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Testing Cold and Hot Cognitive Control as Moderators of a Network of Comorbid Psychopathology Symptoms in Adolescence

James W. Madole[1], Mijke Rhemtulla[2], Andrew D. Grotzinger[1], Elliot M. Tucker-Drob[1], and K. Paige Harden[1]

[1]Department of Psychology, The University of Texas at Austin, and [2]Department of Psychology, University of California, Davis

Abstract

Comorbidity is pervasive across psychopathological symptoms, diagnoses, and domains. Network analysis is a method for investigating symptom-level associations that underlie comorbidity, particularly through *bridge symptoms* connecting diagnostic syndromes. We applied network analyses of comorbidity to data from a population-based sample of adolescents ($N = 849$). We implemented a method for assessing nonparametric moderation of psychopathology networks to evaluate differences in network structure across levels of intelligence and emotional control. Symptoms generally clustered by clinical diagnoses, but specific between-cluster bridge connections emerged. Internalizing symptoms demonstrated unique connections with aggression symptoms of interpersonal irritability, whereas externalizing symptoms showed more diffuse interconnections. Aggression symptoms identified as bridge nodes in the cross-sectional network were enriched for longitudinal associations with internalizing symptoms. Cross-domain connections did not significantly vary across intelligence but were weaker at lower emotional control. Our findings highlight transdiagnostic symptom relationships that may underlie co-occurrence of clinical diagnoses or higher-order factors of psychopathology.

Keywords

psychopathology, comorbidity, network analysis, cognitive control, open materials

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Mental disorders are widely comorbid (Hasin & Kilcoyne, 2012; Kessler, Chiu, Demler, & Walters, 2005). Complicating understanding of comorbidity is that clinical diagnoses aggregate over heterogeneous symptom presentations (e.g., Fair, Bathula, Nikolas, & Nigg, 2012; Lindhiem, Bennett, Hipwell, & Pardini, 2015; Wright et al., 2013). For example, one study of 3,703 outpatients with major depressive disorder found more than 1,000 unique symptom profiles (Fried & Nesse, 2015a). Given this diversity of symptom presentation, *symptomics*, defined as a focus on studying individual symptoms of psychopathology, has been championed as a promising avenue for understanding psychiatric comorbidity (Armour, Fried, & Olff, 2017; Fried et al., 2015). Here, we take a symptomics approach to identifying granular pathways through which mental disorders covary during adolescence, a critical developmental period when more than half of all lifetime cases of psychopathology begin and more than a quarter of cases meet for at least one comorbid disorder (Arcelus & Vostanis, 2005; Kessler, Berglund, et al., 2005).

Network Models of Comorbidity

Network analysis is a methodological tool for modeling unique relationships between psychopathology symptoms. Although multiple types of network modeling exist (for a review, see McNally, 2016), the most commonly employed version of this tool is the concentration network because of its suitability for cross-sectional, correlational data (Epskamp & Fried, 2018; Epskamp, Waldorp, Mõttus, & Borsboom, 2018). In concentration

Corresponding Author:
James W. Madole, Department of Psychology, The University of Texas at Austin, 108 E. Dean Keeton St., Stop A8000, Austin, TX 78712-1043
E-mail: jmadole@utexas.edu

networks, the partial pairwise correlations between symptoms are estimated, controlling for all other symptoms (Epskamp & Fried, 2018). These partial correlations are then typically graphed to allow for both an easily interpretable visualization of the relationships among symptoms and a formal quantification of these relationships using graph theory (Borsboom, 2017; Borsboom & Cramer, 2013). Results from network analysis have informed a burgeoning conceptualization of psychopathology, *network theory*, which suggests that mental disorders are an upstream reflection of activation patterns among symptoms (Borsboom, 2017; Borsboom & Cramer, 2013). Within this conceptualization, comorbidity is understood as the occurrence of symptoms from two distinct symptom clusters. Such symptom co-occurrence can arise via *bridge symptoms*, defined as symptoms from one cluster that have connections with symptoms from another cluster or another clinical disorder (Cramer, Waldorp, van der Maas, & Borsboom, 2010; Fried et al., 2017).

Previous network analyses investigating the large-scale organization (*topology*; Costantini & Perugini, 2016) of psychiatric symptom networks have primarily evaluated (a) how symptoms cluster together and (b) the strength and number of the connections that symptoms display both within and across clusters (Boschloo, Schoevers, van Borkulo, Borsboom, & Oldehinkel, 2016; Boschloo et al., 2015; Cramer et al., 2010; Goekoop & Goekoop, 2014). Few studies, however, have used network analysis to address comorbidity across the broad range of mental health disorders (for a review, see Fried et al., 2017). Instead, most network analyses of comorbidity have examined only two disorders (Robinaugh, Leblanc, Vuletich, & McNally, 2014; Ruzzano, Borsboom, & Geurts, 2015). For example, longitudinal and cross-sectional studies have found symptoms of major depression and generalized anxiety to be densely interconnected, although the precise nature of these interconnections varied by study (Beard et al., 2016; Cramer et al., 2010; Curtiss, Ito, Takebayashi, & Hofmann, 2018; Curtiss & Klemanski, 2016). When examining symptoms across more than two disorders, one study, notable for its size (~34,000 adult patients), found that the network structure of 120 symptoms from 12 disorders generally cohered to clinical boundaries defined by the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–IV*; American Psychiatric Association, 1994) but that individual symptoms differed substantially in their cross-disorder relationships (Boschloo et al., 2015). For example, all diagnoses were connected via specific symptoms to at least three other diagnoses (Boschloo et al., 2015). Similar results were found in a community sample of 2,175 preadolescents ages 10 to 12 years (Boschloo et al., 2016). Studies in this vein, which apply network analysis to symptoms of multiple disorders, are particularly important given the growing awareness that widespread comorbidity exists even across domains of psychopathology that appear quite distinct (such as internalizing and externalizing problems; Caspi & Moffitt, 2018).

Individual Differences in Network Structure

The ubiquitous comorbidity among *DSM*-defined and International Classification of Diseases–defined clinical diagnoses has motivated interest in identifying transdiagnostic risk factors for psychiatric disorders and refining psychiatric nosology accordingly (Clark, Cuthbert, Lewis-Fernández, Narrow, & Reed, 2017). However, hypothesized transdiagnostic risk factors have not generally been integrated into network analyses of symptom relationships. Here, we propose a novel conceptualization of transdiagnostic risk factors in the context of network theory as psychological or neurobiological background conditions that strengthen or exacerbate the symptom-to-symptom connections across psychiatric disorders or domains. No previous network analysis study has examined how transdiagnostic symptom relationships might vary as a function of other individual differences (Fried et al., 2015; Fried & Nesse, 2015b), in part because statistical methods to evaluate moderation of networks by continuously varying individual differences have not been implemented.

We addressed this methodological and substantive gap by examining individual differences in cognitive control as a moderator of symptom coactivation. *Cognitive control* is broadly defined as the ability to coordinate thoughts or actions in relation to internal goals (Koechlin, Ody, & Kouneiher, 2003), and it can be differentiated into "cold" and "hot" forms. Cold cognitive control is defined as the regulatory ability to monitor, direct, and manipulate basic information processing (Zelazo & Müller, 2002), whereas hot cognitive control is defined as the regulatory ability to monitor, direct, and manipulate affective processing (Roiser & Sahakian, 2013). Intelligence-test performance is a robust indicator of cold cognitive control (Chuderski & Nęcka, 2010). Our previous research found that intelligence-test performance is highly correlated, both phenotypically and genetically, with a general factor of performance on executive-functioning tests, which measure the ability to inhibit responses, shift attention, and update information in working memory (Engelhardt et al., 2016).

Research in a latent variable framework has found that intelligence and executive functioning are negatively associated with a general factor of psychopathology (Caspi et al., 2014; Harden et al., 2017; Lahey et al., 2015; Neumann et al., 2016) and with an array of clinically defined diagnoses (for a review, see Snyder, Miyake, &

Hankin, 2015). Meta-analytic work has found that premorbid deficits in cognitive ability, measured by an intelligence test, predicted onset of internalizing, externalizing, and thought disorders (David, Zammit, Lewis, Dalman, & Allebeck, 2008). Focusing on comorbidity specifically, one longitudinal study found that intelligence measured in childhood predicted the co-occurrence of diagnoses in adulthood (Koenen et al., 2009).

Alternatively, some researchers have theorized that cold cognitive deficits might not be the most salient contributors to comorbidity but, rather, that failures in hot, or emotional, cognitive control contribute to a cross-cutting liability to experience psychopathology (Carver, Johnson, & Timpano, 2017; Kret & Ploeger, 2015). Although emotion regulation is a nuanced construct and may be expressed differentially across psychopathologies (Werner & Gross, 2010), emotional control has received much attention as a transdiagnostic marker (Kring & Sloan, 2009). For instance, rash responding to emotion has been tied not only to externalizing disorders such as attention-deficit/hyperactivity disorder and conduct disorder but also to internalizing (e.g., mood and anxiety) disorders in both cross-sectional studies (Johnson, Carver, & Joormann, 2013; Johnson, Tharp, Peckham, Carver, & Haase, 2017; Marmorstein, 2013) and longitudinal studies (Smith, Guller, & Zapolski, 2013; Zapolski, Cyders, & Smith, 2009). Further work has found that problems regulating emotion differentiates clinical groups from healthy controls, but these difficulties are not more pronounced in any particular diagnostic group (Svaldi, Griepenstroh, Tuschen-Caffier, & Ehring, 2012). Meta-analytic work has found strong associations between impulsive responding to emotion and both internalizing and externalizing syndromes (Berg, Latzman, Bliwise, & Lilienfeld, 2015).

Extant work on cold and hot cognitive control has primarily focused on how these individual differences are associated with or predict psychopathology measured at the diagnostic or higher-order level. In this study, we took a different approach toward how cognitive control influences comorbidity, with a specific focus on how cognitive control moderates the strength of symptom-to-symptom connections across diagnostic boundaries. Specifically, we hypothesized that cold and hot cognitive control may exert transdiagnostic influence by strengthening or weakening connections between symptoms of different domains, such that symptom coactivation is heightened in the face of weak regulatory capacity. For instance, individuals high in negative emotionality (internalizing) might be more likely to hit someone (aggression) if they are ill equipped with abilities to monitor, direct, or control that emotion. Likewise, individuals who are restless (hyperactivity) might be more likely to disobey at home or school (rule breaking/conduct problems) if they lack the cognitive resources to regulate and focus attention. In this way, poor cognitive control is hypothesized to demarcate a subset of individuals who have co-occurring behavioral and emotional problems that cross diagnostic boundaries.

Goals of the Current Study

In the current study, we sought to explicate more closely the symptom-level presentation of adolescent psychopathology by estimating its network structure. We further sought to evaluate potential moderators of symptom-level relationships. This is the first study to investigate the network topology of psychopathology in boys and girls during a critical developmental window of adolescence. Further, it is the first study to implement local structural equation models (LOSEM; Briley, Harden, Bates, & Tucker-Drob, 2015; Hildebrandt, Luedtke, Robitzsch, Sommer, & Wilhelm, 2016; Hildebrandt, Wilhelm, & Robitzsch, 2009) to assess moderation of psychological networks by individual-differences variables. We estimated a series of weighted networks, in which data from each participant were weighted by the participant's distance from a focal value of the moderating variable. By varying the focal value of the moderator across the observed range, we arrived at a nonparametric estimate of how network edges vary as a function of individual differences. We hypothesized that both intelligence, as a proxy for cold cognitive control, and hot, or emotional, cognitive control would moderate connections between symptoms of different domains, such that adolescents with low intelligence and poor emotional control would experience greater comorbidity, as indexed by the strength of symptom relationships across different domains.

Method

Procedures were approved by the university ethics board before data collection commenced. Participants and their parents provided written informed consent.

Participants

The current sample consisted of 849 participants ages 13 to 20 years (M = 15.66) from the adolescent subsample of the Texas Twin Project (Harden, Tucker-Drob, & Tackett, 2013), a population-based study of school-age twins from the Austin and Houston metropolitan areas. Twin pairs were identified from public school rosters and invited to participate in a lab-based study consisting of a battery of psychological assessments. Participants either were currently enrolled in

school or had graduated from high school within the past 3 months but had not yet left home for college or full-time work. The sample was approximately gender balanced (50.7% male) and was racially diverse: 59.5% identified as non-Hispanic White, 19.2% as Hispanic/Latino, 11.4% as Black/African American, 2.85% as Southeast Asian, 1.54% as East Asian/Pacific Islander, 1.30% as American Indian/Native American, and 4.16% as other. Participants completed measures of psychopathology, emotional control, and intelligence.

Measures

Psychopathology. Adolescent psychopathology was measured using abbreviated versions of three self-report scales: the Achenbach Child Behavior Checklist (CBCL; Achenbach & Edelbrock, 1991), the *DSM–IV* symptom count scales of the Conners 3 rating scales (Conners, Pitkanen, & Rzepa, 2011), and the neuroticism subscale of the Big Five Inventory (BFI-N; John & Srivastava, 1999). The scales were selected to cover a broad range of typical psychopathological problems in adolescence: depression (e.g., "There is very little that I enjoy"), measured with the BFI-N and CBCL; anxiety (e.g., "I am nervous or tense"), measured with the BFI-N and CBCL; inattention (e.g., "I have trouble concentrating/paying attention"), measured with the CBCL and Conners 3; hyperactivity (e.g., "I am restless"), measured with the CBCL and Conners 3; learning problems (e.g., "I learn more slowly than other kids my age"), measured with the Conners 3; rule breaking and conduct problems (e.g., "I steal at home"), measured with the CBCL and Conners 3; and aggression (e.g., "I break things [when angry/upset]"), measured with the CBCL and Conners 3. More severe and infrequent forms of adolescent psychopathology, including schizophrenia, bipolar disorder, and other thought disorders, were not considered in these analyses.

Scoring of items on the BFI-N ranged from 1 (*strongly disagree*) to 5 (*strongly agree*), scoring of items on the CBCL ranged from 0 (*not true*) to 2 (*very true or often true*), and scoring of items on the Conners 3 ranged from 0 (*not true at all*) to 3 (*very much true*). All scales have demonstrated good validity: Neuroticism has demonstrated strong relationships with internalizing psychopathologies in adolescents (r = .98; Griffith et al., 2010) and has shown substantial genetic overlap with internalizing symptoms (Hettema, Neale, Myers, Prescott, & Kendler, 2006); the CBCL has demonstrated excellent psychometric properties, including concurrent validity with *DSM* diagnoses in children and adolescents (Ebesutani et al., 2010; Nakamura, Ebesutani, Bernstein, & Chorpita, 2009); and the Conners 3 has demonstrated adequate convergent validity with similar measures in children and early adolescents (Erford, 1995).

Emotional control. Emotional control was measured using the urgency subscale of the UPPS Impulsive Behaviour Scale (e.g., "When I am upset I often act without thinking"). Participants responded to items on a scale from 1 (*disagree strongly*) to 4 (*agree strongly*). Items were reverse-scored so that greater scores indicated less urgency, or greater emotional control. The psychometric properties of the UPPS are well established (Whiteside & Lynam, 2001; Whiteside, Lynam, Miller, & Reynolds, 2005). The UPPS-Urgency subscale has demonstrated significant correlations with self-report measures of emotion dysregulation (Fossati, Gratz, Maffei, & Borroni, 2014) and has achieved good reliability and validity as a measure of impulsive responding to emotion (Cyders & Smith, 2007, 2010).

Intelligence. Intelligence was assessed using the Wechsler Abbreviated Scale of Intelligence–II (WASI-II; Wechsler, 2011). The WASI-II measures two domains of intelligence: visuospatial reasoning, consisting of the Block Design and Matrix Reasoning subtests, and verbal ability, consisting of the Vocabulary and Similarities subtests. Scores from the four subtests are individually normed and combined to form Full-Scale IQ (FSIQ). FSIQ in the current sample reflects population norms (M = 103.54, SD = 13.19). The WASI has demonstrated significant associations with cognitive-control measures in children and adolescents (Andrews-Hanna et al., 2011; Solomon, Ozonoff, Cummings, & Carter, 2008).

Analyses

Our analytic plan encompassed three broad aims: (a) to elucidate the cross-sectional network structure of adolescent psychopathology by investigating clustering of symptoms in the network and the nature of the connections within and between those clusters, (b) to evaluate how this network structure differs across levels of cold and hot cognitive control by implementing a novel method of nonparametric moderation, and (c) to examine whether bridge symptoms identified in cross-sectional networks uniquely predict future psychopathology in a longitudinal follow-up analysis.

Scripts for the R software environment (Version 3.4.1; R Core Team, 2017) and for Mplus (Muthén & Muthén, 2010) for all analyses are included in the Supplemental Material available online. Prior to analyzing the data, we coded all items so that higher scores reflected greater severity of psychopathology. All psychopathology items, with two exceptions described below, were treated as ordinal variables, gender and ethnicity were scored as dichotomous variables (male/female; minority/nonminority status), and age was treated as a continuous variable. Both intelligence and emotional control

were *z*-scored prior to analyses and were treated as continuous variables.

Less than .1% of the data were missing. Participants with more than 20% missing data ($n = 7$) were removed from analyses. Single predictive-mean-matching-based imputation was then conducted on the remaining cases using the *mice* package in the R software environment (van Buuren & Groothuis-Oudshoorn, 2011). Single imputation is considered an appropriate technique when less than 5% of data are missing (Graham, 2009).

We included 103 items in our analyses, 61 of which were treated as indicative of unique symptoms. The 42 remaining items were combined to form 15 composite variables according to two justifications. First, on the basis of the wording of the prompt, items that were theorized to tap the same symptom (e.g., BFI-N Item 4: "is depressed, blue," and CBCL Item 44: "I am unhappy, sad, or depressed") were summed to reduce topological overlap (Fried, Epskamp, Nesse, Tuerlinckx, & Borsboom, 2016). Second, 11 items endorsed by less than 10% of the sample were combined with related items to ameliorate the bias created by their skew. Two of these were treated as continuous: a property damage variable created by summing 7 ordinal items and a physical aggression variable created from another 7 ordinal items. Truancy, a sum of 3 ordinal items, was treated as an ordinal variable with seven levels. One item ("I get into trouble with the police") was dropped from the analyses because of low endorsement rate. All final variables were endorsed by at least 15% of the sample.

Network estimation and visualization. Psychopathology networks consist of nodes, representing individual symptoms, and edges, representing connections among symptoms. In concentration networks, edges represent conditional pairwise linear associations between two variables, controlling for all other variables in the network.

A full description of the network estimation and visualization method is provided in the Supplemental Methods in the Supplemental Material. Briefly, we estimated the symptom network from the observed polyserial correlation matrix using the EBICglasso function in the *qgraph* package in the R software environment (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012). To avoid overfitting, coefficients (i.e., edges) are regularized using an l_1 penalty, which shrinks weak edges to exactly zero. Networks estimated using the EBICglasso approach typically have high sensitivity (the edges that are estimated are very likely to be nonzero) but low specificity (edges that are estimated to be zero may or may not truly be zero; Foygel & Drton, 2010). The network structure was visualized using the *qgraph* package in the R software environment (Epskamp et al., 2012). Thicker edges indicate stronger associations. Green edges reflect positive associations, whereas red edges reflect negative associations.

Cluster analyses. The spinglass algorithm, employed using the *igraph* package in the R software environment (Csardi & Nepusz, 2006), was used to identify communities of nodes in the graph; communities are defined as a set of nodes with relatively more edges inside the community and fewer edges connecting the community to the rest of the graph (Reichardt & Bornholdt, 2006). Because the algorithm is prone to variability in grouping, it was run 1,000 times. The number of clusters identified ranged from five to eight, with six being the median number of clusters identified. Of the 457 runs that identified six clusters, we used the most frequently derived clustering arrangement ($n = 239$) to determine group membership. Results are discussed in terms of connections within and between the clusters (i.e., domains) identified using this algorithm.

Network moderation. We used LOSEM to assess intelligence and emotional control as continuous moderators of the unique association between each pair of symptoms (Briley et al., 2015; Hildebrandt et al., 2016; Hildebrandt et al., 2009). LOSEM uses kernel estimation techniques to generate nonparametric estimates of differences in structural-equation-model parameters across levels of a measured moderator. In combination with the capability of structural equation modeling to produce a saturated model representing the full heterogeneous correlation matrix among all pairs of symptoms, we used LOSEM to generate a series of correlation matrices that are generated across the range of observed moderator values. Each correlation matrix was derived by reweighting the sample data, with sample weights reflecting the proximity of each individual's score on the moderator to the focal value being tested for that particular iteration.

Correlation matrices were computed across 4 *SD*s (from −2 to 2) of intelligence and emotional control at increments of .1 *SD* units, resulting in 41 correlation matrices for each moderator. Observed moderator values were included in each LOSEM-weighted correlation matrix and resulting network, to control for the main effect of the moderator on each symptom. This prevented estimates of the moderation of symptom associations from being biased by differences in rates of symptom endorsement across levels of the moderator. The resulting weighted polyserial correlation matrices were estimated in Mplus and analyzed in the R software environment. For instances in which no positive definite matrix was produced,[1] we used the nearPD function in the *Matrix* package in the R software environment (Bates & Maechler, 2016) to find the nearest positive

definite matrix for any observed nonpositive definite matrix. Networks that included the respective moderator as a node were then estimated from each polyserial matrix using the *glasso* function in the R software environment (Friedman, Hastie, & Tibshirani, 2014). This function uses the same regularization procedure as described above but allows the analyst to fix the l_1 penalty rather than choosing it anew using EBIC model selection for each network. For each LOSEM-weighted matrix, we fixed the l_1 penalty to be equal to the optimal EBIC-derived value obtained in the unweighted network that included the moderator as a node (λ = .122 for both). Variation in edge weights thus reflects interpretable differences rather than potential artifacts of the regularization process.

To facilitate comparisons of symptom covariance differences across levels of the moderators, we constrained cluster membership in the LOSEM-weighted matrices to be equal to the unweighted graph. To quantify differences in network structure across the range of each moderator, we calculated an average between-cluster edge weight—that is, a regularized, partial correlation coefficient, $M_{r(BC)}$, for each network across the range of the moderator. $M_{r(BC)}$ was chosen a priori because we predicted that we would observe larger positive edges between symptoms of different psychopathological domains at lower levels of cognitive control. That is, we would expect $M_{r(BC)}$ to decrease as the level of each moderator increases. $M_{r(BC)}$ was calculated by summing edge weights connecting nodes from different clusters and dividing by the total number of possible between-cluster connections. Thus, it can be interpreted as the average positive unique association across symptom domains. $M_{r(BC)}$ is particularly useful in that it accounts for negative coefficients, which, given how our data were scored, would reflect the absence of one symptom in the presence of another and thus would not be indicative of comorbidity.

To determine whether the observed variation in $M_{r(BC)}$ was significantly different from what would be observed by chance, we ran a permutation test in which intelligence and emotional control were randomly reordered across participants, resulting in 1,000 permuted data sets. Each case's observed value for intelligence and emotional control was retained as a variable in the permuted data sets so that the main effect of the moderator on symptom relationships did not vary as a function of the random reordering of the moderator. We then ran each of the permuted data sets (k = 1,000) through the LOSEM procedure and calculated the $M_{r(BC)}$ at each value of moderator (m = 41), resulting in an empirical null distribution of $k \times m$ values of $M_{r(BC)}$. Observed $M_{r(BC)}$ values between −1.5 and +1.5 *SD*s of the moderator were evaluated as significant if they were smaller than the bottom 2.5% or larger than the top 97.5% of the empirical null distribution.

Longitudinal follow-up. To investigate the direction of associations between bridge symptoms identified in the cross-sectional, unmoderated network analysis, we estimated a longitudinal network of symptoms in a subsample of Texas Twin Project participants (n = 218) who completed two waves of assessment. Table S1 in the Supplemental Material contains descriptive statistics for the longitudinal subsample. Each symptom in the longitudinal network was represented by two nodes—one for each time point. Analyses focused on edges between Wave 1 and Wave 2 nodes, which represent the predictive associations between one symptom and future levels of another symptom, above and beyond all other symptoms in the network. We focused primarily on the percentage of connections (i.e., number of observed positive connections divided by number of potential positive connections) between bridge symptoms and disparate domains of psychopathology.

Results

Reliability analyses

Before estimating the network in the full sample, we conducted a split-half reliability analysis to establish confidence in the parameters generated by the network estimation process. Participants in each twin pair were arbitrarily assigned to Twin 1 (n = 417) or Twin 2 (n = 425),[2] and within each of these subgroups, we estimated correlation matrices in Mplus and estimated networks using EBICglasso, as described in the previous section. We then correlated the edge weights across the two twin networks to index network similarity (Borsboom et al., 2017; Fried et al., 2018; Rhemtulla et al., 2016). We focus here on edge weights because our analyses primarily concerned the magnitude and number of these connections. We demonstrated good stability of our strength index, using the bootnet function (Epskamp, Borsboom, & Fried, 2017; see Fig. S1 in the Supplemental Material).

The two correlation matrices, from which Twin 1 and Twin 2 networks were estimated, correlated at .848. We derived an optimal penalization parameter to fix across networks by first estimating each network individually using the EBICglasso function. We reestimated the networks using the glasso function with the penalty parameter fixed to the average value of the two individual networks (λ = .26). The edge weights from these two networks correlated at .782, which we interpreted as adequate reliability given the upper bound established by the correlation between the polyserial matrices. To ensure that split-half and full-sample networks did not diverge as a function of

the penalty parameter, we estimated the twin networks again using the penalty derived from the full sample (λ = .111). The edge weight correlation remained adequate (r = .740).

General network structure of adolescent psychopathology

Figure 1 depicts the estimated network, in which nodes represent psychopathology symptoms and edges represent the unique associations among them (for node reference, see Table S2 in the Supplemental Material). Six clusters were identified using the method described above, displaying general coherence with clinical syndromes. As shown in Table S2, only 5 of 76 nodes were found to cluster with groups different from their self-report subscale. Age, gender, and ethnicity were omitted from clustering analyses, and connections between these correlates and other nodes are not reported.

We focused our analyses on the 2,850 potential connections (i.e., 76 × 75 / 2) among nodes. Figure 2 shows the number and relative average strength of the connections from all nodes to each of the six domains, as well as a summary of the total between-cluster connections for each node. Connection strength was calculated by averaging all edge weights from an individual node to all nodes of a particular domain. Nodes that have an average edge weight with a given domain at or above the 75th percentile of all average edge weights are characterized as relatively strong. Strength of total between-cluster connections (i.e., an individual node's connections with all other nodes outside of its cluster) was calculated by averaging the edge weights from an individual node to every node not within its cluster. Nodes with the most and strongest connections to each domain and to all between-cluster domains are detailed in Table S3 in the Supplemental Material. Reliability of the ordering of these nodes was established by conducting a bridge centrality analysis, which calculates how central (i.e., number of connections, proximity in graphical space) nodes are to clusters outside of their own, using the *networktools* package in the R software environment (Jones, 2018). Figure S2 in the Supplemental Material details the results from this analysis, which demonstrates adequate consistency with our results. Table S4 in the Supplemental Material contains the number and relative strength of connections within and between clusters, in which all present edge weights were rank-ordered to determine percentile cutoffs.

Overall, externalizing symptom domains (rule breaking/conduct problems, aggression, and hyperactivity) were consistently interconnected, with multiples nodes from each externalizing domain showing relatively strong average connections with all other externalizing domains. Rather than being broadly interconnected with externalizing, learning problems showed more specific connections with inattention symptoms. Internalizing symptoms showed the weakest and sparsest connections with other symptom domains. Interestingly, the nodes connecting internalizing and externalizing were specific to aggression, in particular, experiences of interpersonal irritability (e.g., "people make me angry"). In the following sections, we briefly summarize connections involving each domain.

Internalizing. Internalizing nodes (p = 17) displayed 4 to 12 connections with one another, and 2 to 13 connections (of 59 possible) with nodes of other domains. Two internalizing nodes ("I feel confused or in a fog" and "[I] can be moody") displayed relatively strong average between-cluster connections. Of the nodes from other domains, 20 of 59 nodes displayed no connections with the internalizing domain, whereas only 3 nodes from other domains displayed relatively strong average connections with internalizing nodes. These nodes with strong average connections to internalizing ("People make me angry," "I am suspicious," and "I scream a lot") were all from the aggression domain. Longitudinal prediction of these three symptoms in connecting internalizing and aggression was addressed in a follow-up analysis below.

Learning problems. Learning problems nodes (p = 7) displayed 3 to 6 connections with one another, and 2 to 10 connections (of 69 possible) with nodes of other domains. Two nodes ("I need help doing my homework" and "I forget things that I have learned") displayed relatively strong average between-cluster connections. Of the nodes from other domains, 42 of 69 nodes displayed no connections with the learning problems domain, whereas only 5 nodes from other domains displayed relatively strong average connections with learning problems nodes. These nodes ("I have trouble keeping my mind on what people are saying to me," "I am behind in my schoolwork," "I have trouble concentrating/paying attention," "I don't like doing things that make me think hard," and "I have trouble following instructions") were all from the inattention domain.

Hyperactivity. Hyperactivity nodes (p = 14) displayed 5 to 10 connections with one another, and 2 to 17 connections (of 62 possible) with nodes of other domains. Two of these nodes ("I interrupt other people" and "I get out of my seat when I am not supposed to") displayed relatively strong average between-cluster connections. Of the nodes from other domains, 18 of 62 nodes displayed no connections with the hyperactivity domain, whereas 7 nodes from other domains displayed relatively strong average connections with hyperactivity nodes. Three of these nodes came from aggression, 2 from rule breaking/conduct problems, and 2 from inattention.

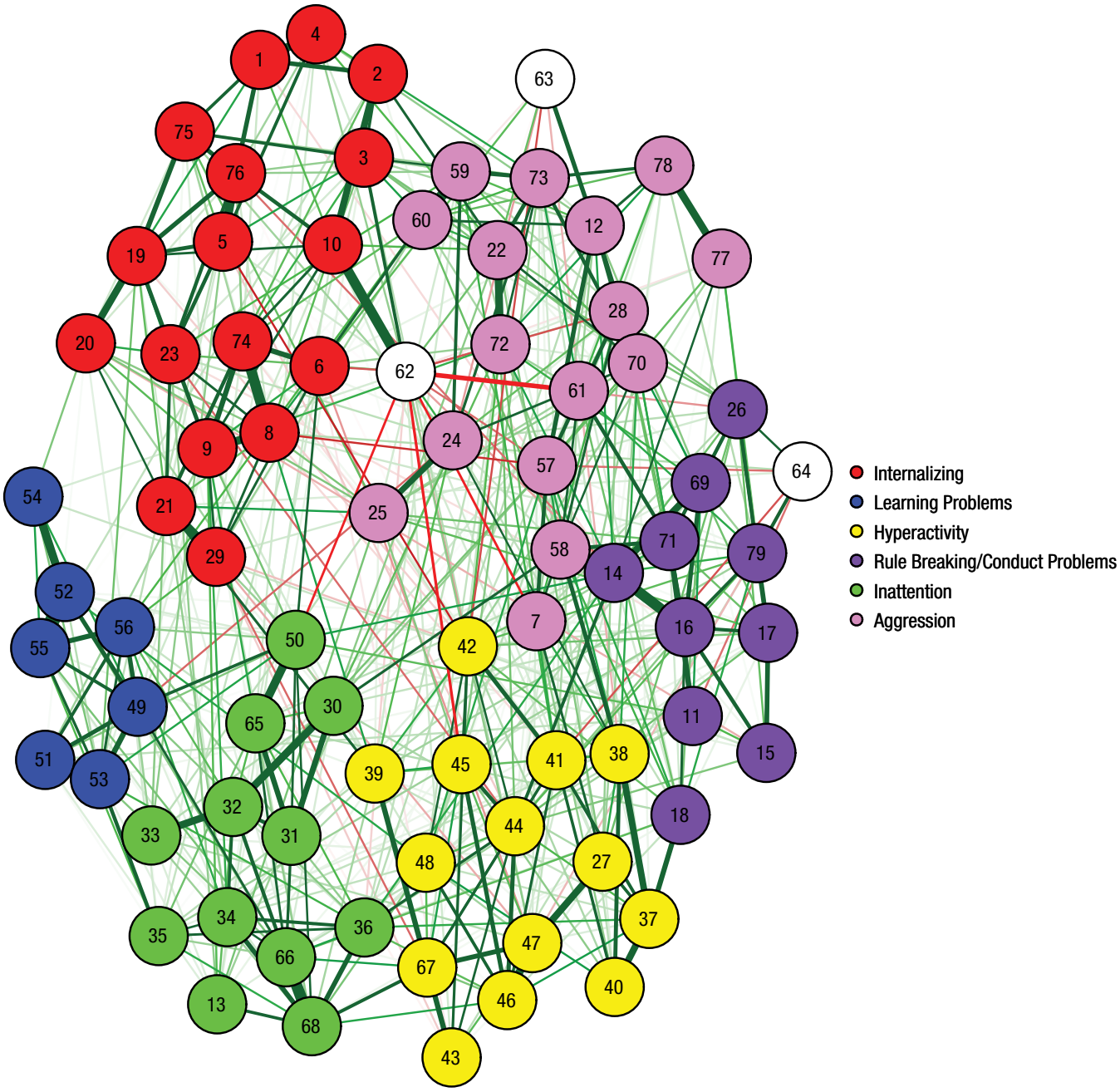

Fig. 1. Network of 76 psychopathology items, controlling for age, gender, and ethnicity (white nodes). Items are represented as nodes and associations between them as edges. Green edges indicate positive associations and red edges indicate negative associations, with the thickness of the edge indicating the strength of the association. Groups are derived from the spinglass algorithm, which maximizes between-cluster separation and within-cluster cohesion on the basis of the number of connections that nodes share (Reichardt & Bornholdt, 2006). Groups are labeled on the basis of the self-report subscale that the majority of the items in the cluster come from.

Rule breaking/conduct problems. Rule breaking/conduct problems nodes (p = 10) displayed 4 to 9 connections with one another, and 5 to 14 connections (of 66 possible) with nodes of other domains. Three of these nodes ("I lie or cheat [to get out of doing stuff]," "I act without stopping to think," and "I disobey at school") displayed relatively strong average between-cluster connections. Of the nodes from other domains, 19 of 66 nodes displayed no connections with the rule breaking/conduct problems domain, whereas 11 nodes from other domains displayed relatively strong average connections with rule breaking/conduct problems nodes. Six of these nodes came from aggression, 3 came from hyperactivity, and 2 came from inattention.

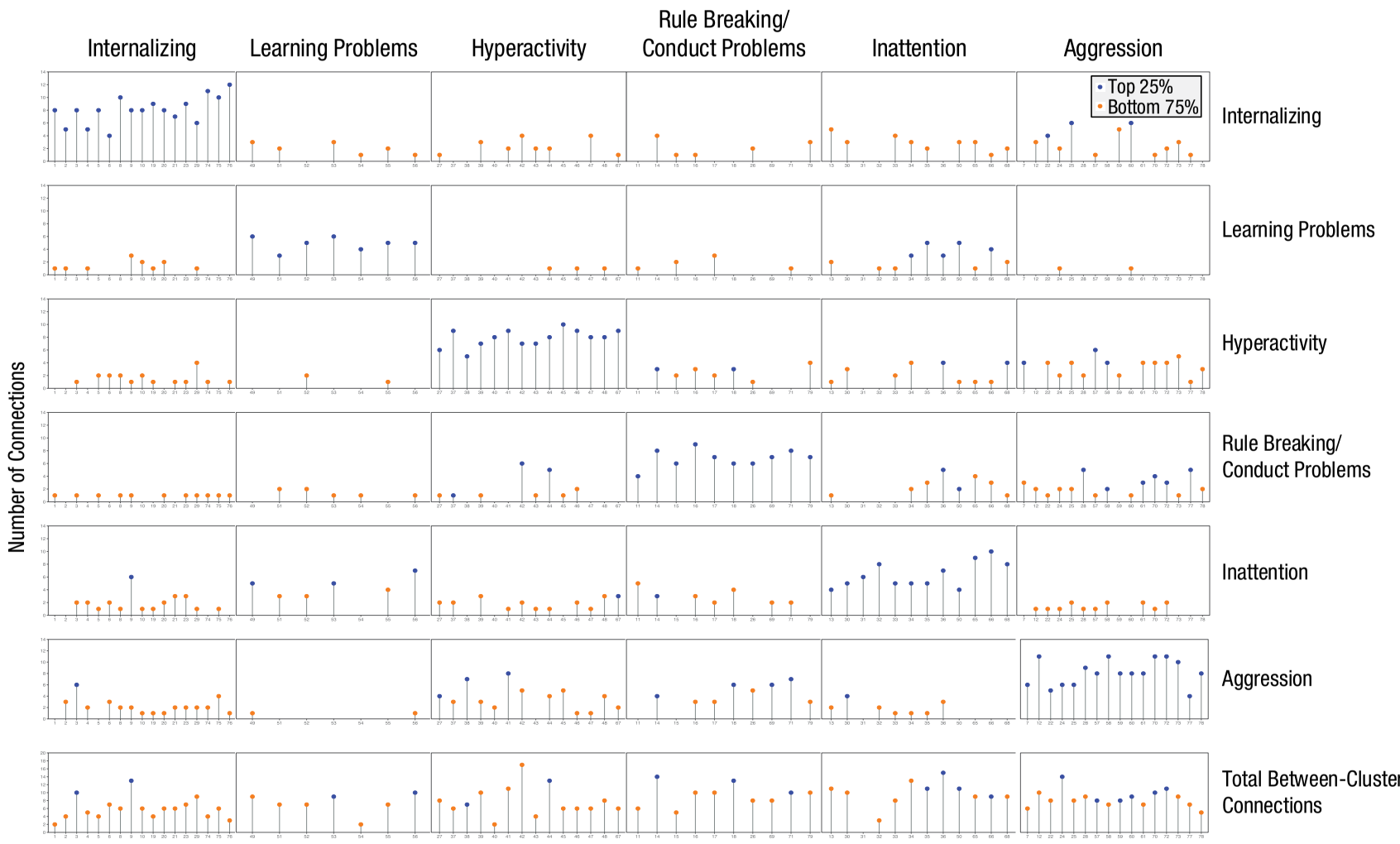

Fig. 2. Number of connections from each individual symptom to each domain of problem behaviors. Horizontal panels represent the domains within the network, in which the *x*-axis of each panel represents each node within the network, grouped by domain. The *y*-axis of each panel represents the number of connections that each node displays with the respective domain. The last panel represents the number and strength of each node's connections to all nodes outside of its domain. Connections are colored according to the average edge weight of each node to each domain (i.e., all nodes within a particular domain). For the six individual domain panels, if the average node to domain edge weight was greater than .0116 (75th percentile and above), the node was colored blue (i.e., relatively strong). Connections for each node to all five between-cluster domains are colored according to the average edge weight from an individual node to all out-of-cluster nodes. For the total between-cluster connections, if the grand average node to domain edge weight was greater than .0262 (75th percentile and above), the node was colored blue.

Inattention. Inattention nodes (p = 12) displayed 4 to 10 connections with one another, and 0 to 15 connections (of 64 possible) with nodes of other domains. Four of the inattention nodes displayed relatively strong average between-cluster connections. Of the nodes from other domains, 17 of 64 nodes displayed no connections with the inattention domain. Six nodes from other domains displayed relatively strong average connections with inattention nodes. Three of these nodes came from learning problems ("I learn more slowly than other kids my age," "I need help doing my homework," and "I forget things that I have learned"), 1 node from hyperactivity ("I have trouble sitting still"), and 1 node each from rule breaking/conduct problems ("I disobey at school") and internalizing ("I feel confused or in a fog").

Aggression. Aggression nodes (p = 16) displayed 4 to 11 connections with one another, and 5 to 14 connections (of 60 possible) with nodes of other domains. Six of the aggression nodes displayed relatively strong average between-cluster connections. Of the nodes from other domains, 15 of 60 nodes displayed no connections with the aggression domain, whereas 9 nodes from other domains displayed relatively strong average connections with aggression. Four nodes came from rule breaking/conduct problems, 3 nodes came from hyperactivity, and 1 node each came from inattention ("I lose stuff that I need") and internalizing ("[I] can be moody").

Total between-cluster connections. Nineteen of the 76 nodes in total displayed relatively strong average between-cluster connections. Clusters with the highest number of nodes with strong average between-cluster connections were aggression (p = 6), inattention (p = 4), and rule breaking/conduct problems (p = 3). Four of the six aggression nodes were related to interpersonal difficulties (e.g., "I try to annoy other people"). Two nodes displayed strong average connections for hyperactivity ("I interrupt other people" and "I get out of my seat when I'm not supposed to"), learning problems ("I need help doing my homework" and "I forget things that I have learned"), and internalizing ("I feel confused or in a fog" and "[I] can be moody").

Moderated network structure across cold and hot cognitive control

Before assessing differences in network structure across the range of cold and hot cognitive control, we first estimated unmoderated networks that included each moderator as a node. We determined the centrality, indexed by the number of connections that each node displays, of each moderator to get a global sense of the relevance of each moderator variable to the network. Intelligence was the most central node to its network. Emotional control was the 11th most central node to its network.

Moderation was evaluated in terms of average between-cluster edge weight, $M_{r(\mathrm{BC})}$. This metric, which represents the average edge weight between a given node and all nodes of different domains (i.e., n = 2,371 potential between-cluster connections), was chosen to provide a global indication of symptom co-occurrence across different domains. To quantify differences in $M_{r(\mathrm{BC})}$ across moderated networks, we created an empirical null distribution from permuted $M_{r(\mathrm{BC})}$ values and evaluated significance on the basis of observed $M_{r(\mathrm{BC})}$ values that fell in the upper or lower 2.5% of the empirical null distribution. Figures 3a and 3b illustrate the observed $M_{r(\mathrm{BC})}$ values in relation to the empirical null distribution.

Across the range of intelligence, none of the observed $M_{r(\mathrm{BC})}$ values fell outside of the upper or lower 2.5% of the empirical null distribution, although there was a nonsignificant pattern of greater comorbidity—higher $M_{r(\mathrm{BC})}$—at lower intelligence. In contrast to the intelligence analysis, the emotional-control analysis revealed a significant pattern of less comorbidity—lower $M_{r(\mathrm{BC})}$—between −1.5 and −0.6 *SD*s of emotional control (empirical $p < .005$ − empirical $p < .025$), indicating that disparate domains of psychopathology are, on average, more weakly connected at lower levels of emotional control. Table S5 in the Supplemental Material contains the unique between-cluster symptom connections that display the greatest variance across the range of each moderator.

To further probe the finding that between-cluster symptoms are more weakly connected at low levels of emotional control, we ran exploratory post hoc analyses to investigate whether connections between specific domains were driving this finding. Figures S3 and S4 in the Supplemental Material illustrate the between-cluster connections between (a) internalizing and aggression symptoms and (b) externalizing domains (aggression, rule breaking/conduct problems, hyperactivity), respectively. We found that the average internalizing to aggression connection was significantly lower than chance at both the lower (−1.5 to −1.1 *SD*) and upper (0.7 to 1.5 *SD*) tails of emotional control, indicating that individuals with strong emotional control as well as individuals with poor emotional control demonstrate significantly weak connections between internalizing and aggression symptoms. We found that the average connection between externalizing domains was significantly lower than chance from 1.4 to 1.5 *SD*s of emotional control (empirical $p < .025$).

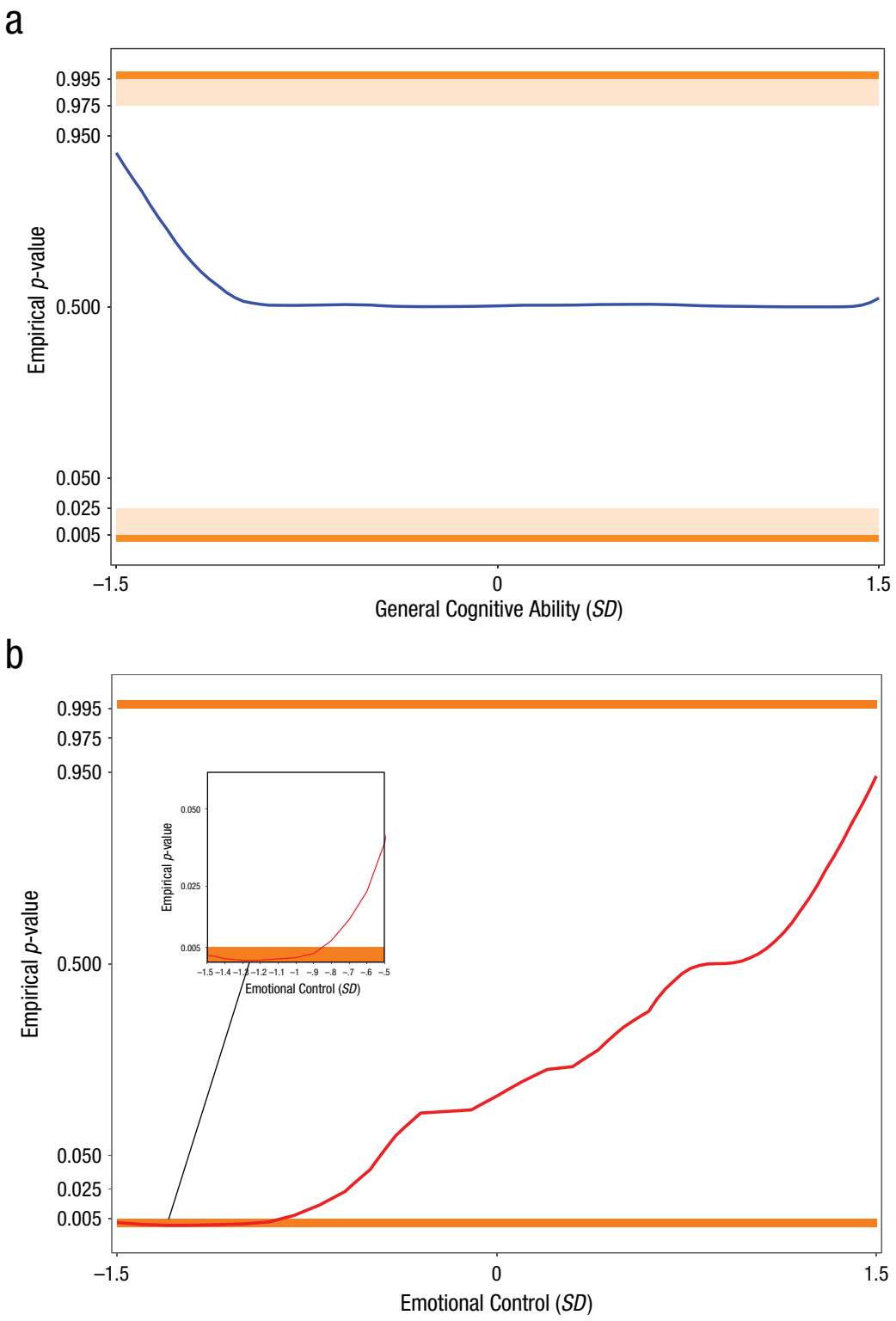

Fig. 3. The average between-cluster edge weight, $M_{r(\mathrm{BC})}$, in 31 local-structural-equation-model-weighted networks across the range of (a) intelligence (blue line) and (b) emotional control (red line). Orange bands indicate empirical *p*-value thresholds ($p < .025$; $p < .005$) at both tails of the distribution. Empirical *p* values were generated by comparing observed $M_{r(\mathrm{BC})}$ values with the empirical null distribution.

Longitudinal prediction of internalizing-aggression bridge symptoms

To determine whether the three aggression nodes identified as bridge nodes in the cross-sectional network prospectively predicted, or were prospectively predicted by, internalizing symptoms, we created two sampling distributions (k = 10,000 each): (a) the percentage of connections between Wave 1 internalizing nodes and three randomly sampled Wave 2 aggression nodes, and (b) the percentage of connections between three randomly sampled Wave 1 aggression nodes and Wave 2 internalizing nodes.

Internalizing at Wave 1 predicting bridge aggression at Wave 2. Internalizing nodes at Wave 1 displayed 7.8% of potential connections with the three bridge-aggression nodes at Wave 2 but displayed only 1.4% of potential connections with non-bridge-aggression nodes at Wave 2. Observed connections from Wave 1 internalizing to Wave 2 bridge-aggression nodes were significantly greater than connections between Wave 1 internalizing nodes and randomly sampled aggression nodes at Wave 2 (empirical $p < .001$; empirical distribution range = 0.0%–7.8%). Figure S5 in the Supplemental Material displays the observed percentage of internalizing to bridge-aggression connections within the empirical cumulative distribution function of the percentage of connections in randomly sampled data.

Bridge aggression at Wave 1 predicting internalizing at Wave 2. Bridge-aggression nodes at Wave 1 displayed 11.8% of potential connections with internalizing nodes at Wave 2, whereas non-bridge-aggression nodes at Wave 1 displayed only 3.2% of potential connections with internalizing nodes at Wave 2. Observed connections from Wave 1 bridge aggression to Wave 2 internalizing nodes were significantly greater than connections between randomly sampled aggression nodes at Wave 1 and internalizing nodes at Wave 2 (empirical $p < .02$; empirical distribution range = 0.0%–13.7%). Figure S6 in the Supplemental Material displays the observed percentage of bridge aggression to internalizing connections within the empirical cumulative distribution function of the percentage of connections in randomly sampled data.

Discussion

To our knowledge, this is the first study to examine transdiagnostic psychopathology symptom covariation in adolescence using a network of partial, regularized correlations. This study was also innovative in its application of a method for assessing the moderating role of individual differences in cognitive control on symptom-level comorbidity. We found that symptoms in the network generally clustered according to clinically defined boundaries, with clustering defined as many and relatively strong interconnections.

Looking across clusters, we found specific patterns of association between different domains. Internalizing symptoms connected strongly to just three symptoms of aggression, all measuring interpersonal irritability. Longitudinal follow-up demonstrated the prognostic value of these symptoms in connecting future internalizing and aggression problems. That is, symptoms of interpersonal irritability were significantly predictive of, and predicted by, internalizing symptoms relative to other aggression symptoms. This finding is consistent with recent work that found irritability and interpersonal difficulty to be among the most salient bridge symptoms connecting these domains (Rouquette et al., 2018). That frustration and displeasure with other people are bridge symptoms for the internalizing and externalizing domains complements previous work showing that reactive, but not proactive, aggression is related to internalizing symptoms in adolescents (Fite, Rathert, Stoppelbein, & Greening, 2012; Fite, Rubens, Preddy, Raine, & Pardini, 2014; Fite, Stoppelbein, & Greening, 2009). Learning problems displayed similar between-cluster specificity, demonstrating strong average connections with only five symptoms of inattention. The specificity of this relationship is consistent with literature demonstrating that teacher-reported attention problems predict poor academic performance (Lundervold, Bøe, & Lundervold, 2017) more strongly than other common forms of child and adolescent psychopathology (Sijtsema, Verboom, Penninx, Verhulst, & Ormel, 2014). Externalizing domains (rule breaking/conduct problems, aggression, and hyperactivity) showed more disperse interconnectedness, consistent with factor-analytic work that has demonstrated the nonspecificity of externalizing symptoms to diagnostic categories (Krueger et al., 2002; Krueger, Markon, Patrick, & Iacono, 2005).

Nineteen symptoms emerged as having relatively strong, average connections with all other cross-cluster symptoms. We interpreted these as transdiagnostic bridge symptoms, or symptoms that might be important unifiers of psychopathology in adolescence. Six of these symptoms were again relevant to interpersonal irritability, a finding that is consistent with interpersonal theories of developmental psychopathology, which posit that diverse psychopathologies arise from conflict between interpersonal difficulties and basic needs for kinship (Rudolph, Lansford, & Rodkin, 2016). Particularly given that our longitudinal analyses demonstrated that symptoms of interpersonal irritability predicted

future internalizing symptoms (and vice versa), it is intriguing to speculate whether psychological interventions targeting interpersonal irritability would decrease rates of comorbidity between internalizing and externalizing psychopathology.

Considering the contribution of cognitive control to symptom-level comorbidity, we found that intelligence, when added as a node in the network, demonstrated the greatest number of connections to all other nodes in the network. This supports the well-established relevance of cognitive ability to transdiagnostic psychopathology (Caspi & Moffitt, 2018; Snyder et al., 2015). Our finding extends this work by highlighting that cognitive ability may be centrally important to psychiatric comorbidity via its pervasive connections to specific symptoms. However, we found that intelligence was not significantly related to the average strength of between-cluster connections.

In contrast, we found that emotional control was less central to the network but displayed more relevance in moderation analyses than intelligence. Contrary to our hypothesis, between-cluster symptom connections were significantly weaker at lower levels of emotional control. Given the counterintuitiveness of this finding, we conducted exploratory post hoc analyses to probe connections between specific domains. Analyses of the average connection between internalizing and aggression domains and between externalizing domains were more consistent with the hypothesized trend of greater between-cluster symptom coactivation at lower levels of emotional control. These were post hoc exploratory analyses that warrant replication, and they do not account for the global trend observed across all domains of psychopathology. Taken together, our findings do not support the hypothesis that cognitive control moderates the co-occurrence of symptoms across domains of psychopathology. However, the method we introduced for generating LOSEM-weighted networks to analyze moderation of psychological networks can be productively applied to examine other potential moderators, both experimentally manipulated (e.g., type of psychological treatment) and naturally occurring (e.g., treatment adherence).

Our study has four major limitations. First, although a prominent version of network theory, distinct from but informed by network analysis, suggests that causal relationships between symptoms drive and sustain psychopathological networks (Borsboom, 2017; Borsboom & Cramer, 2013), our data were primarily cross-sectional correlations that cannot be used to ascertain causal relationships. Indeed, the measurement of causal processes within an idiographic system is most proximally captured using high-density sampling methods (e.g., ecological momentary assessment; Fisher, 2015; Hofmann, Curtiss, & McNally, 2016). Cross-sectional data or between-person longitudinal data cannot be used for such processes. Rather, such data offer the capacity to draw nomothetic inferences about symptom covariance and the factors that impinge on that covariance in a network. Second, data were self-reported. Child and adolescent behavior is subject to contextual variability, and the use of multiple reporters can help to increase the accuracy and coverage of emotional and behavioral problems (Dirks, De Los Reyes, Briggs-Gowan, Cella, & Wakschlag, 2012; Hunsley & Mash, 2007). Network analyses of child and adolescent samples may benefit from using diverse assessment instruments to capture symptom-level presentation more precisely in these populations. Third, although our data covered the most common forms of psychopathology in adolescence (Achenbach, 1966; Achenbach & Edelbrock, 1983; Michaud & Fombonne, 2005), symptoms from rarer forms of psychopathology, such as schizophrenia, bipolar disorder, or autism spectrum disorders, were not assessed. Future studies would benefit from a more comprehensive scope of transdiagnostic psychopathology symptoms in adolescence. Fourth, cross-cluster comorbidity was quantified using a single, global metric that is opaque regarding which disorders, and which symptoms within those disorders, most robustly drive the metric.

In conclusion, our study extends work on psychiatric comorbidity by highlighting unique symptom relationships that potentially drive the co-occurrence of distinct domains of psychopathology. We highlighted a number of bridge symptoms that may be salient conduits of comorbidity in adolescence. Particularly, we illustrated the specificity of symptoms of interpersonal irritability in uniting internalizing and aggression symptoms over time. Further, we demonstrated that intelligence, as a proxy for cold regulatory capacities, is pervasively associated with psychopathological symptoms but does not impact liability for comorbid symptom-to-symptom relationships in a network. In contrast, emotion-based regulatory ability is associated with the strength of symptom comorbidity, although its association is dependent on the specific domains in question. This study highlights interpersonal irritability as a promising intervention target for adolescents dealing with both internalizing and externalizing problems.

Action Editor

Stefan G. Hofmann served as action editor for this article.

Author Contributions

K. P. Harden, M. Rhemtulla, and J. W. Madole developed the study concept and design. J. W. Madole performed the data

analysis and interpretation under the supervision of M. Rhemtulla and K. P. Harden. All the authors helped in drafting the manuscript and providing critical revisions. All the authors approved the final manuscript for submission.

ORCID iDs

James W. Madole https://orcid.org/0000-0002-2301-0004
Mijke Rhemtulla https://orcid.org/0000-0003-2572-2424

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Declaration of Conflicting Interests

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Supplemental Material

Additional supporting information can be found at http://journals.sagepub.com/doi/suppl/10.1177/2167702619842466

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Notes

1. Polychoric correlation matrices are often nonpositive definite because the entire correlation matrix is not estimated at one time, and this problem appears to be compounded when using weighted polychoric matrices (Rigdon, 1997).
2. Sibling 3 was grouped with Twin 2 for those families with triplets.

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