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The severity and role of somatic depressive symptoms in psychological networks in a longitudinal sample of peripartum women

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ABSTRACT

The inclusion of somatic symptoms in assessing peripartum depression (PPD), which encompasses depression during pregnancy and the postpartum period, has remained controversial, as there is substantial overlap between somatic depression symptoms and normal features of pregnancy/postpartum. This study examined whether trajectories differed by PPD symptom subscale and whether PPD symptom networks changed as a function of the peripartum phase. 418 women with a history of neuropsychiatric illness participated in a longitudinal observational study, completing symptom questionnaires assessing affective, cognitive, and somatic symptoms throughout pregnancy and the first year postpartum. Assessments were grouped into five peripartum phases: three trimesters of pregnancy and early/late postpartum. Two analyses were performed. First, a series of multilevel spline regression models examined depression subscale trajectories over peripartum phase. Second, symptom networks and related metrics were estimated for each peripartum phase and compared. Somatic symptoms were most severe and had the most variable peripartum trajectory. The role of somatic symptoms within the networks also changed as a function of peripartum phase. Our results suggest that somatic symptoms can be severe and may play a crucial role in the maintenance of PPD. Thus, somatic symptoms should not be disregarded when assessing for PPD in obstetrical, psychiatric, and pediatric clinics, and clinical research.

1. Introduction

In the American ethos, pregnancy and motherhood are romanticized as transformative experiences characterized by joy. Research indicates, however, that the period during and following pregnancy (collectively known as the "peripartum period") is a complex time in a woman's life that leaves her vulnerable to psychiatric illness. Depression is perhaps the most common peripartum disorder; prevalence rates are 10–15% among pregnant or postpartum women (Gaynes et al., 2005).

Depression, peripartum or not, includes affective, cognitive, and somatic symptoms (Manian et al., 2013). There is considerable overlap between somatic symptoms of depression and sequelae of comorbid physical conditions. This overlap muddies the root cause of somatic symptoms, and may result in these symptoms being overlooked. However, in a variety of conditions, somatic depressive symptoms are critical diagnostic and prognostic indicators. For example, in primary care settings, depression is often under-detected among patients with physical complaints and pain because these physical symptoms are not recognized as potential somatic presentations of depression (Menchetti et al., 2009). Furthermore, in older adults with medical comorbidities, assessing somatic symptoms is key to the detection of depression (Drayer et al., 2005). These studies and others underscore the important contribution of somatic symptoms in the phenomenology of depression among patients with physical comorbidities.

It follows then that assessing the overlapping depression/peripartum-related somatic symptoms such as energy loss, fatigability, sleep disturbances, appetite change, and libido change may be similarly vital. This is supported by research suggesting that women

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with peripartum depression (PPD) experience high levels of somatic symptoms across the peripartum period (Bernstein et al., 2008; Kelly et al., 2001; Yonkers et al., 2009). Further, women reporting somatic symptoms during pregnancy are at increased risk for postpartum depression (Chaudron et al., 2001).

It is unclear, however, whether peripartum somatic symptoms are reliable indicators of the depressive syndrome or natural by-products of peripartum physiological change (Klein and Essex, 1994). Prior work suggests that assessment of somatic symptoms may lead to inflated prevalence estimates of PPD (Klein and Essex, 1994). This perception is reflected in the widespread use of the Edinburgh Postnatal Depression Scale (EPDS (Cox et al., 1987);), which assesses cognitive and affective symptoms but omits somatic symptoms.

Despite the absence of items assessing somatic symptoms in the EPDS, Ji and colleagues (Ji et al., 2011) demonstrated that EPDS scores varied across peripartum time: EPDS scores were as high or higher in the first and third trimesters of pregnancy as in they were in the postpartum period. The same study also measured PPD using the Beck Depression Inventory (BDI (Beck et al., 1961); which does assess somatic symptoms. They found that, in contrast to the EPDS, the BDI cut points linked to MDE during pregnancy were equal to or lower than the BDI cut points in postpartum. Thus, assessing somatic symptoms in peripartum does not appear to artificially inflate scores, and may not explain any inflated prevalence estimates previously reported (Klein and Essex, 1994). Moreover, the lack of items assessing somatic symptoms in the EPDS may actually lead to spuriously high cutoff scores during pregnancy, and potentially result in missed diagnoses. Taken together, this suggests that somatic symptoms of depression should be assessed during peripartum.

To date, much PPD research has emphasized sum-total-score approaches to discriminate women with and without PPD (Ji et al., 2011; Ross et al., 2003). Yet studies that have examined somatic symptoms suggest that they may play a specific role in the pathogenesis of postpartum depression—for example triggering other symptoms of depression (Chaudron et al., 2001). One way to further investigate the nuances of somatic symptoms is using the network framework, which conceptualizes syndromes as a set of probabilistically determined causal interactions (network edges) between symptoms (network nodes) (Borsboom, 2017). Network analysis could suggest a *potential* (underlying) causal model of PPD (Borsboom and Cramer, 2013). Thus, while sum score approaches implicitly assume all measured items contribute equally to overall severity and represent an underlying latent construct, network approaches make no such assumptions and are ideal for determining the controversial role of somatic symptoms within the syndrome of PPD.

Few studies have applied network theory to the study of PPD. In the first study of its kind, Santos and colleagues estimated the network of 20 Center for Epidemiological Studies-Depression (CES-D) symptoms in a sample of 515 low-income Latina women 22–24 weeks into their first pregnancy (Santos et al., 2017). They compared networks of more (CES-D $\geq$ 10, N = 264) and less depressed (CES-D $\leq$ 9, N = 240) women, and although overall network structures were similar, the somatic symptoms ("appetite changes" and "sleep disturbance") were more connected to other symptoms in the network of depressed women than non-depressed women. While this study did not specifically examine the role of somatic symptoms in women with and without PPD, it supports the notion that somatic symptoms differentially affect other symptoms in women with PPD.

This preliminary work (Santos et al., 2017) demonstrates the feasibility of estimating depression symptom networks in a peripartum population and lays the foundation for a closer examination of somatic symptoms within PPD networks. The current study sought to synthesize both subscale trajectories and symptom networks to enhance our understanding of how depression is experienced over peripartum time. In this study, we conceptualized PPD as a mutually reinforcing set of symptoms that operate within and between the affective, cognitive, and somatic subscales. First, we examined how affective, cognitive, and somatic depression symptoms changed across the peripartum period. Second, we used the network framework to examine how relationships among symptoms evolved across the peripartum period. Given the controversial and potentially critical role of somatic symptoms in diagnosis and treatment of PPD, we particularly focused on their role in the depressive syndrome over peripartum time.

2. Materials and methods

1. Participants, Recruitment, and Procedures

Data were collected in a prospective observational study of the peripartum course of mental disorders at the Emory Women's Mental Health Program (methodological details described elsewhere) (Ji et al., 2011). This study was carried out in accordance with the latest version of the Declaration of Helsinki and was approved by the Emory University Institutional Review Board. Pregnant women with any current or past mental illness were eligible. All participants received a full explanation of the study before providing written informed consent. Participants were enrolled before conception or during early gestation, no later than 16 weeks estimated gestational age (EGA). Treatment was delivered by a board certified psychiatrist who specialized in peripartum mental health and was not dictated by study participation. Lifetime psychiatric diagnoses were assessed at study entry using the Structured Clinical Interview for DSM-IV Axis I disorders (First and Gibbon, 2004). The Beck Depression Inventory (Beck et al., 1961) was completed by participants every 1–3 months until at least one year postpartum. Participants were included in the analysis on the basis of a full-term pregnancy resulting in a live birth, and complete item-level BDI scores in each of three trimesters of pregnancy, and two postpartum periods (outlined below). 418 women were included in this sample.

2. Measures

The BDI (Beck et al., 1961) is a 21-item self-report scale that assess depression symptoms and has been validated for use in women with PPD (Ji et al., 2011). The BDI was selected over the EPDS for this analysis because it contains the somatic items of interest. Each BDI item is rated on an ordinal scale ranging from 0 to 3.

Three BDI subscales were adopted from a previous study of women with postpartum depression utilizing the second edition of the BDI (9–20 weeks; (Manian et al., 2013). The subscales used here were constructed based on item similarity between the two versions of the BDI (Table S1).

3. Statistical Analysis

All analyses were conducted in R version 3.6.0 (R Core Team, n.d.). The two-tailed significance level for all analyses was $\alpha = 0.05$. Methodological details are in the supplement, and summarized below.

Five peripartum phases were derived a priori: one per pregnancy trimester (13 weeks), one early postpartum phase (first 8 weeks after delivery), and one late postpartum phase (9 weeks–52 weeks after delivery). If a woman enrolled for multiple pregnancies, one pregnancy was selected at random for inclusion in this analysis. If a woman completed multiple assessments within the same peripartum phase, one was randomly selected.

Repeated measures ANOVAs were used to test differences in BDI subscale scores across the five peripartum phases. Next, a series of multilevel linear spline regression models were used to predict the trajectory of each BDI subscale score (using the R package lme4 (Bates et al., 2019). This approach accounts for the hierarchical data structure: observations nested within women. Of interest were the fixed effect slopes between each phase. The errors associated with the fixed effects intercept and slope parameters were estimated with Satterthwaite's method (using R package *lmertest*; (Kuznetsova et al., 2019). Tests of these 18 a priori hypotheses were conducted using Bonferroni adjusted

alpha levels of 0.003 (0.05/18).

Network structures for each peripartum phase were estimated separately using the R-package *bootnet* (Epskamp and Fried, 2018). Edge weights represent partial Pearson's correlations between symptoms to reveal the unique associations between symptoms, net of their associations with other symptoms within the network. The L1-regularization technique was employed to prevent overfitting by minimizing the Extended Bayesian Information Criterion and shrinking edges that may be false positives to zero. These methods have been shown to yield accurate and stable network estimates (Foygel and Drton, 2010). L1-regularization employs a hyperparameter ɣ, which was set to 0.5 as a reasonable balance between edge discovery and overfitting (Epskamp and Fried, 2018).

In order to describe global network features, small-worldness was calculated. Networks with high small-worldness have high local clustering and a short average path length connecting two nodes (Humphries and Gurney, 2008). This is an important metric because small-world networks exhibit two important global properties: efficient (due primarily to short path length) and rapid (because nodes tend to be activated in clusters) spread of information (Watts and Strogatz, 1998). Importantly, networks with small-world properties are more robust to change than random networks because the removal of a single edge in a small-world network is unlikely to have a dramatic effect on the overall network (Watts and Strogatz, 1998).

The R-package *NetworkComparisonTest* (NCT (van Borkulo et al., 2017),) with 1000 permutations was used to calculate pairwise difference scores (D) in network structure and global strength (i.e., the sum of all edge weights) in the five peripartum phases.

The R-package *mgm* (Haslbeck and Waldorp, 2015) was used to estimate the predictability of each node within the network. Predictability was operationalized as the proportion of variance explained (R^2) in one node by the linear combination of every other node in the network.

Node strength represents how strongly a node is directly connected to all other nodes (Freeman, 1978). Strength centrality was calculated for each node then averaged and plotted over peripartum phase.

Clustering coefficients were calculated according to the Watts and Strogatz (WS) model for each symptom using *qgraph's clustercoef_auto* function (Epskamp et al., 2012). Clustering coefficients indicate the extent to which a node is connected to other nodes that are themselves interconnected.

Bootnet was used to assess accuracy and stability of the resulting networks.

3. Results

3.1. Sample Characteristics

A total of 418 women had complete longitudinal data and were included in the analyses. This subsample represents 64% of the 651 women enrolled in the larger study. The mean Estimated Gestational Age (EGA) at baseline for this sample was 9 weeks (range = 0.1–12.9 weeks). This sample was largely homogeneous in race (91% White), ethnicity (98% non-Hispanic) and marital status (90% married). This sample of women fulfilled a variety of vocational functions with 38% holding a full time job. The majority of women characterized their pregnancy as planned (72%) and desired (77%). While analyses were not limited to women with a current mood disorder, the majority of women in this sample fulfilled criteria for a lifetime mood disorder: 49% for Major Depressive Disorder, 16% for Bipolar I disorder, 3% for Bipolar II, and 1% for Bipolar NOS. 31% of women did not fulfill criteria for any lifetime mood disorder (Table 1). Women were also assessed for lifetime psychotic, substance use, and anxiety disorders (not reported). The majority of women in this sample were prescribed and taking at least one antidepressant medication (79% during pregnancy; 89% during postpartum) Information on antidepressant use was missing for 30 and 23 women during pregnancy and postpartum, respectively. Diagnoses were not included in the analyses for this study as the focus was to examine current symptoms of depression dimensionally, as reported on the BDI.

Table 1
Demographic Characteristics (N = 418 women).

Characteristic	Sample Mean (SD)
Age	33.87 (4.4)
Education	16.2 (1.92)
Gravidity	2.3 (1.39)
Parity	0.7 (.81)
Characteristic	***N (%)***
Race	
White	381 (91%)
Black	19 (5%)
Asian	9 (2%)
Other	9 (2%)
Ethnicity	
Non-Hispanic	410 (98%)
Hispanic	8 (2%)
Marital Status	
Married	372 (90%)
Never Married, Lives alone	31 (7%)
Never married, lives with partner	10 (2%)
Divorced/separated	5 (1%)
Function At Work	
Full time at home	87 (21%)
Full time at job	157 (38%)
Full time at school	12 (3%)
Part time at job	53 (13%)
Part time at school	3 (1%)
Unable to work	10 (2%)
Unemployed, able to work	11 (2%)
Unknown	83 (20%)
Pregnancy Planned	
Yes	300 (72%)
No	80 (19%)
Unknown	38 (9%)
Pregnancy Desired	
Yes	322 (77%)
No	9 (2%)
Ambivalent	44 (11%)
Unknown	43 (10%)
Live Delivery	418 (100%)
Lifetime Mood Disorder	
Bipolar I	68 (16%)
Bipolar II	14 (3%)
BP NOS	3 (1%)
Major Depressive Disorder	203 (49%)
None	130 (31%)

3.2. Peripartum Phase Subscale Differences

BDI subscales varied significantly across peripartum phase: Affective ($F(4,413) = 4.9$, $p = .0006$), Cognitive ($F(4,413) = 8.5$, $p < .0001$), and Somatic ($F(4,413) = 13.6$, $p < .0001$). Effect sizes varied among subscales, but were small overall (Affective $\eta^2 = 0093$; Cognitive $\eta^2 = 0.016$; Somatic $\eta^2 = 0.025$) (Fig. 1; Table S2).

Multilevel linear spline regression models demonstrated that trajectories differed by subscale (Fig. 1; Table S3). Affective symptoms significantly decreased from first to second trimester but did not change significantly thereafter. Cognitive symptoms significantly decreased from first to second trimester, remained constant, and then significantly increased from early to late postpartum. Somatic symptoms varied the most across peripartum phase. They decreased significantly from first to second trimester, increased significantly from second to third trimester and again from third trimester to early postpartum (trending), then decreased significantly from early to late postpartum. These results suggest that depression subscales vary differentially over the peripartum phases.

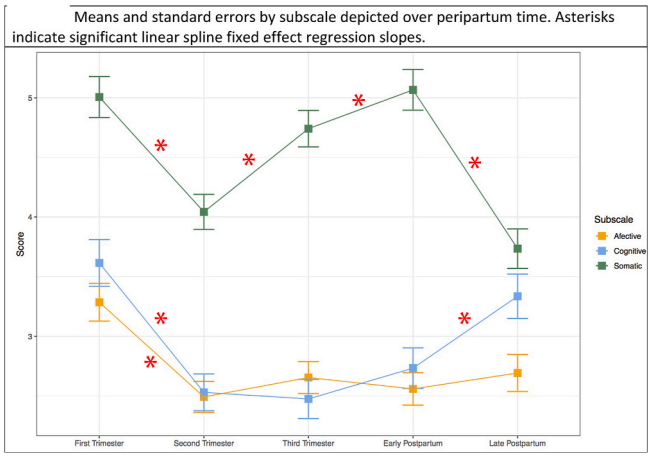

Fig. 1. Means and standard errors by subscale depicted over peripartum time. Asterisks indicate significant linear spline fixed effect regression slopes.

3.3. Network Analysis

3.3.1. Global Network Characteristics

When estimating item-level BDI networks, networks self-organized into subscale clusters such that, in general, the affective symptoms were organized together and bracketed by somatic and cognitive symptoms. This suggests that affective PPD symptoms may be critical in connecting somatic and cognitive symptoms (Fig. 2).

3.3.1.1. Global network comparisons. The NCT yielded largely null results (Table S4). The first trimester had marginally weaker global connectivity than the third trimester (difference score D = 1.4, p = .08) and late postpartum (D = 1.3, p = .09) networks. Early and late postpartum networks differed marginally in global network structure (D = 0.31, p = .08).

3.3.1.2. Small-worldness. First trimester small worldness was 0.65, second trimester: 3.25, third trimester: 0.68, early postpartum: 1.1, and late postpartum: 2.3. A liberal definition suggests that networks with an index >1 exhibit small-world qualities (Humphries and Gurney, 2008). These results suggest that depression symptom networks of the first trimester, third trimester, and early postpartum do not have a small-world structure. In contrast, the second trimester and late postpartum networks exhibit more small-world qualities, indicating that these periods may be characterized by maintaining mechanisms that are quickly activated and more resistant to change.

3.3.2. Network Node Characteristics

3.3.2.1. Predictability. Affective and cognitive symptoms had the greatest predictability over peripartum phase. The predictability (i.e. total variance explained) in affective symptoms peaked in the first trimester and late postpartum. Cognitive symptom predictability peaked in late postpartum. Throughout peripartum phases, somatic symptoms were the least predictable, but their predictability was highest during late postpartum. This suggests that somatic symptoms are more likely caused by factors outside of the network in pregnancy and early postpartum, while symptoms are more likely caused by nodes within the network in late postpartum (Fig. 3a).

3.3.2.2. Strength centrality. Symptom subscales differed in strength centrality over the peripartum phases. Affective symptoms peaked in centrality in the third trimester. Cognitive symptom strength centrality increased from the first to second trimester, and then remained relatively constant. As with node predictability somatic symptoms were lowest in strength centrality and peaked in the third trimester and late postpartum (Fig. 3b; Fig. S1). Results examining individual notes suggest that Node 15 (*Work Inhibition (energy/effort)*), an item that is related to loss of energy and anhedohia, is driving this effect (Fig. S1).

3.3.2.3. Clustering. Symptom subscales also differed in local clustering over peripartum phase. Generally, cognitive symptoms maintained the highest clustering level over peripartum time. Somatic symptoms appeared to have the lowest clustering coefficient throughout peripartum time, but displayed a spike from early to late postpartum, indicating that somatic symptoms may form a self-perpetuating feedback loop in late postpartum. Lastly, affective symptoms were the most variable in their clustering coefficient across peripartum phases. (Fig. 3c; Fig. S2).

4. Discussion

To our knowledge, this was the first prospective longitudinal study to examine depression symptom facets (measured as BDI subscales) and symptom network changes in a large sample of women in treatment over peripartum time. Integrating multilevel modeling and network analysis to the study of PPD offer complimentary insights into the presentation of depression over peripartum time.

Somatic symptoms stood out as particularly variable in their severity and network characteristics. This is consistent with findings that somatic symptoms vary more than psychological symptoms during pregnancy (Castro et al., 2017). Women in our sample reported remarkably high levels of somatic symptoms overall. More importantly, the trajectory of somatic symptoms was markedly different from that of the other subscales: somatic subscale severity was most severe in the first and third trimesters, and again in early postpartum. This finding is critical because research studies and clinics often rely solely on total scores to reflect overall depression severity. This approach implicitly assumes that PPD symptoms manifest similarly across peripartum phase (Fried and Nesse, 2015). Our results are consistent with prior work demonstrating that PPD is heterogeneous and symptoms, especially somatic symptoms, are not interchangeable (Nylen et al., 2013). Furthermore, while early work demonstrated that rates of depression diagnoses are equivalent when comparing peripartum and non-peripartum women, peripartum women report greater symptom severity as measured by the BDI, the same measure employed in this study that includes somatic symptoms (O'Hara et al., 1990). While O'Hara et al. interpreted their findings as part of "increased psychological distress" broadly (O'Hara et al., 1990), they also point to the physical changes during pregnancy and childbirth (and concomitant somatic symptoms) as major contributors to the discrepancy between diagnosis and severity. Our results support this explanation and highlight that using binary diagnosis obscures important differences in the possible drivers of depression symptoms during the peripartum period.

Results from the network analysis point to potential explanations for the varying levels of somatic symptoms across peripartum phase. Somatic symptom node predictability and clustering were low throughout pregnancy and into early postpartum yet peaked in late postpartum. Similarly, somatic symptom node centrality peaked in the third trimester and late postpartum, suggesting that somatic symptoms affect other symptoms the most during these peripartum phases. These findings suggest that somatic symptoms are caused by an evolving set of other factors across peripartum phase. For example, in late postpartum, somatic symptoms are explained to a greater degree by other depression symptoms compared to other peripartum phases. One interpretation of this effect is that women shift their attribution of symptoms from pregnancy- or early postpartum-related causes (i.e. by-products of pregnancy/recent birth) to within-network causes (i.e. other depression symptoms).

These results may inform recommendations for clinical assessment of

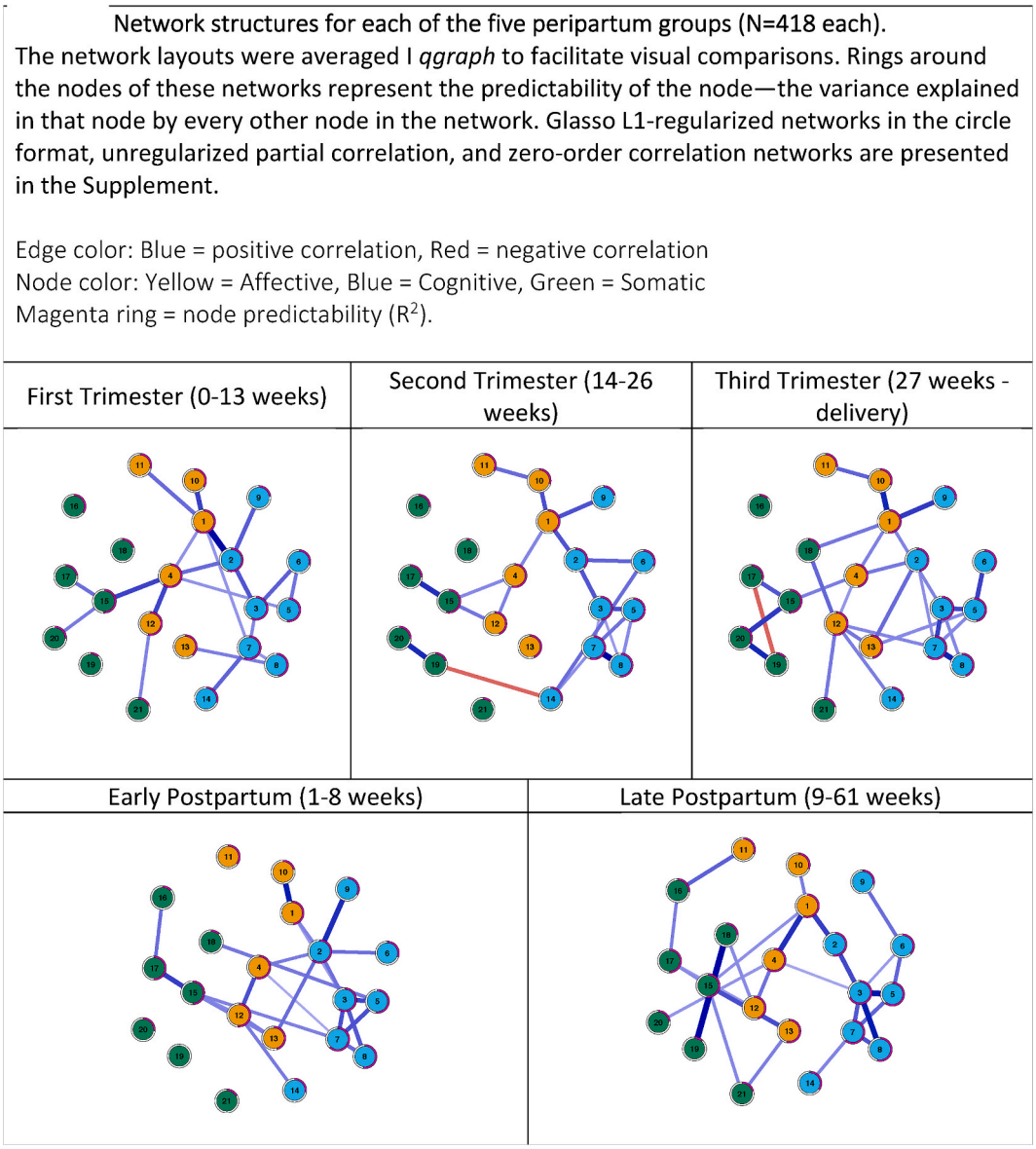

Fig. 2. Network structures for each of the five peripartum groups (N = 418 each). The network layouts were averaged I *qgraph to facilitate visual comparisons. Rings around the nodes of these networks represent the predictability of the node—the variance explained in that node by every other node in the network. Glasso L1-regularized networks in the circle format, unregularized partial correlation, and zero-order correlation networks are presented in the Supplement.Edge color*: Blue = positive correlation, Red = negative correlation
Node color: Yellow = Affective, Blue = Cognitive, Green = Somatic
Magenta ring = node predictability (R2). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

PPD. First, because symptoms are not interchangeable, reports including individual symptom or subscale profiles may be more useful than total sum-scores when treating women suffering from PPD. This would require administering a screening tool that assays a wider range of symptoms than the EPDS, such as the BDI or the semi-structured Hamilton Rating Scale For Depression (Hamilton, 1960; Ji et al., 2011). Scores from such assessments could be used to guide treatments based on the specific symptoms or clusters of symptoms causing the most impairment.

Second, because somatic symptoms were relatively severe but low in predictability, women in our sample may have attributed their somatic experiences to other issues when reporting depressive symptoms. This observation has been suggested elsewhere (Ji et al., 2011). Thus, given concerns that somatic symptoms may not be entirely due to depression during the peripartum period, it would be useful to obtain information from women about the attributions they are making regarding somatic symptoms. This may offer insight into whether those symptoms would likely respond to treatments targeting the depressive syndrome, or whether ancillary treatments specific to the somatic symptom(s) may be indicated.

Our results also suggest avenues for future research of women experiencing PPD. For example, additional explanatory nodes could be added to network models to explain more variance of the symptoms earlier in peripartum time. For example, given the neuroregulatory properties of estrogen and progesterone (Bloch et al., 2003), inclusion of biological measures such as hormones or menstrual function may further explain somatic symptoms. The practice of including biomarkers in psychological networks of pregnant women is in its infancy, but is feasible (Santos et al., 2017). Other candidate nodes include anxiety symptoms, which are pervasive and covary with depressive symptoms (Farr et al., 2014). It may also be viable to include nodes representing other factors such as pregnancy complications and breastfeeding, as

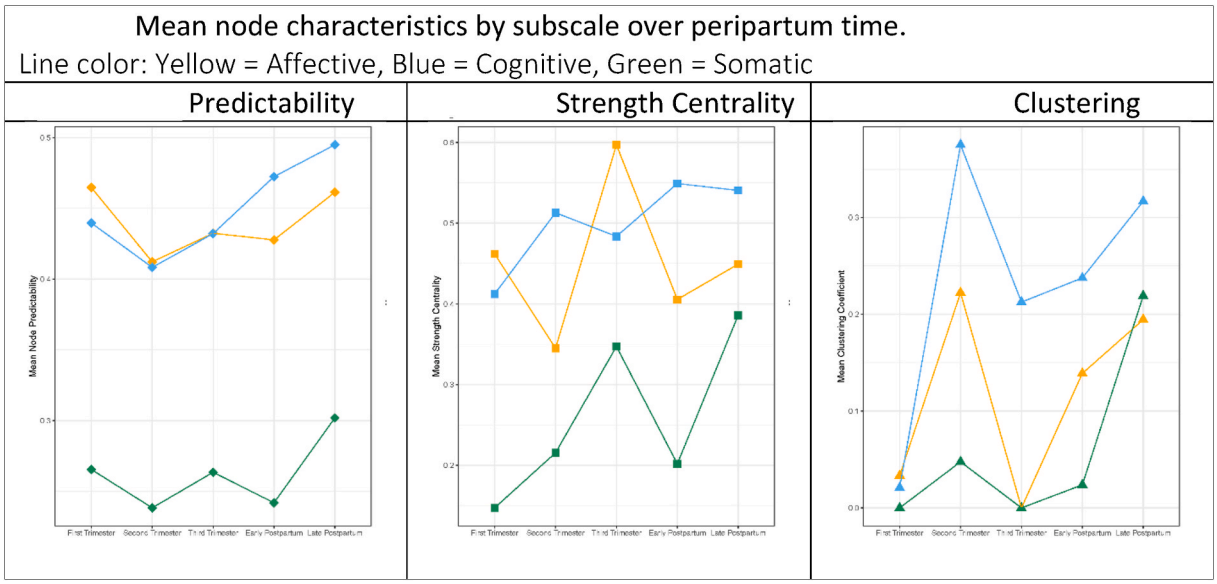

Fig. 3. Mean node characteristics by subscale over peripartum time.Line color: Yellow = Affective, Blue = Cognitive, Green = Somatic. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

these are somatic conditions associated with PPD (Blom et al., 2010; Pope and Mazmanian, 2016). Finally, nodes representing a mental health history may explain some unique variance in somatic symptoms (Winkel et al., 2013).

This study was not without limitations. First, the sample composition was homogeneous, which limits generalizability. Second, the sample was exposed to varying levels of psychotropic medications throughout the study. It remains to be determined whether treatment uniquely effect symptoms network structures (Bos et al., 2018). Though it was not possible to disentangle whether the observed changes in symptoms were due to response to treatment or to true changes in the depression phenomenology, the uniform decrease in severity from first to second trimester was likely due to treatment response. Beyond the second trimester, differences in subscale trajectory may be due to a combination of treatment and peripartum phase. Third, this study was based in a specialty clinic and did not include a control group in which to study somatic symptoms, which precluded us from making definitive claims about the specificity of our results. Future work might focus on exploring the role of somatic symptoms in depressed women outside of the peripartum phase to further elucidate the role somatic symptoms might play in women the etiology and maintenance of peripartum depression specifically. Fourth, this study was subject to Berkson's bias which occurs in statistical models based on covariance matrices (such as network models) when the population studied is selected based upon the matrix input variables (i.e. restricted range in the covariance matrix). Berkson's bias can limit the interpretability of symptom networks, limit the accuracy and stability of the networks, and can lead to spurious and uninterpretable negative edges (Ron et al., 2019). Women were selected for this study based on presentation to a specialty clinic in which they were seeking treatment for psychological distress. Berkson's bias was partially mitigated in this study because there were no inclusion criteria requiring a current depressive episode. However, it is possible that the two strong negative edges in the second and third trimester could be related to Berkson's bias.

In conclusion, across pregnancy and the postpartum period, somatic symptoms were most severe relative to other cognitive/affective symptoms, exhibited a unique trajectory, and played a distinct role in the complex causal mechanism that maintains depression during and after pregnancy. These data support the recommendation that somatic symptoms should not be ignored when assessing PPD. Probing for somatic symptoms in clinical research is also recommended to further elucidate the etiology and pathophysiology of PPD. Linking the pathophysiology underlying the co-occurrence of somatic symptoms in depression and medical conditions such as pregnancy/postpartum and others is an exciting avenue for future research.

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Declaration of competing interest

Dr. Stowe has received research support from Eli Lilly, Glaxo SmithKline (GSK), Janssen, Sage Therapeutics, the Center for Disease Control, the National Institutes of Health (NIH), and Wyeth. He has served on speakers' bureaus and/or received honoraria from Eli Lilly, GSK, Pfizer and Wyeth. He has served on advisory boards for GSK, and BSM. Neither he nor family members have ever held equity positions in biomedical or pharmaceutical corporations. Dr. Newport has received research support from Eli Lilly, Glaxo SmithKline (GSK), Janssen, the National Alliance for Research on Schizophrenia and Depression (NARSAD), the National Institutes of Health (NIH), SAGE, Takeda Pharmaceuticals, the Texas Health & Human Services Commission, and Wyeth. He has served on speakers' bureaus and/or received honoraria from Astra-Zeneca, Eli Lilly, GSK, Pfizer and Wyeth. He has served on advisory boards for GSK, Janssen, and Sage Therapeutics. He has never served as a consultant to any biomedical or pharmaceutical corporations. Neither he nor family members have ever held equity positions in biomedical or pharmaceutical corporations. Ms. Knight has received research support from Janssen, Sage Therapeutics, Boerhringer Ingelheim, Eli Lilly, Pfizer, Wyeth and the National Institutes of Health (NIH). Her adult son is employed by GlaxoSmithKline and has stock options as part of his employment. Ms. Baez and Dr. Heller report no financial

relationships with commercial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.07.049.

Author statement

Lara Michelle Baez: Conceptualization, methodology, formal analysis, writing-original draft. D. Jeffrey Newport: Conceptualization, investigation, writing-reviewing and editing, project administration, funding acquisition, supervision. Zachary N. Stowe: Investigation, writing-reviewing and editing, data curation, project administration, funding acquisition. Bettina T. Knight:, Investigation, writing-reviewing and editing, data curation, project administration. Aaron Shain Heller: Conceptualization, methodology, writing, supervision.

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