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ORIGINAL RESEARCH

Brain injury in women experiencing intimate partner-violence: neural mechanistic evidence of an "invisible" trauma

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Abstract Traumatic brain injury (TBI) in women experiencing intimate-partner violence (IPV) is common, and IPV afflicts 30 % of women worldwide. However, the neurobiology and related sequelae of these TBIs have never been systematically examined. Consequently, TBI treatments are typically absent and IPV interventions are inadequate. There has been a call for a comprehensive assessment of IPV-related TBIs and their relationship to aspects of women's cognitive and neural functioning. In response, we examined brain-network organization associated with TBI and its cognitive effects using clinical interviews and neuropsychological measures as well as structural and functional Magnetic Resonance Imaging (fMRI) in women experiencing IPV-related TBI. We hypothesized that TBI severity would be related to poorer cognitive performance and be associated with structural and functional connectivity between cognitive networks previously implicated in other TBI populations. As predicted, severity of TBI was negatively associated with inter-network intrinsic functional connectivity indicative of TBI, between the right anterior insula and posterior cingulate cortex/precuneus (FLAME1 + 2; family-wise error-corrected $Z > 2.3$, cluster- based $p < 0.05$). This association remained significant when controlling for partner-abuse severity, age, head motion, childhood trauma and psychopathology. Additionally, intrinsic functional connectivity between the same regions correlated positively with cognitive performance on indices of memory and learning. These data provide the first mechanistic evidence of TBI and its association with cognitive functioning in women sustaining IPV-related TBI. These data underscore the need to address and consider the role TBI may be playing in the efficacy of IPV interventions ranging from emergency first responder interactions to specific treatment plans.

Keywords Intimate-partner violence · Traumatic brain injury · Functional connectivity · Default mode network · Salience network · Domestic violence

Introduction

Internationally, intimate-partner violence (IPV) is reported by 30 % of women over 15 years of age (Devries et al. 2013) and is recognized as an urgent public health issue (Liebschutz and Rothman 2012). Traumatic brain injury (TBI) has also been recognized as a serious public health concern (Levin and Diaz-Arrastia 2015). In a previous report, we showed that approximately 75 % of a sample of 99 women who had experienced IPV sustained at least one partner-related TBI and 50 % sustained multiple partner-related TBIs (Valera and Berenbaum 2003). Additionally, brain injury severity was negatively related to measures of memory, learning and cognitive flexibility. Notably, the cumulative sequelae of TBIs most typically sustained in this population are possibly unique (Kwako et al. 2011) since many women suffer from repetitive mild TBIs

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(e.g., multiple TBIs weekly overs years sometimes in the form of anoxia or hypoxia from strangulation), which go virtually unrecognized by both the women themselves and caregivers (Murray et al. 2016). This is in contrast to other populations (e.g., often male sports players, single TBI accident victims) who are often aware of their TBIs and modify behavior according to resolution of initial sequelae for each TBI.

Surprisingly, there has been no systematic evaluation of the neurobiological effects of TBI in women sustaining IPV. Consequently, the mechanisms underlying partner-related TBI and its cognitive effects are not understood, and appropriate therapeutic interventions are typically absent. For example, the cognitive sequelae of TBIs have likely gone unrecognized and hampered the success of the few IPV-related interventions that have been attempted in medical settings (Klevens et al. 2015; Rhodes et al. 2015). Critically, since cognitive sequelae of repetitive brain trauma likely contribute to the many difficulties women experience in trying to leave the relationship, (Eisenstat and Bancroft 1999) a greater understanding of TBI mechanisms to inform interventions is urgent (Kwako et al. 2011).

Cognitive impairments in TBI are thought to arise from diffuse axonal injuries that disconnect brain networks important for attention, memory and executive function (Bonnelle et al. 2011; Kinnunen et al. 2011). Converging evidence from neuroimaging of functional and structural connectivity suggests that default mode network (DMN) and salience network abnormalities are key contributors to cognitive impairment in TBI (Sharp et al. 2014). Typically, in healthy individuals, the DMN is deactivated whereas the salience network is activated during externally-oriented, focused attention (Buckner et al. 2008; Menon and Uddin 2010). Therefore the coordination of activity between these two networks is thought to underlie successful and efficient cognitive performance (Kelly et al. 2008; Sharp et al. 2014).

The right anterior insula (rAI) within the salience network is postulated to have an influential role in coordinating DMN-salience network interactions. Multiple functional imaging studies suggest that the rAI influences activity of the DMN, salience network, and other networks in a diverse range of tasks (Cai et al. 2015; Goulden et al. 2014; Sridharan et al. 2008; Uddin et al. 2011). As such, the rAI has been labeled a "causal outflow hub" that directs and coordinates activity across cognitive brain networks (Uddin 2015). In healthy individuals the rAI shows increased interactions with the DMN during switches in behavior and inhibited behavioral responses, but these increases are not found in TBI patients (Jilka et al. 2014). Notably, abnormal rAI-DMN connectivity has been convincingly reproduced in such patients (Bonnelle et al. 2012; Jilka et al. 2014). If TBIs resulting from IPV have similar effects on brain-network function as other forms of TBI, then we would expect abnormal rAI-DMN connectivity for IPV-related TBI as well.

Therefore, our goal was to test the hypothesis that severity of IPV-related TBIs would be negatively associated with intrinsic interactions between the rAI and DMN nodes. Furthermore, since rAI-DMN connectivity has been critically implicated in cognitive function, about which we had specific hypotheses from our previous work (Valera and Berenbaum 2003), we also predicted that this interaction would be associated with cognitive impairment. Finally, Sharp and colleagues demonstrated simultaneous functional (via FC) and structural (via diffusion tensor imaging; DTI) rAI-DMN connectivity abnormalities in subjects sustaining a TBI (Bonnelle et al. 2012; Jilka et al. 2014). Therefore, using DTI in the same cohort, we aimed to test the hypothesis that *structural connectivity* via white matter within the salience network would be associated with rAI-DMN functional connectivity.

To do this, for the first time, we collected clinical and neuropsychological data along with neuroimaging scans from women who have experienced IPV. Resting state scans are often used to examine patterns of synchronous activity within and between neural networks, namely functional connectivity (FC), and have been shown to be sensitive to detecting neural abnormalities subsequent to TBI (Sharp et al. 2014); as mentioned above). DTI, a measure of structural connectivity, is often used to acquire measures of fractional anisotropy (FA), an index of water diffusion in the axonal fibers suspected to be affected in diffuse axonal injury (e.g., shear and strain injury of the axons; (Shenton et al. 2012). Based on previous work demonstrating abnormal rAI-DMN FC and DTI in subjects sustaining a TBI (Bonnelle et al. 2012; Jilka et al. 2014), we took a highly focused approach. Specifically, we looked for associations among brain injury severity, cognitive functions and rAI-DMN structural and functional connectivity.

Materials and methods

Participants were 20 women recruited from women's shelters, domestic violence programs and word-of-mouth. Our study design was retrospective in nature because when working with women experiencing IPV, relying on either emergency room visits or hospital records is unsuccessful and misleading, as most women never seek medical attention for their TBIs (Banks 2007). For example, in our previous work (Valera and Berenbaum 2003), 75 % did not seek medical attention for any abuse-related injuries. In the current sample, less than half reported going to the hospital for medical attention related to any partner-induced injuries ever and all but two women failed to seek medical attention for most of the reported TBIs they sustained (see Table 1**)**. Also, as is the case with many individuals sustaining TBIs, even if they had sought medical attention, it is possible that the relevant information would not be collected (Ruff et al. 2009). Demographic characteristics of the women were as follows: mean age = 33.9 (SD = 11.6);

Table 1 Descriptive characteristics of IPV-related TBI

ID	Clinical read of T2-FLAIR	General description of IPV-related TBI history*	# of IPV- TBIs	Strang-ulation with AIC**	LOC ever (#)	PCS	Ever went to hospital?***
1	Small foci of increased T2 signal intensity in right frontal region	AICs (dizzy/disoriented/spots) 1-3x/wk for 1.5 years from being strangled, dragged, banged/punched in head/ear	> 20	No	No	No	Yes – for stitches in lip when punched in mouth
2	Ventricle enlargement with negative sulcal enlargement	AIC (stars/spots) from being punched, dragged, attempted strangulation with chain	1	No	No	Yes	Yes – after he drugged her and beat her up
3	Ventricle enlargement with negative sulcal enlargement	AIC (stars/spots) from being punched in face	1	No	No	No	No – thought she should have
4	Negative	LOC from being punched in nose; AICs (dizzy) from being shaken	3	No	Yes (1)	Yes	No – should have when punched in nose
5	Negative	AICs (dizzy/confusion) every 2 wks from hitting, shaking and strangulation for ~5 years	>20	Yes	No	Yes	Yes – for stitches 2×; should have other times as well
6	Negative	AIC (dizzy) from hits or slaps to head over a 6 month period	6–10	No	No	Yes	No – but should have after he hit her
7	Negative	LOC from head being smashed off wall and punched several times; AICs (dizzy/stars) from hits/punches to head 3-5×/wk for ~5 years; head smashed on cement, thrown down stairs	>20	No	Yes (1)	Yes	Yes – needed stitches for bleeding head after it was smashed on ground
8	Negative	AICs (dizzy) from being grabbed by neck, having head banged against wall while being strangled 0-3x/wk for 1 yr (1× felt like she was dying while being strangled)	>20	Yes	No	N/A	No -but thinks she should have when hit by car and was strangled (bruised neck)
9	Sulcal enlargement with negative ventricle enlargement	LOCs from being hit in head with baseball bat and from fall after heavy object was thrown at her; AICs (dizzy/stunned/ spots) from being slapped in head 3-4×/wk for ~3 years	>20	No	Yes (2)	Yes	Yes - when hit in head with bat
10	Ventricle enlargement with negative sulcal enlargement	LOC from head being pushed against wall; head split open when head was hit against concrete; AICs (spots/ amnesia) from being punched in face and jaw	3–5	No	Yes (1)	No	No - but thinks she should have when head was split open
11	Ventricle enlargement with negative sulcal enlargement	LOC from strangulation; AICs (dizzy/stars/spots) from head being bashed against wall/door, repeated slaps to head, pushed down stairs	>20	Yes	Yes (1)	Yes	Yes - her family took her for facial injuries; had head smashed into object; knee smashed
12	Multiple foci of increased T2 signal intensity in frontal cortical and sub-cortical white matter	LOCs from getting hit by car, severely shaken, head hitting bed frame; AICs (dizzy/ disoriented/stars) from punches to face and hits to head	>20	No	Yes (3)	No	Yes - for LOC from getting hit by car
13	Negative	LOC from head hitting wall when beat up	1	No	Yes (1)	No	No – but should have when he hit her in stomach and she blacked out
14	Increased T2 signal intensity in left calcarine cortex and white matter; Linear increase in T2 signal intensity, left centrum	AIC (dizzy) from head hitting against wall while being strangled	1	Yes	No	No	No - but thinks she should have
15			1	No	No	Yes	Yes - for scratches, sore, bruised

Table 1 (continued)

ID	Clinical read of T2-FLAIR	General description of IPV-related TBI history*	# of IPV- TBIs	Strang-ulation with AIC**	LOC ever (#)	PCS	Ever went to hospital?***
	Ventricle enlargement with negative sulcal enlargement	AIC (dizzy/stars) from hard slap/hit to head; then strangled, dragged across the ice/snow					
16	Increased T2 signal intensity in cortical white matter junction and superior frontal gyrus (classic trauma spot)	LOC from punch to back of head; AIC (dizzy/amnesia) from strangulation and punch to face	3–5	Yes	Yes (1)	Yes	No
17	Innumerable punctate foci of increased T2 signal intensity in frontal and parietal regions; ventricle and sulci enlargement	LOCs from hitting head and strangulation; AIC from being hit in the head 2×/month for 1.25 yrs	>20	Yes	Yes (2)	Yes	Yes - for collapsed lung, hit in face with hammer, when strangled
18	Several foci of increased T2 signal intensity in frontal subcortical white matter and right temporal regions (looks like trauma)	AIC (dizzy) from punches to head 1-3x/week for 2 yrs	>20	No	No	Yes	No - because no bleeding
19	Ventricle and sulcal enlargement	AICs (dizzy) from hard slaps to face over the course of 5–6 yrs	>20	No	No	Yes	No- thinks maybe she should have, may have broken finger
20	Several foci of increased T2 signal intensity in frontal regions	LOCs after being thrown down stairs, kicked in face with boot; AICs (dizzy/stars/spots) punched repeatedly in face on and off for period of 8 yrs	>20	No	Yes (20+)	Yes	Yes - for LOC from being run into by partner

IPV intimate partner violence, *TBI* traumatic brain injury, *AIC* alteration in consciousness (dizzy = feeling dizzy, stars/spots = seeing stars or spots, disoriented = feeling disoriented), *LOC* loss of consciousness, *PCS* endorsed at least 3 symptoms from the Post-concussive Symptom Questionnaire as being worse after sustaining the last TBI, *Ever went to hospital* After anything your partner ever did to you did you ever have to go to the hospital? Did you ever feel that you should have gone to the hospital even if you didn't go to the hospital?

*It should also be noted that these are only TBI-related abusive incidents. These do not include other abusive incidents that did not result in a TBI

**There were numerous other reports of strangulation for a number of these women. However, for the purposes of this table, only strangulations reportedly resulting in an AIC (and reported in response to AIC questions per the TBI definition) are indicated in the "Strangulation with AIC" column. Some women reported AICs following incidents during which they had their heads hit and were strangled simultaneously (e.g., Head was slammed against the wall while they were being strangled)

***This includes reports of going to a hospital for any abusive incident (not limited to going for a suspected TBI; reason for hospital visit is listed)

50 % African American, 35 % Caucasian, 5 % Latina, 10 % mixed race. Six other women were enrolled but did not have resting-state scans. Women needed to report at least one incident of physical abuse to be included in the study.

Women were initially phone screened and excluded for a range of conditions that could confound results or make the women ineligible (e.g., alcohol or drug dependence within the past six months, current bipolar disorder or schizophrenia, autoimmune disorders such as lupus, current pregnancy). Women with histories of non-partner related mild TBI within the past three months or a moderate to severe non-partner related TBI ever were excluded. Also, any women with questionable alcohol or substance use ($N = 4$) and/or who were taking psychotropic or anticonvulsant medication ($N = 3$; see Online Resource for more details) were noted, and functional connectivity analyses were conducted both with and without those women included. Participants provided written informed consent and the local ethics committee approved the study. The study was conducted in one session and the brain injury interview was always administered before cognitive testing which was always administered before scanning.

Measures

Brain injury As has been done previously (Valera and Berenbaum 2003), history of non-partner and partner-related TBI was assessed using a semi-structured interview in which participants were asked questions in accord with the diagnostic criteria for Mild TBI by the American Congress of Rehabilitation Medicine Special Interest Group on Mild TBI (Committee on Mild Traumatic Brain Injury, American Congress of Rehabilitation Medicine 1993). Specifically, a TBI was defined as: "A traumatically induced physiological disruption of brain function, as manifested by at least one of the following: any loss of consciousness; any loss of memory for events immediately before or after the accident; any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); focal neurologic deficit(s) that may or may not be transient." It should be noted that, under this definition, alterations in consciousness (AICs) following strangulation-induced anoxia or hypoxia are considered TBIs. Therefore, subjects were asked about possible AICs following abuse-related potential traumas to the brain; a standard approach used in clinical practice. Specifically, they were asked about periods of dizziness, seeing stars and spots, being stunned or disoriented, blacking out/loss of consciousness, or sustaining post-traumatic amnesia (memory loss surrounding an incident). For example, "After anything that your partner has ever done to you, have you ever lost consciousness or blacked out?" If subjects reported AICs, they were asked about the conditions of the incident, duration of AIC, when the last and first times AICs occurred and on how many occasions. Also according to the committee guidelines, (Committee on Mild Traumatic Brain Injury, American Congress of Rehabilitation Medicine 1993) for reports of loss of consciousness and post-traumatic amnesia, brain injury was considered mild if the loss of consciousness was ≤30 min and/or the post-traumatic amnesia was ≤24 h. A brain injury severity score based on number, recency and severity of AICs was generated identically to that of previous work (Valera and Berenbaum 2003); see Online Resource Methods). Data were also acquired for non-partner related AICs to assess for non-partner-related TBI exclusion criteria.

It should be noted that there is no one universally accepted definition of TBI. However, we chose this definition for two reasons: 1) to maintain consistency and reproducibility with the only previously published work we are aware of that systematically examined prevalence and correlates of IPV-induced TBI; and 2) this is a long established definition (since 1993) that has more recently been essentially endorsed by the WHO's Collaborative Center Task Force on Mild Traumatic Brain Injury (Carroll et al. 2004). Although strangulation-induced AICs technically fall under this definition, we recognize the potential uncertainty of neural effects of anoxia - and hypoxia - induced AICs resulting from strangulation. We also recognize that a general description of the number and nature of TBIs in IPV has not been systematically examined and published previously. Therefore, we have provided descriptive information on IPV-related TBI history including whether there was a history of strangulation induced AICs (Table 1). There were no women for whom their only AIC resulted solely as a consequence of being strangled. There was one woman whose only AIC occurred after her head was hit against the wall while being simultaneously strangled. Finally, for exploratory purposes, we also examined the relationship between functional connectivity (as described below) and both frequency and recency of partner-related TBI separately (See Online Resource).

Post-concussive symptoms (PCSs) To assess for the presence and severity of possible current post-concussive symptoms, we administered the Rivermead Post Concussion Symptom Questionnaire, (King et al. 1995; Potter et al. 2006) a commonly used 16-item questionnaire, to assess for emotional, cognitive and behavioral symptoms following a TBI. Although many PCS symptoms are frequently observed in the general population, we used the Rivermead Post Concussion Symptoms Questionnaire to acquire these data. In the Rivermead, information is obtained regarding the presence of post-concussive symptoms both immediately after the TBI and also "now" (i.e., at the time of the interview), *relative to before the TBI*. Therefore, responses to the Rivermead items should not reflect symptoms that the individual had been experiencing prior to suffering a TBI. (One woman could not reliably report symptoms immediately following the TBI for the Rivermead since she suffered from many of the

symptoms since her childhood. Thus, we excluded her post-concussive data from analyses.) We report data for post-concussive symptoms experienced "currently" at the time of the interview.

Cognition A brief neuropsychological battery sensitive to TBI was administered. Here, we sought to replicate previous findings linking brain injury severity with memory, learning and cognitive flexibility (Valera and Berenbaum 2003). Variables of interest were the California Verbal Learning Test (CVLT) sum of trials 1–5 and long-delay free-recall, as well as Trails-B completion time (see Online Resource).

Other questionnaires To help rule out the possible confounding effects of partner abuse severity, depression, anxiety, post-traumatic stress disorder (PTSD) symptomatology or childhood abuse, we also administered a modified version of the Conflict Tactics Scale, the Mood and Anxiety Symptom Questionnaire, the Clinician Administered PTSD Scale for DSM-IV- One Week Symptom Status Version and the Childhood Trauma Questionnaire (see Online Resource for details).

Neuroimaging scans

Resting-state and diffusion scans

Participants underwent 6 min of resting-state fMRI on a 3-Tesla Siemens Magnetom TrioTim scanner with a 32-channel head coil. Prior to the resting state fMRI, subjects were instructed to keep their eyes open and stay as still as possible and that they did not need to think about anything in particular. The fMRI acquisition parameters were as follows: TR = 3 s; TE = 30 ms; flip angle =85°; FoV = 216 mm; 47 slices; interleaved acquisition; voxel size: 3 × 3 × 3 mm. A diffusion-weighted imaging scan was acquired with the following parameters: 68 slices per volume; 1.9 × 1.9 × 1.9 mm^3 voxels; b = 700 s/mm^2; 60 diffusion-encoding directions; 10 non-diffusion-weighted B0 images; TE = 82 ms; TR = 7640 ms). A high-resolution T1 anatomical scan was also acquired for coregistration purposes: TR = 2.53 s; flip angle =7°; 176 slices; FoV = 256 mm; voxel size: 1 × 1 × 1 mm.

Resting-state fMRI preprocessing

Data were preprocessed with similar procedures to those reported previously (Kucyi et al. 2013; Kucyi et al. 2015). Resting state fMRI data were preprocessed with a combination of softwares: FMRIB Software Library (FSL) v5.0.7, (Jenkinson et al. 2012) MATLAB R2013b (Mathworks, Natick MA), and fMRISTAT (Worsley et al. 2002). First, using FSL's FEAT, we performed motion correction (MCFLIRT), brain extraction (BET) and linear registration (FLIRT) among fMRI, T1 anatomical, and standard MNI152 ($2mm^3$ resolution) spaces. Using FSL's FAST, we segmented the T1 image into white matter, cerebrospinal fluid, and gray matter volumes. We registered the white matter and cerebrospinal fluid partial volume maps to fMRI space and applied thresholds to retain only the top 198 cm^3 (white matter) and 20 cm^3 (cerebrospinal fluid) with highest values. Following aCompCor procedures for removal of physiological- and scanner-related noise (Behzadi et al. 2007; Chai et al. 2012), we applied principal components analysis to the fMRI data within retained white matter and cerebrospinal fluid voxels (each separately). We regressed the top 5 white matter components, top 5 cerebrospinal fluid components, and 6 motion parameters obtained with MCFLIRT out of the fMRI data. Finally, we performed spatial smoothing (6 mm full-width half-maximum kernel) and bandpass temporal filtering (0.005–0.05 Hz; main results remained consistent when using 0.01–0.08 or 0.01–0.1 Hz ranges that are common in the field).

Resting-state fMRI analysis

To assess intrinsic resting-state networks, we used a seed-based connectivity analysis, in which a region of interest (the seed) is defined, its time-course of fluctuating activity is extracted, and the rest of the brain is searched for regions showing correlated activity with the seed (Fox and Raichle 2007). The seed region was defined as a 6 mm-radius sphere in the rAI centered on Montreal Neurological Institute (MNI152) coordinates (x = 36, y = 24, z = −6) reported to have altered functional and structural connectivity with the DMN in previous TBI studies (Bonnelle et al. 2012; Jilka et al. 2014). To register the rAI seed region from standard (MNI152) space to native subject space, the linear transform obtained from FLIRT was used. For each subject, the mean time-course across voxels within the rAI seed was entered as a regressor to obtain a functional connectivity map. General linear model regressions were used to estimate rAI functional connectivity with all other brain regions using the FSL (Jenkinson et al. 2012).

Since our objective was to test for *a specific relationship between* brain injuries and neural (and cognitive) function independent of other potential confounds, a series of regression analyses were performed next. Maps were submitted to a second-level general linear model in which group-level functional connectivity with the rAI was calculated and in which the demeaned brain injury score was entered as a regressor. All group-level statistics were conducted with FMRIB's Local Analysis of Mixed Effects (FLAME 1 + 2) and significance set at cluster-determining threshold of $Z > 2.3$ (corresponding to $p < 0.01$) and cluster-based $p < 0.05$ (family-wise error corrected for voxels across the whole brain). Notably, a recent

report suggests that this cluster-determining threshold combined with FLAME 1, in some cases, can still result in an unacceptable false positive rate of >5 % (although the authors do not report on FLAME1 + 2), while increasing the threshold to $p < 0.001$ is highly conservative and may lead to false negatives (Eklund et al. 2016). Thus to improve confidence in our main analysis (testing the association between brain injury score and connectivity), we performed a supplementary analysis in which we slightly increased the cluster-determining threshold to $Z > 2.5$ (corresponding to $p < 0.006$). To account for a possible impact of current/recent substance and medication use, we performed the main general linear model analysis with demeaned brain injury scores entered as a regressor and removal of a) the 4 subjects with potential substance use confounds; and b) the 3 subjects currently using prescribed psychotropic or anticonvulsant medications. Additionally, to account for a possible impact of anoxic or hypoxic brain injury, we re-conducted the main general linear model analysis with the presence of strangulation-induced anoxic or hypoxic brain injury (in 6 subjects) entered as a confounding variable of no interest.

We conducted additional control analyses to assess specificity and validity of relationships between rAI functional connectivity and the brain injury score. We reasoned that if the relationship between rAI functional connectivity and TBI were, as we would predict, independent of demographic factors, other abuse factors, psychological factors that either preceded or were a cause of TBI, or technical factors at the time of the scan (head motion), the relationship would hold even when controlling for these and other potentially confounding variables. Thus, second-level general linear models (as described above) were repeated with demeaned brain injury scores as well as demeaned values each for age, mean relative frame-wise head displacement (motion), partner abuse severity within the past year, mood and anxiety symptoms, childhood trauma, and PTSD scores as regressors. We also conducted partial correlations between brain injury scores and mean rAI functional connectivity with averaged voxels within any clusters significant in the whole-brain analysis, controlling for each of the aforementioned variables. For the head motion analysis, we focused on controlling for mean relative head displacement because this metric has specifically been shown to bias functional connectivity estimates (Power et al. 2015).

In follow-up analyses, we assessed whether brain regions whose functional connectivity with the rAI showed a significant relationship with brain injury severity were linked to individual differences in cognitive performance. Our previous work demonstrated negative associations between the partner-related brain injury score and memory, learning and cognitive flexibility as measured by CVLT sum of trials 1–5, CVLT long-delay free-recall and Trails-B (Valera and Berenbaum 2003). Therefore, we tested whether these three scores correlated with either brain injury severity or the mean rAI functional connectivity in any clusters that were significant in the brain injury score whole-brain analysis. We predicted negative correlations between brain injury severity and cognitive performance (Valera and Berenbaum 2003), and positive correlations between functional connectivity (that was negatively correlated with brain injury severity) and cognitive performance; we report two-tailed Pearson's correlation r and p-values for these analyses. Due to a subject outlier, Spearman's rank was used for correlations of Trails-B with rAI connectivity and the brain injury score.

Diffusion MRI preprocessing and analysis

Using FSL, diffusion images were preprocessed with motion correction, eddy current correction and brain extraction. Images were then transformed to T1-weighted image and MNI152 standard space using linear registration (FLIRT, six degrees-of-freedom). Fractional anisotropy (FA) was calculated in voxels within white matter using the tract-based spatial statistics (TBSS) approach (Smith et al. 2006). A weighted least-squares approach was used to generate FA maps. The FA maps were transformed to the FMRIB58_FA standard template via non-linear registration (FNIRT) and averaged across subjects. To isolate voxels specific to whiter matter, a "skeleton" representing the common center of tracts across subjects was created. The skeleton was thresholded at FA > 0.2, and peak FA values in voxels perpendicular to the skeleton within each subject were projected onto the skeleton for group analysis.

In a previous study, the degree of functional connectivity during cognitive performance between the rAI and DMN in TBI was associated with FA within a white matter tract connecting the rAI with mid-cingulate/pre-supplementary motor area (a tract within the salience network; (Jilka et al. 2014)). As we found a relationship between resting-state rAI-DMN functional connectivity and the brain injury score (see Results), we aimed to assess whether this functional connectivity was also associated with FA within the salience network. The authors of the previously described TBI study shared with us the image of the white matter tract connecting the rAI with the mid-cingulate/pre-supplementary motor area from their study (Jilka et al. 2014). We masked this image with the white matter skeleton obtained from TBSS and calculated mean FA within the tract. We then correlated mean tract FA values with mean rAI functional connectivity with a cluster within the DMN that had a significant relationship with the brain injury score. (Redoing this analysis without masking with the white matter skeleton, as done by Jilka et al., did not change the results).

T2-weighted-fluid-attenuated inversion recovery (T2-FLAIR) and susceptibility-weighted imaging (SWI) scans

For descriptive and exploratory analyses only we acquired structural T2-FLAIR and SWI scans. There is an abundance

of data indicating that standard structural imaging scans such as the T2-FLAIR often lack the sensitivity to detect brain abnormalities that result from the types of mild TBIs typically sustained during IPV (Shenton et al. 2012). Nonetheless, given the potentially unique nature of IPV-related TBIs, we acquired such scans for review by a neuroradiologist. We also collected SWI scans that tend to be sensitive to microhemorrhages that result from shear injuries (Benson et al. 2012) likely sustained by women experiencing IPV. The T2-FLAIR parameters were as follows: TR = 6 s; 176 slices; FoV = 256 mm; voxel size: 1 × 1 × 1 mm. The SWI parameters were: TR = 28 ms; 96 slices; FoV = 220 mm; voxel size: .5 × .5 × 1.5 mm (20 % distance factor).

Results

Incidence of partner-related brain injury

All the women in this sample reported at least one partner-related TBI and 75 % reported multiple TBIs. These rates are consistent with the hypothesis that TBIs are highly prevalent in women who have experienced IPV. Of these women, five reported anoxic or hypoxic effects from being strangled in addition to other partner-related TBIs, and one woman reported sustaining her only AIC as a result of being strangled while simultaneously having her head hit into a wall (Table 1). Additional women reported being strangled, but unless an AIC was also reported, this was not considered a TBI.

Post-concussive symptoms

The mean number of PCSs currently reported across women in this sample was 5.3 symptoms. All but two women (89 %) reported at least one current post-concussive symptom subsequent to her most recent TBI. Although there is more than one accepted definition of "post concussive syndrome" or "postconcussional disorder", at least two definitions (World Health Organization 1992; American Psychiatric Association 2000) require the presence of at least three symptoms. In this sample, 63 % of the women reported experiencing at least 3 of the 16 possible post-concussive symptoms. Excluding mood-related symptoms (i.e., being irritable or easily angered, feeling depressed or tearful, feeling frustrated or impatient) that theoretically could also be related to the partner conflict at the time of the TBI rather than the TBI per se, the mean number of symptoms was 3.7 with 53 % of the women experiencing at least 3 of the 13 possible symptoms. For each woman, most of the reported symptoms were spread across domains of functioning (i.e., emotional, cognitive and behavioral), in contrast to reporting several symptoms in just one domain. The most commonly reported symptom was "feeling depressed or tearful" (reported by ~58 % of the women) followed by "headaches" (~53 %), "being irritable, easily angered", "feeling frustrated or impatient" and "restlessness" (each ~47 %), "poor concentration" (~42 %) and "sleep disturbance", "forgetfulness, poor memory", and "taking longer to think" (reported by ~37 %). (See Table 1.)

Resting-state functional connectivity linked with partner-related brain injury

As expected, the rAI exhibited functional connectivity with numerous regions known to comprise the salience network, including: bilateral anterior insula, mid-cingulate cortex, dorsolateral prefrontal cortex, and temporoparietal junction (Fig. 1a; Kucyi et al. 2012; Seeley et al. 2007). Consistent with our TBI-related predictions, the brain injury score showed a negative correlation with rAI functional connectivity to a cluster in the posterior cingulate cortex/precuneus (PCC/PCu), a hub of the DMN (Fig. 1b, c). The association with this PCC/PCu cluster remained significant when we conservatively increased the cluster-determining threshold to $Z > 2.5$ (instead of the default $Z > 2.3$).

Specificity and validity of functional connectivity relationships with brain injury

In whole-brain analyses testing for relationships between rAI functional connectivity and brain injury severity, similar clusters in the PCC/PCu were obtained when controlling each for age, head motion, partner abuse severity within the past year, childhood abuse, depression, anxiety and PTSD symptomatology. In Table 2, we report partial correlation values for the relationship of rAI-PCC/PCu functional connectivity with brain injury severity, controlling for each of these variables. Supporting specificity and validity of the identified relationship between brain injury severity and rAI functional connectivity, partial correlations were all significant. When removing subjects with potential current substance-use confounds, the PCC/PCu cluster remained significant and additional clusters in other DMN regions (right lateral parietal cortex, retrosplenial cortex) were significant as well (Online Resource Fig. 1). The PCC/PCu cluster also remained significant when removing subjects using medications (Online Resource Fig. 2). These findings indicate that heavy substance use, recent past dependence, or psychotropic or anticonvulsant medications were not accounting for the observed effects. Furthermore, when controlling for potential strangulation-induced anoxic or hypoxic brain injury, the PCC/PCu cluster remained significant (Online Resource Fig. 3).

Cognitive performance correlates with brain injury-related functional connectivity

The correlations among performance on three cognitive measures (CVLT sum of trials 1–5 and long-delay free-

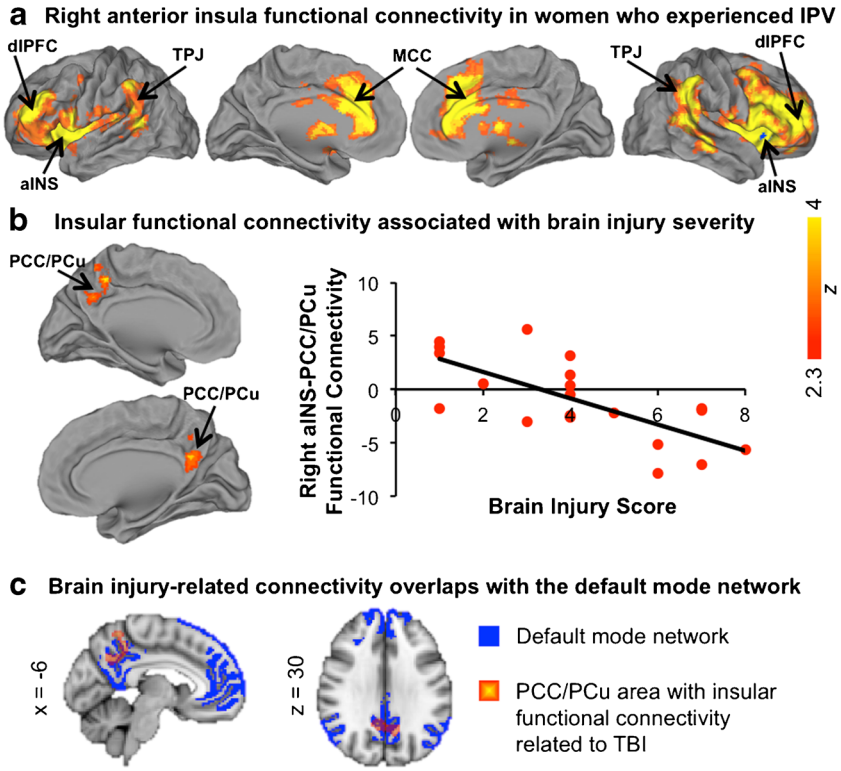

Fig. 1 Resting-state functional connectivity relates to brain injury severity in women with partner-related TBI. **a** Whole-brain group-level map of regions showing functional connectivity with a seed region in the anterior insula (shown in blue). **b** A cluster in the posterior cingulate cortex/precuneus showing functional connectivity with the anterior insula that significantly correlates with the brain injury score. The plot shows the brain injury score versus functional connectivity (contrast of parameter estimate values) averaged across voxels in the significant cluster. **c** An overlay of the posterior cingulate cortex/precuneus cluster (shown in b as red/yellow) on a map of the default mode network (blue), as defined independently in 1000 healthy individuals (Yeo et al. 2011), demonstrates that the cluster was largely confined to this default mode network. All maps are shown in Montreal Neurological Institute (MNI152) standard space, projected onto the cortical surface with the Computerized Anatomical Reconstruction Toolkit, with a significance threshold of $Z > 2.3$ and cluster-based $p < 0.05$, corrected for multiple comparisons across all voxels of the brain using the family-wise error rate. IPV = intimate partner violence; aINS = anterior insula; dlPFC = dorsolateral prefrontal cortex; MCC = mid-cingulate cortex; PCC = posterior cingulate cortex; PCu = precuneus; TPJ = temporoparietal junction

Table 2 Partial correlations for relationships between the brain injury score and resting state functional connectivity between the right anterior insula (of the salience network) and posterior cingulate cortex/precuneus (of the DMN), controlling for age, head motion during resting state fMRI scanning (mean relative head displacement), partner abuse severity within the past year, Childhood Trauma Questionnaire, Mood and Anxiety Symptom Questionnaire and Clinician Administered PTSD Scale scores

	Partial correlation: BI score and rAI-PCC/PCu functional connectivity	
Controlling for:	*r*	*p*
Age	-0.72	0.001
Head motion	-0.71	0.001
Partner abuse severity	-0.61	0.006
CTQ	-0.72	0.001
MASQ	-0.73	0.0004
CAPS	-0.72	0.0005

CTQ Childhood Trauma Questionnaire, *MASQ* Mood and Anxiety Symptom Questionnaire, *CAPS* Clinician Administered PTSD Scale. *BI score* brain injury score, *rAI-PCC/PCu* right anterior insula - posterior cingulate cortex/precuneus

recall and Trails-B), brain injury severity and rAI-PCC/PCu functional connectivity are summarized in Table 3. *Right anterior insula-PCC/PCu* functional connectivity positively correlated with both of the CVLT scores (Fig. 2). These relationships remained, with nearly identical correlations, when presence of a strangulation-induced anoxic or hypoxic incident were removed (r's = .46 and .45 for CVLT sum of trials 1–5 and long-delay free-recall respectively, p's = .05). *Brain injury severity* showed a numerically stronger negative correlation with CVLT sum of trials 1–5 ($r = -.40$), than was reported previously ($r = -.33$; (Valera and Berenbaum 2003)). However, likely due to the smaller sample size, the effect fell just short of statistical significance when reporting two-tailed p-values. There was no significant correlation of Trails-B score with brain injury severity or with rAI-PCC/PCu functional connectivity. Notably however, one woman, with the maximum brain injury score of 8, was excluded from the analysis of Trails-B as she was unable to successfully perform the task.

Table 3 Correlations for relationships among cognitive scores, brain injury score, and resting state functional connectivity between the right anterior insula and posterior cingulate cortex/precuneus. One subject (with a high brain injury score) was unable to learn and complete Trails-B resulting in an N = 19. Pearson's correlations were used to examine the relationship of CVLT variables with right anterior insula and posterior cingulate cortex/precuneus connectivity and the brain injury score. Due to a subject outlier, Spearman's rank was used for correlations of Trails-B with the right anterior insula and posterior cingulate cortex/precuneus connectivity and brain injury score

	Trails-B		CVLT sum of trials 1–5		CVLT long-delay free-recall	
	ρ	p	r	p	r	p
rAI-PCC/PCu functional connectivity	.12	.63	0.44	0.05	0.45	0.05
Brain injury score	-.09	.71	-0.40	0.08	-0.23	0.34

rAI-PCC/PCu right anterior cingulate-posterior cingulate cortex/precuneus, *CVLT* California Verbal Learning Test

Diffusion MRI results

Across subjects, there was no significant correlation between resting-state rAI-PCC/PCu functional connectivity and FA in the tract connecting the rAI with the mid-cingulate/pre-supplementary motor area ($r = 0.11$, $p = 0.65$).

Clinical reads of T2-FLAIR and SWI scans

Descriptions of the clinical reads of the T2-FLAIR scans are reported for each subject in Table 1. Consistent with what is frequently found when examining structural scans for signs of mild TBIs (Hammoud and Wasserman 2002), a number (five) of the scans appear unremarkable with no apparent abnormalities. However, findings from other scans suggest signs of trauma, whereas other notable findings are non-specific (i.e., could be trauma or something else). No abnormalities or microhemorrhages were noted on any of the SWI scans.

Discussion

Despite some awareness that brain injuries are a common consequence of IPV, brain injuries and their associated cognitive impact on affected women are typically ignored. Here, we show associations between partner-related TBI severity and neural network interactions that are also associated with indices of memory and learning. This is the first study to systematically examine and provide mechanistic evidence of brain injury in women sustaining partner-related TBI.

We showed here that greater TBI severity resulting from IPV is associated with resting-state functional connectivity of cognitive brain networks, specifically less positive/more negative connectivity between two networks known to be involved in one's ability to rapidly switch behavior. Critically, this relationship between TBI and brain-network connectivity was not accounted for by partner-abuse severity, childhood trauma, psychopathology, current or recent substance dependence, or medication use, suggesting a specific effect of TBI on cognitive brain network reorganization. This finding is consistent with our previous work (Valera and Berenbaum 2003) showing that the relationship between brain injury severity and cognitive functioning was not accounted for by these other factors in a different sample of women who had sustained IPV-related TBIs. We build on those findings here, including neuroimaging measures in our analyses. In this current study, we also show that less positive/more negative coupling of specific cognitive brain networks was associated with poorer cognitive performance on tasks that engage memory and learning.

TBI and DMN-salience network interactions

Recent neuroimaging studies, primarily involving diffusion MRI and resting-state fMRI, have emphasized the importance of altered structural and functional connectivity in large-scale brain networks to TBI and its associated cognitive deficits. The DMN, anatomically the largest intrinsic brain network (Power et al. 2013), has received overwhelming attention,

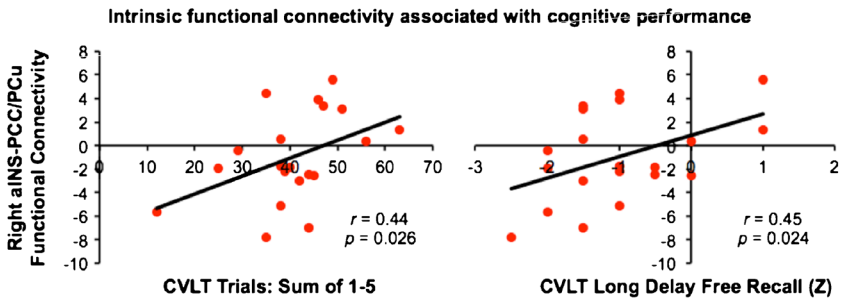

Fig. 2 Resting-state functional connectivity relates to cognitive performance in women with partner-related TBI. Across 20 subjects, average functional connectivity between the right anterior insula and voxels within the posterior cingulate cortex/precuneus that were negatively correlated with brain injury scores (see Fig. 1) are plotted against individual scores on the California Verbal Learning Test sum of trials 1–5 and long-delay free-recall. aINS-PCC/PCu = anterior insula -posterior cingulate cortex/precuneus; CVLT = California Verbal Learning Test

likely because DMN function is broadly associated with cognition in health and in a wide range of brain diseases (Anticevic et al. 2012; Leech and Sharp 2014; Whitfield-Gabrieli and Ford 2012). Disrupted DMN structural and functional connectivity has been found in many TBI populations (Mayer et al. 2011; Nathan et al. 2015; Palacios et al. 2013; Venkatesan et al. 2015), and DMN abnormalities in TBI have been linked with cognitive performance (Bonnelle et al. 2012; Kim et al. 2009; Sharp et al. 2011).

However, the DMN does not function in isolation and is not likely the only network damaged in cases of TBI. The study of interactions with other cognitive networks, including the salience network, may give a more comprehensive mechanistic account of the cognitive impact of TBI. In line with previous studies (Bonnelle et al. 2012; Jilka et al. 2014), we show that interactions of the rAI of the salience network with the DMN are linked with TBI and its cognitive effects. Our findings may be interpreted in the context of work by Jilka et al. (2014), who showed reproducibly in two cohorts that healthy individuals have increased interactions of rAI with the DMN during sudden changes in behavior; such increases, however, were not found in TBI patients. Individuals with lower, or negative, intrinsic rAI-DMN functional connectivity (e.g., women with greater brain injury severity examined here) may have a reduced capacity to engage cross-network interactions that are needed for efficient cognitive performance. Supporting this notion, we found that less positive/more negative rAI-DMN functional connectivity was associated with poorer performance on tasks that engage memory and learning.

Clinical implications

Brain-based therapeutic interventions for TBI are typically absent for women who experience IPV, in part because there is limited general awareness that partner-related TBI even occurs. Additionally, there is currently no gold-standard to definitively rule in-or-out the presence of TBIs (especially mild ones) using MRI. However, our TBI assessment and examination of brain-network interactions revealed associations between brain injury severity-linked functional connectivity and cognitive functions. Examining network interactions in women sustaining partner-related TBIs as we have done here provides useful information in characterizing a woman's abuse that may be used in future research and possibly considered in the context of treatment and predicting cognitive outcomes. For example, IPV advocates and healthcare workers should consider the possibility of TBI-related cognitive sequelae in the context of IPV interventions. If the occurrence of one or multiple TBIs is identified in the context of apparent cognitive or post-concussive symptoms, a neuropsychological assessment should be offered (consistent with standard practice for non-partner-related TBIs). Consequently, if results suggest impairment, neurorehabilitation designed for IPV should be considered in the treatment plan (Banks 2013; Murray et al. 2016). As indicated earlier, neuroimaging may have limited utility in assessing such TBI cases since imaging scans often lack the sensitivity to detect brain abnormalities that result from the types of mild TBIs typically sustained during IPV (Shenton et al. 2012) as demonstrated here with our own data (See Table 3). However, on an individual basis, neuroimaging may be appropriate and should be considered, consistent with procedures typically used for non-partner-related TBIs. Future research should certainly be carried out to help clarify the utility, cost-effectiveness, and impact of individualized neuroimaging assessment on subsequent service-delivery and IPV survivors' quality-of-life. Also, clinical treatments targeting interactions between these networks, either through cognitive training or possibly non-invasive neurostimulation (Demirtas-Tatlidede et al. 2012) could prove effective for improving cognitive abilities of women with partner-related TBI. Recent advances characterizing the molecular mechanism of repetitive TBI suggest that cognitive impairment and neurodegeneration may be prevented with effective treatment if TBI is detected early (Kondo et al. 2015). Changes in intrinsic brain-network activity, possibly a downstream effect of such molecular changes due to TBI, can track TBI severity and its associated cognitive impact, and thus could be monitored for early TBI detection to guide treatment.

Limitations

While we feel this study produces credible results of strong importance, this should be viewed as a preliminary study providing a call for much needed additional research in this area. In this study, we chose to examine the relationship between TBI severity and functional connectivity within a group of women sustaining IPV-related TBI, rather than acquiring a control group of women who had never sustained TBI. Although this allowed us to answer our primary questions of interest, there are other questions that could be addressed with a control group of women who have never sustained partner-related TBIs. Given the varied backgrounds, abuse histories and potential comorbidities of women in the study, the identification of a valid control group would be a major challenge but should be addressed in future work.

We used a retrospective design to acquire TBI information. Ideally, it would be possible to obtain fully validated information on TBI history either at the time of injury or by obtaining medical records. However, as noted earlier, most women did not seek medical attention and if they did, it was often for non-TBI related injuries and certainly not for all TBIs (in part because women are not always aware they are sustaining TBIs or their partners prevent them from seeking medical attention). Therefore, relying on such information would result in inaccurate and incomplete data with a high rate of false

negatives, likely from a nonrepresentative sample of the women sustaining partner-related TBIs. Nonetheless, a possible concern could be that women sustaining TBIs would have memory deficits for the data we are requesting. However, there is no reason to suspect that there would be a systematic misremembering of AICs such that women would recall a greater number of AICs with poorer cognitive performance and lower rAI-DMN functional connectivity. If anything, having a poor memory should make these effects more difficult to detect rather than generating false positives.

Another limitation in our work is the small sample size. As we correlated individual differences with TBI severity using whole-brain voxelwise analyses in 20 participants, our study lacked the power to detect potential small- or moderate-sized effects (Yarkoni 2009). There was heterogeneity across our subjects in types and sequelae of brain injuries sustained. Although we summarized severity by calculating a brain injury score, it remains unknown how and to what degree specific injury types may have contributed to variability across individuals and our observed effects. Future studies acquiring larger samples affording power to detect more subtle effects will be important to conduct going forward. Recruitment of women with IPV-related TBI for neuroimaging studies remains a challenge, but increased public awareness and support for research in this area could enable large-scale studies.

Future directions

Much work is needed to better characterize the neural mechanisms by which partner-related TBI may lead to cognitive impairment and psychopathology. While our work suggests a key role of DMN-salience network interactions in partner-related TBI and its cognitive effects, neuroimaging studies in other TBI populations have shown that activity and connectivity of other networks is also related to clinical and behavioral effects and outcomes (Kasahara et al. 2011; Shumskaya et al. 2012; Stevens et al. 2012; Turner and Levine 2008). Additional research examining within and between network connectivity and its relationship to IPV-related TBI is still needed. Additionally, it will be critically important for future work to examine the potential long-term impact of these repetitive brain traumas in light of evidence that they could lead to significant neurodegenerative changes such as tauopathies (Kondo et al. 2015).

Impact summary

Women typically do not seek medical attention for and/or are unaware that they have sustained IVP-related TBIs. Our data not only shed light on the mechanisms of the largely ignored issue of IPV-related TBI, but they also provide women a reason/mechanism for their cognitive difficulties. This is turn, may motivate women to seek treatment so that they can recover and possibly save their own lives.

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Compliance with ethical standards

Disclosure of potential conflicts of interest The authors report no conflicts of interest.

Research involving human participants and informed consent Participants provided written informed consent and the local ethics committee (Partners IRB) approved the study.

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