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Supplementary Material

Article Title: Symptom Network Analysis of Attention-Deficit/Hyperactivity Disorder and Emotional Symptoms in Adults: Results From the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

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DISCLAIMER

Supplementary Material: Methods

Details on the NESARC

The NESARC-II is a representative sample collected in 2004-2005 on the non-institutionalized U.S. population, consisting of 34,653 civilian participants over the age of 18, with 86.7% response rate. Trained members of the U.S. Census Bureau conducted face-to-face interviews. The study protocol, which included written informed consent procedures, obtained full approval from the U.S. Census Bureau and the Office of Management and Budget. Sampling weights were employed to ensure that the sample reflected the U.S. population and accounted for nonresponse and sample attrition, regarding socioeconomic variables based on the 2000 Decennial Census [1]. Detailed information regarding the sampling and weighting procedures are given in [2,3]. Missing data is processed by deleting individuals with at least one missing value.

AUDADIS-IV

The AUDADIS-IV methods to diagnose ADHD are detailed elsewhere [4–6]. To summarize, in these different validation and reliability studies, Wave 2 NESARC respondents who completed the entire Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV) interview were randomly selected for a retest interview at one of four Census Bureau regional offices. Each office conducted in-person reinterviews within 10 weeks of the initial survey. In Boston, sections on acculturation, discrimination, stress, social networks, support, adverse childhood experiences, and abuse were tested with a 91.9% response rate (518 initial, 476 interviewed). Philadelphia tested DSM-IV personality disorders with an 87.9% response rate (552 initial, 485 interviewed). Detroit focused on DSM-IV PTSD and discrimination with a 92.8% response rate (526 initial, 488 interviewed). Denver tested ADHD, sexual orientation and behavior, intimate partner violence, and sexual orientation discrimination with a 93.7% response rate (480 initial, 450 interviewed).

Regarding ADHD, the test–retests concentrated on five DSM-IV diagnoses, including two Axis I disorders: PTSD and ADHD. The test–retest statistics cover 12-month and lifetime diagnoses of PTSD, as well as ADHD diagnoses during childhood (before age 18) and adulthood (since age 18). Additionally, the reliability of DSM-IV lifetime diagnoses of Axis II disorders, specifically borderline, schizotypal, and narcissistic personality disorders (PDs), was assessed. For each DSM-IV disorder, intraclass correlation coefficients were calculated based on scales constructed from the associated diagnostic symptom items, such as symptom counts. For ADHD, the test-retest reliability showed a kappa of 0.71 (SE = 0.12) for childhood diagnoses and 0.63 (SE = 0.09) for adult diagnoses, with prevalence rates of 0.05/0.06 and 0.03/0.02 respectively, and an intraclass correlation coefficient (ICC) of 0.75 (95% CI: 0.71, 0.78) for adult ADHD symptom scales, with an alpha of 0.89 [4–6].

ADHD symptoms

These symptoms had to be present for at least 6 months, have onset before the age of 18 and significantly interfere with social, school, or work functioning. The age of onset criterion was increased to 18 years old, with a diagnosis in adults which is made if the symptoms began before the age of 12, as endorsed by the DSM-5 ADHD committee [7,8]. Test-retest reliability for ADHD was good (k=0.71) [9]. Internal consistency reliability of the ADHD symptom items (Cronbach's α= 0.89) was excellent [9].

ED symptoms

ED encompasses emotional experiences and expressions that are: i) excessive and context-inappropriate as regards social norms, ii) rapid, poorly controlled shifts in emotion (i.e., "emotional lability"), iii) characterized by an anomalous allocation of attention to emotional stimuli [10]. ED-related symptoms comprise sudden mood changes or loss of emotional control, as well as explosive anger or anger related to minor events, e.g., leading individuals with ADHD to engage in aggressive behaviour towards objects, themselves or others [11–13].

The ED dimension showed satisfactory reliability and validity [14,15], an independent effect on the functional consequences of ADHD (e.g., in social relationships, comorbidities or quality of life) [12,13,16–18] and constitutes a potential pharmacological and psychotherapeutic lever [19,20].

In this study, participants were asked if they "had a lot of sudden mood changes", if they "often had temper outbursts or gotten so angry that [they] lose control", if they have "hit people or thrown things when [they] got angry" and if "even little things made [them)] angry or have [them] had difficulty controlling [their] anger". Participants reporting at least one of these reactions and who did not fulfill all of the criteria for borderline personality disorder were considered as presenting ED. We did not include patients with this disorder because our focus is on emotional symptoms rather than the singular construct of borderline personality disorder, which have to be diagnosed based on a certain threshold of symptoms. We aim to compare emotional symptoms with ADHD symptoms, rather than comparing the "construct of borderline disorder" with the "construct of ADHD".

The choice of the ED symptoms in this study was based on the definition of ED [10] and justified as follows:

1) One symptom is related to sudden mood changes (here referred to as "Lot of sudden mood changes"), related to emotional lability and poor control shift in emotions.

2) Two symptoms are related to explosive anger and anger related to minor events (here referred to as "Anger for little things" and "Outburst angry"), related to excessiveness in relation to social norms and context-inappropriate.

3) One symptom is related to the functional impact of relationship difficulties, leading individuals with ADHD to potentially engage in aggressive behavior with others (here referred to as "Hit people or thrown things"), related to the inability to promote adaptive and goal-oriented behaviors.

Test-retest, as well as convergent, discriminant or construct validity could not be specifically tested for this set of symptoms.

Weighted prevalence of ADHD symptoms and ED symptoms

We provide the number and percentage of patients meeting ADHD criteria (≥ 6 symptoms in at least one dimension), and the number of patients who have more than 6 symptoms in both dimensions. Regarding the diagnosis of ADHD symptoms and ED symptoms, separately, weighted prevalence of estimates with standard errors (SEs) and adjusted odds-ratio (aOR) estimates and 95% confidence intervals (95% CI) were computed (using multiple logistic regressions). Weighted prevalence, given in a specific table (**Table 1**), refer to an adjustment of the frequencies to the total number of symptoms for each individual. Percentage of each symptom by dimension is also given in **Supplementary Table 1**.

Network estimation and visualization

Network analysis characterizes structures of a system, in terms of nodes (aka "symptoms" or "diagnostic criteria") and edges which connect the nodes (aka correlation coefficients). The focus on symptoms rather than factorial analysis allows to avoid using the notion of latent variable, which are entities, by definition, not directly observed in clinical practice. A latent variable like the "ADHD category" is never directly observed by clinicians; it is inferred based on a collection of symptoms that are clinically measured. The significance for clinical practice is that it enables direct measurement of what clinicians observe during consultations, rather than relying on a theoretical, inferred diagnosis that exists independently of the symptoms.

In this study, symptom networks consist of nodes built on symptoms of the DSM-5 ADHD, belonging to the attentional and/or impulsive/hyperactive dimension, and ED symptoms, belonging to the ED dimension) and edges (the connections between these symptoms), which represent the conditional pairwise relations between two symptoms, controlling for all other symptoms in the network [21].

A computational network analysis was conducted according to the network guidelines for the computational analysis of network properties [21(p20)]. The estimation of pairwise relationships between criteria can be seen as conditional dependence relations. With such partial correlations, association between two diagnostic criteria means that they remain conditionally dependent after controlling for all other associations among criteria in the global network. Conversely, if no edge emerges between two criteria, they are conditionally independent after controlling for the associations among all other criteria. In parallel, a correlation matrix was provided to visualize the pairwise correlations, based on simple correlations between each pair of variables. In the network, based on partial correlations, these direct negative relationships may be attenuated or disappear because partial correlations control for the influence of other variables in the model. For instance, a negative relationship observed in simple correlations might be due to the influence of a third variable, which is accounted for in partial correlations.

The criteria network of the two scales are graphically represented according to a Fruchterman-Reingold algorithm. In this representation, the weight of the connection between two nodes is proportional to the correlation measure, and the place of the node is positioned according to a force-directed graph measure, so that criterion with stronger and/or more connections are placed closer to each other. Nodes that are nearer to the center of the graph have the strongest connections to other nodes.

We estimated a network via an Ising model whereby edges signify conditional independence relationships among the nodes (i.e., partial correlations between pairs of nodes controlling for the influence of all other nodes).
We regularized our model by running the graphical LASSO (Least Absolute Shrinkage and Selection Operator) [22] to avoid false-positive edges. The aims of this regularization are to compute (regularized) partial correlations between pairs of criteria (thereby eliminating spurious associations attributable to the influence of other criteria in the network), and to shrink trivially small associations to zero, removing them from the graph as potentially "false positive" edges (thereby returning a sparse graph comprising only the strongest edges).
Additionally, we use extended Bayesian Information Criterion (EBIC) model selection [23] in a two-step procedure: 100 different network models with different degrees of sparsity are estimated, and then the model with the lowest EBIC is selected, given a certain value on the hyperparameter gamma (γ), which controls the trade-off between including false-positive edges and removing true edges. The hyperparameter γ is usually set between zero and 0.5 [24]. We opted to set γ to 0.5 to be confident that our edges are truly authentic, given that the closer one chooses a value of γ near 0.5, the more the EBIC will favor a simpler model containing fewer edges, whereas the closer one chooses a value of γ near zero, the more the EBIC will favor a model with more edges.
Nodal predictability was calculated based on models derived from Mixed Graphical Models (MGM) [25] and graphically represented as a pie chart in the ring around each variable. Predictability has a value between 0 and 1, provided on the basis of the variance of the prediction error calculated according to the R^2 of the MGM. It refers to how well a given node in the network can be predicted by all remaining nodes. It thus shows how relevant edges are, e.g., a node may be connected to many other nodes but if these only explain only 1% of its variance, it is unlikely that this node is very relevant. This has further implications: for example, designing an intervention to affect certain nodes, or detecting where data is lacking (e.g., when parts of the network are little influenced by related nodes and thus must depend on external factors). In clinical practice, predictability of a symptom indicates "whether an intervention on that symptom through the symptom network is promising" [25].
Concerning the computational analysis, processing and graphical visualizations used the R (4.2.3) package *bootnet* (version 1.2.3) [24], which leads more strongly connected sets of nodes to cluster closer together than the R-packages *IsingFit* (version 0.3.1) [26(p201)], Pearson correlations for the binary data in our dataset and with the *qgraph* package for visualization (version 1.6.3) [27]. Expected influence and bridge symptoms (see below) were calculated with the *networktools* R package.

Network inferences: centrality and bridge measures

Network analysis provides interesting inferences, both qualitative (visual) and quantitative (statistically determined). Concerning these network inferences, the clustering coefficient can be approximated to three times the number of triangles divided by the number of connected triples of vertices (Newman, 2001; Newman et al., 2002). The shortest path length between two nodes equals the minimum number of edges that must be passed over to get from one to the other. The average shortest path length is the average over the shortest path lengths of all node pairs.
The local measures of a network are related to centrality measures. Centrality measures play a crucial role in connecting two or more nodes (Cramer et al., 2010; Jones et al., 2018). Nodes with high centrality index measures represent criteria that are highly connected to other criteria. In a nutshell, centrality can be understood to reflect how connected and thus potentially clinically relevant a diagnostic criterion is in a network (via paths through other diagnostic symptoms, intervening on a highly central diagnostic criterion, other nodes will be both directly and indirectly affected). Measures of centrality are given with standardized z-scores, i.e., standardized coefficients calculated by subtracting the mean and dividing by the standard deviation for each observation. The correlations between criteria may be considered as stronger when the nodes have higher centrality. In the network graph based on a Fruchterman-Reingold algorithm, central nodes often end up in the center of the graph and nodes with low centrality in the periphery. Four centrality measures are classically given in network studies of symptoms of psychopathology: *Strength*, *Closeness*, *Betweenness* and *Expected Influence*. To help understand these measures, by analogy, the ADHD network can be considered like a railroad network map, with the city being considered as a node, and the railroad between two cities as a connection.
Node strength is the sum of the weights of the edges attached to that node. The weighted number of connections for a given node, and the degree to which it is connected with all the other nodes of the network can be computed (Barrat et al., 2004). A criterion has high strength centrality if this criterion is highly connected to all the other criteria. In the rail network metaphor, a city has high strength if it is connected to an extremely large number of other cities, e.g., Washington in the USA.
The closeness of a node is computed according to the shortest path length measure and is inversely proportional to the shortest mean distance from all the other nodes (Boccaletti et al., 2006). Closeness centrality indicates the average distance of a node from all other nodes in the network and is computed as the inverse of the weighted sum of shortest path lengths to a given node from all other nodes in the network. A criterion has high closeness centrality if the criterion can be connected shortly to other criteria (Bringmann et al., 2019; Richetin et al., 2017; Smith et al., 2017). Using the rail network metaphor, a city has high closeness if it is central compared to many other cities, i.e., it is "close" to many others, e.g., like Kansas City which is geographically central on the map of the USA.
The betweenness of a node computes the degree to which a given node connect different parts of the network, thus reflecting the degree to which it controls the flow of information across the network. The betweenness centrality of a node equals the number of times that it lies on the shortest path length between any pair of other nodes. A criterion has high betweenness centrality if the criterion can influence the connection between non-adjacent (i.e., not directly connected) criteria, thus acting as gatekeeper (Bringmann et al., 2019; Bringmann et al., 2013). In the railroad network metaphor, a city has high betweenness if it is necessary to transit through that city to reach other cities, like Las Vegas, which should be passed through on the route between San Francisco and New York City.
Finally, the expected influence of a node is computed to improve the measurement of centrality of the nodes in a network (Robinaugh et al., 2016). It is computed as the sum of all edges which extend from a given node, accounting for both positive and negative correlation values with regard to the entire network. A criterion with high Expected Influence has an influence on the criteria network based on its positive correlations, negative correlations being corrected by this centrality measure. In the railroad network metaphor, a city has a high expected influence if it is connected to an extremely large number of connected neighboring cities, considering possible negative correlation values between cities.
Centrality measures are differentiated from bridge measures, which can be assessed by using bridge centrality statistics (Heeren et al., 2018; Jones et al., 2018; Opsahl et al., 2010). Bridge symptoms connect different clusters of symptoms [28]. They can specifically be used to detect and quantify interacting symptoms between "modules" [29], aka ADHD dimensions. They can specifically be used to detect and quantify interacting symptoms between "modules" [29], herein ADHD attentional and hyperactive/impulsive dimensions. Two conceptions of bridge symptoms should be distinguished [28]: either there are symptoms belonging to two or more clusters/disorders and allow an overlap between them; either these symptoms belong to just one cluster/disorder, or alternatively are not specific symptoms of a cluster/disorder, and play an important role in connecting different clusters/disorders. In this article, we refer to the second conception: bridge symptoms account for the connection between clusters of symptoms (of ADHD). In this study, we provide bridgeness in terms of strength (defined as the sum of the absolute value of all edges that exist between a specific node and all nodes that are not in the same community as this specific node). This comparison is completed with the calculation of the small-worldness, measured using clustering coefficient (degree to which nodes in a graph tends to cluster together) and the average shortest path length between two nodes (the average over the shortest path lengths of all node pairs) relatively to a random network.

Network robustness (stability)

Concerning the robustness, we refined the analyzes based on the classical bootstrap methods used in the literature on symptom networks, to provide a more precise approach. Two steps were conducted to assess the accuracy of symptom network structures: i) estimating the confidence intervals on the edge-weights; ii) assessing the stability of centrality indices under observing subsets of cases. Network robustness was calculated by the analysis of the centrality stability, with the use of a correlation coefficient (CS-coefficient). The CS-coefficient represents the maximum proportion of participants that can be dropped while maintaining 95% probability that the correlation between centrality metrics from the full data set and the subset data are at least 0.70. Based on a simulation study (Epskamp et al., 2017), a minimum CS-coefficient of 0.25 is recommended for interpreting centrality indices.

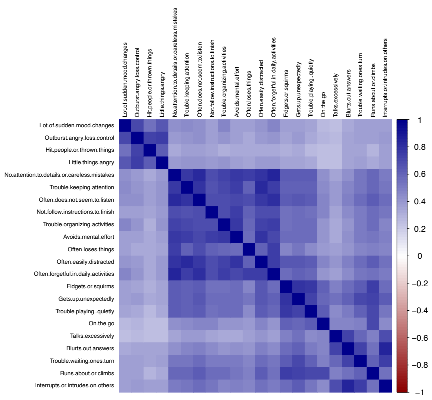
Small-worldness

We provide a small-world measure for the network. Small-worldness is measured using clustering coefficient (degree to which nodes in a graph tend to cluster together), the average shortest path length (APL – the average over the shortest path lengths of all node pairs), relatively to a random network (i.e., a network whose distribution can be described by a random process). Thus, the ADHD-ED network small-worldness index (SWI) is calculated according to the following formula: SWI = (Clustering-ADHD-ED / Clustering-Random) / (APL-ADHD-ED / APL-Random). Small-world measures for the ADHD and emotional symptoms network may be used to evaluate the degree of association between symptoms in this network. This helps clinicians to rapidly look for the other symptoms of such a syndrome (known in network theory as "high signal-propagation speed"), and the global consistency and manipulability of these disorders for clinicians. A network can be called a small-world if its index is higher than 1 [30].

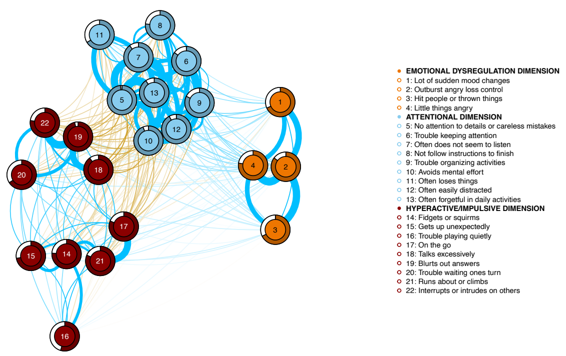
Supplementary Materials: Results

Supplementary Table 1. Number and non-weighted percentages of symptoms on the 33,546 non-institutionalized U.S. civilian participants of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-II). ED: emotion dysregulation. It is interesting to note that the prevalence of the hyperactive/impulsive dimension is relatively high in our sample. In the literature, the prevalences relating to the dimensions of ADHD differ widely depending on the cohorts studied.[31]

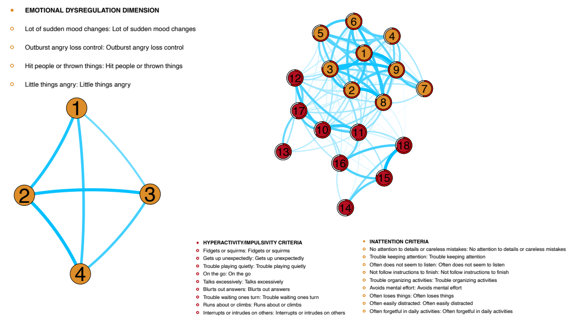
Dimensions	Name of the symptoms	Number of symptoms (N = 33,546)	Percentage of symptoms
Hyperactive/impulsive	On the go	9884	29%
Hyperactive/impulsive	Talks excessively	6994	21%
Hyperactive/impulsive	Runs about or climbs	6771	20%
Attention	Not follow instructions to finish	5440	16%
Attention	Avoids mental effort	4504	13%
Hyperactive/impulsive	Fidgets or squirms	4378	13%
Hyperactive/impulsive	Blurts out answers	4184	12%
Attention	Often does not seem to listen	4170	12%
Attention	Often easily distracted	3833	11%
Hyperactive/impulsive	Interrupts or intrudes on others	3667	11%
	No attention to details or careless mistak	3157	9%
ED	Hit people or thrown things	3041	9%
Hyperactive/impulsive	Trouble playing quietly	2717	8%
ED	Little things angry	2508	7%
ED	Outburst angry loss control	2409	7%
Attention	Trouble keeping attention	2377	7%
Hyperactive/impulsive	Gets up unexpectedly	2350	7%
ED	Lot of sudden mood changes	2341	7%
Attention	Often loses things	2178	6%
Attention	Often forgetful in daily activities	2096	6%
Attention	Trouble organizing activities	2079	6%
Hyperactive/impulsive	Trouble waiting ones turn	2030	6%



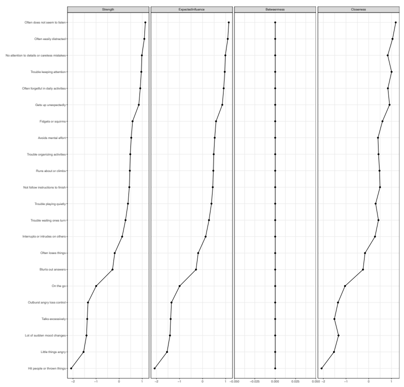
Supplementary Figure 1. Correlation matrix of Attention Deficit Hyperactivity Disorder (ADHD) symptoms and Emotional Dysregulation (ED) symptoms on the 33,546 non-institutionalized U.S. civilian participants of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-II). Regarding differences in negative relationships, the correlation matrix shows direct negative relationships between variables, indicating that an increase in one variable is associated with a decrease in another, without considering other variables.



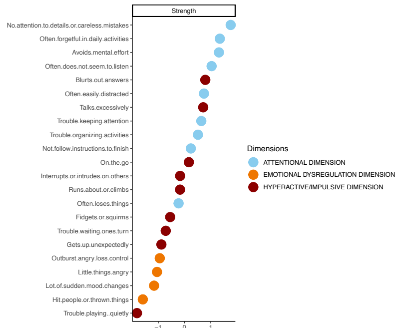
Supplementary Figure 2. Symptom network of the ADHD symptoms and emotional dysregulation (ED) symptoms in patients exceeding ADHD threshold (N= 3397), in non-institutionalized U.S. civilian participants of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-II). The thickness of the lines (edges) represents the level of correlation between two symptoms. Positive correlations are represented in blue. The three dimensions are presented: attentional dimension, hyperactive/impulsive dimension and ED dimension. Predictability of a node is depicted as a pie chart in the rings around nodes: the area in the outer ring of nodes represents the percentage of variance of the node that is explained by all neighboring nodes.



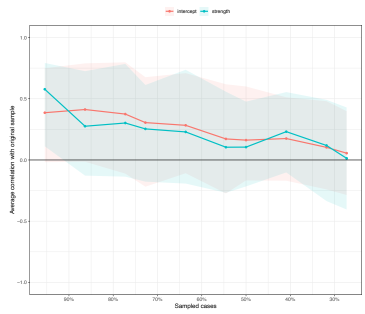
Supplementary Figure 3. **Left**: Symptom network of the Emotional Dysregulation (ED) symptoms. **Right**: Symptom network of the Attention Deficit Hyperactivity Disorder (ADHD) symptoms, based on the 33,546 non-institutionalized U.S. civilian participants of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-II). The thickness of the lines (edges) represents the level of correlation between two symptoms. Positive correlations are represented in blue.



Supplementary Figure 4. The four measures of centrality (Strength, Closeness, Betweenness and Expected influence) of the Attention Deficit Hyperactivity Disorder (ADHD) and Emotional Dysregulation (ED) symptom network on the 33,546 non-institutionalized U.S. civilian participants of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-II). Each of the four vertical tables corresponds to a measure of centrality. Within each table, the highest centrality is on the right, the lowest is on the left. Thus, the rightmost symptoms are the most central. All the tables are classified according to the decrease in centrality of the Strength (from top to bottom). Centrality numbers at the bottom of each vertical table, on the x-axis, show standardized z-scores (i.e., standardized coefficients, calculated by subtracting the mean and dividing by the standard deviation for each observation). A z-score at ~[-2] on the x-axis for Strength (e.g., "Hit people or throw things") indicates that that node has the least strength on the network.



Supplementary Figure 5. Strength-type centrality of the ADHD symptoms and ED symptom network in patients exceeding ADHD threshold (N= 3397), in non-institutionalized U.S. civilian participants of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-II). The rightmost symptom is the most central. Centrality numbers at the bottom of the figure, on the x-axis, show standardized z-scores (i.e., standardized coefficients, calculated by subtracting the mean and dividing by the standard deviation for each observation).



Supplementary Figure 6. Stability analysis based on the bootstrap on the Strength for the Attention Deficit Hyperactivity Disorder (ADHD) and Emotional Dysregulation (ED) network on the 33,546 non-institutionalized U.S. civilian participants of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-II). More precisely, the red curve, read from left to right, corresponds to the modification of the centrality relations (Strength) of the network as the participants are dropped (in %). Thus, if the red curve falls rapidly according to the average correlation with the original sample, the stability of the network is lower than if the curve remains more horizontal. The robustness is low for this model.

Supplementary Materials: Results

Details on the weighted prevalence of ADHD symptoms (Table 2)

The prevalence of attention symptoms varied from 5.93% ("Trouble organizing activities") to 16.84% ("Does not follow instructions"). For hyperactive/impulsive symptoms, the prevalence ranged from 5.92% ("Trouble waiting one's turn") to 30.49% ("Often on the go"). In the ED dimension, the prevalence of symptoms spanned from 28.34% ("Anger for little things") to 33.46% ("Lots of sudden mood changes") (**Table 2**).

On the precaution of interpreting bridge symptoms

This result should be interpreted with great caution regarding its potential for refining phenotypes. The symptoms "Lots of sudden mood changes" and "Outburst angry loss control" certainly appear to act as bridges between the ED dimension and at least one dimension of ADHD, specifically the attentional dimension. However, other symptoms, not necessarily related to ED, could also have been added to the network and potentially functioned similarly as bridges. Therefore, the importance of ED symptoms as bridge symptoms does not imply that they are specific to the ADHD construct. This finding highlights the bridging role of ED symptoms but does not suggest that these symptoms are unique to ADHD or necessarily refine its phenotype.

Such a result should therefore not be interpreted as a need to include ED symptoms in ADHD with a view to nosological refinement. ED symptoms could serve as red flags, acting as warning signs that can support the diagnosis of ADHD, particularly when other symptoms, such as those from the inattention dimension, are more difficult to identify. As bridges, ED symptoms reinforce the possibility to clinically identify ADHD symptoms (and especially of the attentional dimension).