcome language barriers), as well as careful consideration of the implications and ramifications of data interpretation and results.

### **Knowledge translation of research to clinicians and community stakeholders**

—An integrated knowledge translation (iKT) approach is suggested to ensure research findings are disseminated beyond conference presentations and traditional peer reviewed publications and used by stakeholders such as clinicians and domestic violence organizations. The iKT approach makes use of a dynamic and iterative process consisting of knowledge creation and action cycles for ensuring research knowledge is used in practice (Straus et al. 2013). Using an iKT approach, stakeholders collaborate with the researchers to inform research questions, data collection and analysis, and assessment tool development. This is especially important in research examining IPV-related head trauma because of the stigmatization of survivors and the lack of knowledge and awareness of the intersection of IPV and head trauma amongst survivors, those who provide support for them, and the general population. Taking an iKT approach ensures that the knowledge generated on this understudied topic will be turned into evidence-based tools and resources to ultimately help improve the long-term health and well-being of this underserved population.

## **Discussion**

In this manuscript, we outline the importance of advancing our understanding of IPV-related head injury research and the outcome of discussions regarding data collection and collaboration within the ENIGMA IPV working group. We have provided details regarding demographic information, TBI history, and IPV-specific assessments, as well as neuroimaging, cognitive, psychosocial, and mental health measures to maximize consistency in data collection across sites involved in the working group. By harmonizing measures across sites, we anticipate being able to complete large-scale mega- and meta-analyses thus increasing our understanding of the effect of IPV-related head trauma. This includes

basic suggestions for the collection of neuroimaging measures that are consistent with the neuroimaging CDEs included in NINDS studies. Further, inclusion of a broad battery of cognitive, psychosocial, and mental health assessments for studies within the working group is suggested as research demonstrates that IPV impacts a number of domains of function and can result in significant psychiatric comorbidities; all of which seem to be more impacted by IPV-related TBI. As it is extremely important to examine the frequency and severity of abuse, relationship status, and other health conditions which may result from years of physical violence and psychological abuse, we also suggest inclusion of IPV-specific measures historically used in these populations (e.g., ACE, TLEQ, CTS2, Danger Assessment and LAP outcomes), as well as a clinical interview that targets abuse and resultant head trauma. Finally, although standard measures to retrospectively assess history of TBI have been shown to be sensitive to objectively assessing frequency and severity of head trauma in this population (see Goldin et al. 2016), we also suggest the use and development of semi-structured clinical interviews to further probe information relevant for IPV-related head trauma.

Although IPV has significant negative effects on physical and mental health in both men and women, the majority of existing research has focused on women likely due to women experiencing severe physical aggression and reporting more negative psychological and physical health outcomes (Brush 1990; Dobash and Dobash 2004; Tjaden and Thoennes 2000). Past research also suggests that 60–92% of women with a history of IPV have experienced IPV-related head and facial injuries (Campbell et al. 2017; Roberts and Kim 2008; St Ivany and Schminkey 2016; Valera and Berenbaum 2003), and that between 50% and 75% of women report experiencing multiple hits to the head or occasions of violence resulting in repetitive exposure to head trauma (Valera and Berenbaum 2003; Valera and Kucyi 2017), with some individuals reporting having experienced too many hits to the head to provide an accurate account of frequency (Valera 2018). As such, not only the effect of IPV-related TBI and head trauma need to be examined, but also the effects of repetitive hits to the head in this population as these confer greater neural, cognitive, and psychological impairment over the lifespan.

Assessing the repetitive head trauma in individuals who have experienced IPV may also provide insight into the chronic effects of repetitive brain trauma, particularly with respect to unhealthy brain aging in women given the higher prevalence of exposure to severe physical aggression. Past research in high-level male athletes suggests that repetitive head trauma, which includes both concussive and subconcussive head impacts, is associated with the development of chronic traumatic encephalopathy and other neurodegenerative diseases (Mackay et al. 2019; McKee et al. 2009; McKee et al. 2013; Mez et al. 2017; Omalu et al. 2005; Stern et al. 2013), as well as an increased risk of mild cognitive impairment (Guskiewicz et al. 2005), mental health complaints (Esopenko et al. 2017; Guskiewicz et al. 2007), and alterations in brain function and structure during aging (De Beaumont et al. 2009; Ford et al. 2013; Hampshire et al. 2013; Koerte et al. 2016; Multani et al. 2016; Tremblay et al. 2013; Tremblay et al. 2014), although not all data are consistent (Deshpande et al. 2017; McMillan et al. 2016; Terry and Miller 2017; Willer et al. 2018; Zivadinov et al. 2018). In general, TBI has been associated with an increased risk, and earlier onset, of dementia (Kalkonde et al. 2012; Lehman et al. 2012; Schofield et al. 1997), particularly in

cases with premorbid cerebral amyloid angiopathy, arteriolosclerosis or other neurovascular pathologies (Irimia et al. 2018). The odds of developing dementia are higher in those with repetitive TBI, regardless of sex (Nordstrom and Nordstrom 2018). Thus, one would expect individuals with repetitive exposure to brain trauma and TBI due to IPV are at a similar risk of experiencing negative long-term outcomes as athletes participating in high-level contact and collision sports, but this has not been examined to date (Leung et al. 2006). We anticipate that the lifetime assessment of head trauma and IPV exposure, comprehensive cognitive and psychosocial measures, and advanced neuroimaging techniques we have suggested will enable our group to examine the long-term effects of IPV-related head trauma and the risk for unhealthy aging in this population.

Importantly, we also provide information regarding the ethical considerations and additional safety measures that should be undertaken by investigators within the working group when recruiting and assessing individuals who have experienced IPV. One major concern of research involving those who have experienced IPV is whether it is safe for them to participate in research studies. To this end, we want to ensure that researchers participating in the IPV working groups are not increasing the risk of further abuse in this already vulnerable population. This can be addressed through standard research guidelines of participant anonymity. However, additional measures that can be taken to ensure participant safety are described above in detail. Furthermore, the goal of the working group is to examine the effect IPV-related head trauma has on the neural, psychological, and cognitive outcomes of these injuries to identify targets for interventions. However, as Hunnicutt and colleagues highlighted in their recent call for research on this topic, there is a risk that increased attention to the prevalence and sequelae of head trauma in this population could lead to additional stigmatization and discrimination against this already vulnerable population (Hunnicutt et al. 2017). As such, we want to ensure that all investigators reporting results of research from the working group do so in a sensitive way that does not increase stigma, but instead highlights how understanding the effects of IPV-related head trauma can be used to increase the accessibility of resources and to adjust methods of rehabilitation and intervention to help improve the ability to work, engage in psychotherapy, navigate the legal system, and engage in safety planning in individuals who have experienced IPV.

## Limitations

There are limitations to this article that need to be taken into account. First, we did not undertake a systematic review of the literature; instead we relied on recent publications in the field of IPV, input from clinicians involved in assessment, intervention, and provision of support to the IPV population, as well as working group members' expert knowledge and experience in the fields of IPV, TBI, cognitive function, mental health and neuroimaging. Second, we did not undertake a Delphi approach to reaching consensus; instead we debated all aspects at in-person meetings and over email and attempted to synthesize views in this way. Third, we have relied on the NINDS CDEs in order to optimize consistency across studies, but we are aware that a range of domains and measures not included here may be useful in IPV TBI research. As such, the goals and expectations for sites participating in

the ENIGMA IPV working group represent a starting point for the development of a global collaboration to examine IPV-related head trauma.

## Conclusions

IPV is a significant public health concern affecting millions of individuals worldwide each year, with past work indicating that individuals who experienced IPV are at very high risk to sustain head trauma. While research on TBI in other populations (e.g. athletes and military personnel) has dramatically increased over the past two decades, research on IPV-related TBI is still limited. The heterogeneity and complexity of injuries and comorbid factors in this population provides an opportunity to understand how multiple factors intersect to predict outcomes, which will have significant impact on personalized treatment and intervention strategies used in this population. Further, given this complexity, the study of IPV-related TBI would benefit strongly from global collaborative efforts using consistent testing paradigms across study sites to facilitate acquisition of larger samples of individuals exposed to IPV. Larger sample sizes would allow for increased statistical power to examine the heterogeneity of injury factors and comorbidities in this unique and complex population. The methodology and measures proposed in this paper serve to set the foundation for a global collaboration through the ENIGMA IPV working group to facilitate meta- and mega-analyses to examine the effects of TBI on neural, cognitive, and psychological outcomes in individuals who have experienced IPV.

## Funding

KDO has been supported by the NIH/NINDS/NICHD (1U01NS086625–01). ELD has received grants from NIH/NINDS (K99NS096116). KBW is supported by the Department of Veterans Affairs, National Center for PTSD (36C24118C0076). EAW received support from the Department of Veterans Affairs (B6812C; 5 I01 RX00162). FGH is supported by a PA Health Research Grant (SAP #4100077082). DJS is supported by the South African Medical Research Council. AL has been supported through the BWH Program for Interdisciplinary Neuroscience Women's Brain Initiative. IKK is supported by the NIH (5R01NS100952, U01NS093334) and the European Research Commission (ERC Starting Grant 804326). PvD is supported by grants from the Canadian Institutes of Health Research (PJT-168863), the Canadian Department of Women and Gender Equality (GV-18385), and the Max Bell Foundation (MB-18-A-15). AI is supported by the NIH/NINDS (R01 NS 100973), by the US Department of Defense (W81XWH-18-1-0413) and by a Hanson-Thorell research scholarship. ADM is supported by the NIH, NICHD (1R01HD098172–01).

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Table 1

## IPV/Family Violence Assessment

Measure	Domain of Assessment
Type of IPV	
Campbell Danger Assessment (Campbell et al. 2009a) <i>Available forms:</i> 20-item form and 5-item Short form (DA-5)	Physical
Lehality Assessment Program (LAP; Messing et al. 2015) This is an 11-item version of the Campbell Danger Assessment.	Physical
Revised Conflict Tactics Scale (CTS2; Straus et al. 1996) <i>Available forms:</i> Short form (CTS2S; Straus and Douglas 2004); Parent-Child version (CTS2PC)	Physical, psychological, and sexual; child maltreatment & parent-to-child violence (CTS2PC form)
Index of Spouse Abuse (ISA; Hudson and McIntosh 1981)	Physical, emotional, and sexual
Abusive Behavior Inventory (ABI; Shepard and Campbell 1992) <i>Available forms:</i> Original and revised (ABI-R; Postmus et al. 2016)	Physical, psychological, and sexual
Composite Abuse Scale (CAS; Hegarty et al. 1999) <i>Available forms:</i> Original, revised short form (CAS <sub>R</sub> -SF; Ford-Gilboe et al. 2016)	Physical, emotional, and sexual
Women's Experience with Battering Scale (WEB; Smith et al. 1995); otherwise known as the Relationship Assessment Tool	Emotional
IPV-Related Trauma Assessment	<b>Domain of Assessment</b>
Adverse Childhood Experiences (ACE; Felitti et al. 1998) <i>Available forms:</i> Multiple methods exist (Bethell et al. 2017)	Physical, emotional, and sexual
Traumatic Life Events Questionnaire (TLEQ; Kubany et al. 2000)	Physical or sexual assault (in childhood or adulthood); witnessing family violence; other threats
Childhood Trauma Questionnaire (Bernstein et al. 1994)	Physical, emotional, and sexual
Trauma Symptom Checklist – 40 (TSC-40; Briere 1996)	Emotional, sexual abuse (in childhood or adulthood)
Childhood Maltreatment Interview Schedule (CMIS; Briere 1992) <i>Available forms:</i> Original (46-item) and short version (17-item; CMIS-SF)	Physical, emotional, and sexual
Clinician-Administered Posttraumatic Stress Disorder Scale for DSM-5 (CAPS-5; Weathers et al. 2013a) <sup>a,b</sup> <i>Available forms:</i> Adult (original) and Child/Adolescent versions	No specific reference to IPV. In assessing for PTSD it inquires about symptoms of intrusion, avoidance, negative alterations of cognition and mood, and alterations in arousal and reactivity related to an index traumatic event, which may include physical or sexual assault.
PTSD Checklist for DSM-5 (PCL-5) <sup>a,b</sup> (Weathers et al. 2013b)	No specific reference to IPV. In screening for PTSD it inquires about symptoms of intrusion, avoidance, negative alterations of cognition and mood, and alterations in arousal and reactivity related to a specific "stressful experience."
Child PTSD Symptom Scale for DSM-5 <sup>b</sup> (CPSS-5; Foa et al. 2018)	PTSD screening tool. No specific reference to IPV or family violence, although the optional trauma screen inquires about physical or sexual assault.

Note: This is not an exhaustive list of available instruments and specifically does not include many of the brief screening measures used primarily for clinical purposes

<sup>a</sup>CAP PTSD CDE Core

May also be used to assess psychological outcomes

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**Table 2**

**TBI Exposure History Assessment Instruments**

<b>Measure</b>	<b>Populations</b>	<b>Scope &amp; Format</b>
Ohio State University TBI Identification Method (OSU TBI-ID)	Various populations, including IPV, children, adolescents, & older adults	Allows informant to safely & privately endorse an event of possible TBI without implicating a perpetrator or requiring acknowledgment of IPV; Interview & online formats available
Brain Injury Screening Questionnaire (BISQ)	Various populations, including IPV, children & adults	Allows informant to safely & privately endorse an event of possible TBI without implicating a perpetrator or requiring acknowledgment of IPV; Interview, online, & self-administration formats available
Brain Injury Severity Assessment (BISA)	TBI as outcome of IPV specifically	Specifically inquires about IPV events; Interview format
HELPS Brain Injury Screening Tool	Various populations, including IPV	Allows informant to safely & privately endorse an event of possible TBI without implicating a perpetrator or requiring acknowledgment of IPV; Interview format with 5 questions

Goldin et al. (2016) identified six additional instruments as suitable for screening in IPV, with recommendations for modifying use of the instruments with this population. The additional instruments include the Philadelphia Head Injury Questionnaire (PHQ), Traumatic Brain Injury Questionnaire (TBIQ), Brief Traumatic Brain Injury Screen (BTBIS), Military Acute Concussion Exam (MACE), Preliminary Screening Tool for Identification of Acquired Brain Injury in School Aged Children (STI), and Athlete Survey on Concussion (ASC). However, no studies to date were found that used these six additional instruments for IPV specifically.



Table 3

## Measures of Cognitive Function

Domain of Measurement	Measure
Premorbid Functioning Estimate	<i>The Test of Premorbid Functioning</i> (TOPF; Wechsler 2011)
Attention/Working Memory	<i>Wechsler Adult Intelligence Scale-IV (WAIS-IV) Digit-Span</i> (Wechsler 1997, 2008) <i>WAIS-IV Letter Number Sequencing</i> (Wechsler 1997, 2008)
Learning & Memory	<i>California Verbal Learning Test, Third Edition</i> (CVLT3; Delis et al. 2017) - Version (CVLT-II vs. CVLT3) can also be determined based on collection of longitudinal data) OR <i>Rey Auditory Verbal Learning Test</i> (RAVLT; <sup>a</sup> Schmidt 1996; Strauss et al. 2006) <i>Brief Visuospatial Memory Test-Revised</i> (BVMTR; Benedict et al. 1996; Benedict 1997) <i>Memory for Intentions Screening Test</i> (MIST; Raskin 2009)
Processing Speed	<i>WAIS-IV Coding</i> <sup>a</sup> (Wechsler 1997, 2008) OR <i>Symbol Digit Modalities Test</i> (SDMT; L. K. Sheridan et al. 2006; A. Smith 1991) <i>WAIS-IV Symbol Search</i> <sup>a</sup> (Wechsler 1997, 2008) <i>Trail Making Test</i> <sup>a</sup> (Reitan 1958)
Executive Functioning	<i>Delis-Kaplan Executive Function System (D-KEFS), Color Word Interference Test</i> (Delis et al. 2001, 2004) <i>DKEFS Sorting Test</i> (Delis et al. 2001, 2004) <i>DKEFS Verbal Fluency Test</i> (Delis et al. 2001, 2004) OR <i>Controlled Oral Word Association Test</i> (COWAT; Benton et al. 1994) <i>Wisconsin Card Sorting Test</i> (WCST; Milner 1963; H. E. Nelson 1976)
Multidomain (Memory, Working Memory, Executive Functioning, Processing Speed)	<i>Brief Test of Adult Cognition by Telephone</i> (BTRACT; Tun and Lachman 2006) <i>NIH Toolbox Cognitive Battery</i> (Gershon et al. 2013)
Validity	<i>Medical Symptom Validity Test</i> (MSVT; Armistead-Jehle 2010; Green 2003) OR <i>Test of Memory Malingering</i> (Tombaugh 1996, 1997)

<sup>a</sup>NIH TBICDE Core

Again, we have provided multiple tests that cover the same domain (e.g., CVLT-3 vs RAVLT) but suggest that investigators select the measure(s) that best fit their research question.

Table 4

## Measures of Psychosocial, Behavioral, and Psychological Functioning

Construct	Measure
PTSD-related Psychosocial Functional Impairment	<i>Brief Inventory of Psychosocial Functioning</i> (B-IPF; Marx, 2013)
Diagnosis of Mental Health Disorders	<i>Structured Clinical Interview of the DSM-5</i> (SCID-5; First et al. 2016) OR <i>Mini-International Neuropsychiatric Interview (MINI)</i> – Depression and GAD modules (Sheehan et al. 1998)
Aggression & Impulsivity	<i>Impulsive/Premeditated Aggression Scales</i> (IPAS; Stanford 2011; Stanford et al. 2003)
Substance Use and Dependence	<i>Alcohol Use Disorders Identification Test</i> (AUDIT <sup>a</sup> ; Saunders et al. 1993) AND <i>Drug Abuse Screening Test</i> (DAST-10; Bohn et al. 1991) OR <i>Alcohol, Smoking, and Substance Use Involvement Screening Test</i> (ASSIST; Humeniuk et al. 2010)
Sleep Quality	<i>Patient-Reported Outcomes Measurement Information System (PROMIS)</i> – Sleep Disturbance and Sleep-Related Impairment Short-form <sup>a</sup> (Buysse et al. 2010; Yu et al. 2012) <i>Pittsburgh Sleep Quality Index</i> (PSQI; Buysse et al. 1989) <i>Insomnia Severity Index</i> (ISI; Bastien et al. 2001)
Quality of Life	<i>Neuro-Quality of Life Questionnaire</i> (Neuro-QOL; Gershon et al. 2012) <i>Satisfaction with Life Scale</i> (SWLS; Diener et al. 1985)
Resilient Coping	<i>Response to Stressful Experience Scale</i> (RSES; Johnson et al. 2011) <i>Connor-Davidson Resilience Scale-10 item</i> (CD-RS-10; Campbell-Sills et al. 2009)
Multidomain	<i>NIH Toolbox Emotion Toolbox</i> (Gershon et al. 2013) <i>Brief Symptom Inventory – 18</i> (BSI-18 <sup>b</sup> ; Derogatis 2001)

<sup>a</sup>CAP PTSD CDE Core<sup>b</sup>NIH TBI CDE Core

**Table 5**

## Neuroimaging Measures and suggested sequences

Domains	Measures	Sequences
Structural Neuroimaging	T1-Weighted	176 slices, voxel size = 1.0x1.0x1.0, TR = 2300 msec, TE = 2.98 msec, FoV of 256 mm
Functional Neuroimaging	3D fluid attenuated inversion recovery	176 slices, voxel size = 1.0x1.0x1.0, TR = 6000 msec, TE = 390 msec, FoV of 256 mm
	Diffusion Tensor Imaging	64 directions, 59 slices, voxel size = 2.7x2.7x2.7, TR = 9000 msec, TE = 94 msec, FoV of 350 mm
	3D Susceptibility Weighted Imaging	128 slices, voxel size = 1.3x1.3x1.3, TR = 45 msec, TE = 25 msec, FoV of 256 mm
	Resting State Functional MRI	48 slices, voxel size = 3.3x3.3x3.3, TR = 3000 msec, TE = 30 msec, FoV of 212 mm. Minimum 6-min sequence with eyes open.
Metabolic Neuroimaging	Magnetic Resonance Spectroscopy (MRS) *	<u>PRESS voxel imaging</u> : (TE = 30 ms, TR = 2000 ms, voxel size 20x20x20mm, 128 averages, water reference). <u>Semi-LASER chemical shift imaging</u> : (TE = 30 ms, TR = 1500 ms, voxel size 10x10x15mm, FoV 160 mm, 16 × 16).

\* Collection of T1-Weighted sequences is required for MRS. PRESS single voxel should be acquired in the anterior and posterior cingulate and parietal white matter and chemical shift imaging as a slab across the corpus callosum localized on the MPRAGE or FLAIR images

**Table 6**

Proposed genes of interest

Gene	Polymorphism
Apolipoprotein E (APOE)	e2, e3, e4 differ in amino acids at positions 112 and 158
Brain-Derived Neurotrophic Factor (BDNF)	G/A SNP in promoter region (codon 66) resulting in Val-to-Met switch
Interleukin-1 $\beta$ (IL-1 $\beta$ )	Restriction site at position +3953 exon 5
Interleukin-6 (IL-6)	G/C SNP in promoter region (position -174)
Ankyrin Repeat And Kinase Domain Containing 1 (ANKK1; at dopamine D2 receptor region)	Multiple SNPs
Catechol-O-Methyltransferase (COMT)	G/A SNP (Val158Met) resulting in Met-to-Val switch at position 472

SNP = single-nucleotide polymorphism.