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PSYCHOPATHOLOGY

A UCL BSc Psychology 3rd Year Research Project

Investigating Psychopathological Comorbidity
in Childhood and Adolescence using Network Analysis

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Abstract

Background: Network approaches present a novel reconceptualization of psychopathology. By viewing disorders as clusters of highly interrelated symptoms, comorbidity can be understood as the patterns of connections between symptom clusters. To identify symptoms that ‘bridge’ disorder groups, a network of internalizing and externalizing symptoms was constructed.

Method: A symptom network was constructed using maternal report data from the Avon Longitudinal Study of Parents and Children (ALSPAC, $N = 15,444$). 59 symptoms from eight disorder categories of psychopathology were included. A machine-learning algorithm was used to compare different possible combinations of symptom connections. This process removed spurious links while retaining important connections within the network. A sparse network containing only significant connections was produced as a result. Central symptoms hold connective importance within networks. Two indices were used to assess symptom centrality: “Betweenness” and “Two-step-expected-influence”. The symptom network was then visually filtered to produce a summary of high strength, trans-diagnostic comorbid symptom connections.

Results: The organization of our network fit the DSM. Interestingly, connections between symptoms also changed across time. The number of important symptom-to-symptom relationships, and the significance of their connections within the network increased over time. Multiple clinically relevant symptom bridges were found. Symptoms within separation anxiety and obsessive-compulsive disorders were identified as important connective bridges. This may indicate these symptoms play either an important causal or connective role within the network.

Conclusion: Our findings show that different patterns of symptom level relationships are responsible for disorder comorbidity. Furthermore, our network suggests that these symptom relationships change across development. Therefore, symptom level connections reveal important relationships between disorders. These connections thus have clinical significance and may reflect causal pathways to comorbidity.

Keywords: Developmental · Psychopathology · Comorbidity · Network analysis · ALSPAC · Bridge nodes · Obsessive-compulsive disorder

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In mental health research, it is widely acknowledged that individuals treated for an incident psychopathological disorder are at risk of subsequently developing comorbid psychopathologies. Community surveys report that among respondents with at least one mental disorder, 45% to 54% go on to develop at least one additional lifetime diagnosis (Andrews G, Slade T, Issakidis C, 2002; Robins & Reiger, 1991; Bijl, Ravelli & Van Zessen 1998). Comorbidity is associated with disorder severity and disruption to everyday life. Patients with comorbid psychopathologies express greater need for professional help, higher suicide rates, and a poorer prognosis (Albert et al., 2008; Brown et al., 1995; Schoevers et al., 2005).

Latent construct and *p* factor explanations of comorbidity

Our understanding of why disorders are comorbid is incomplete. Clinical measurements of comorbidity suggest the covariation between two disorders can be the product of a genuine connection between disorders, or an artefact created by the structure of our diagnostic tools (Zachar, 2009). Frequencies of comorbid diagnoses are too high for comorbidity to merely be a diagnostic artefact (Van Loo & Romeijn, 2015; Zachar, 2009). Therefore, what is becoming evident is that our understanding of comorbidity is dependent on the way that we classify and portray psychometric variables.

Modern classification systems use a latent variable model. The latent variable model assumes that disorders can be represented as latent attributes. Therefore, the presence of a disorder – for example, depression – is estimated by the frequency of its reported symptoms. This implies that the latent attribute has caused such symptoms to appear. (Borsboom, 2008; Borsboom et al., 2003; 2004) Accordingly, comorbidity is the relation between two latent variables (Borsboom & Cramer, 2013). Diagnostic systems

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hence account for comorbidity by framing psychopathology in a small number of connected, broader, trans-diagnostic dimensions (e.g. Internalizing and externalising disorders).

Further research demonstrating correlations between these disorder dimensions have led researchers to theorize on the presence of a general psychopathological factor, *p*. This has been proposed to explain the co-occurrence of all psychiatric symptoms and disorders (Caspi & Moffitt, 2018; Lahey et al., 2012). While research has supported the presence of such a factor, a solid theoretical interpretation has proven elusive (Caspi et al., 2013; Lahey et al., 2012; Patalay et al., 2015). The most popular interpretation suggests that the *p*-factor represents a shared etiological factor, or set of factors that predispose an individual to the development of other forms of psychopathology (Murray, Eisner and Ribeaud, 2016).

The latent variable approach however is far from perfect at describing the psychometric properties of psychopathology. A key issue raised by psychometricians relates to the axiom of local independence (Borsboom & Cramer, 2013; Borsboom 2008). According to this axiom, for an inference to a latent variable as the common cause of a symptom covariance to be justifiable, the covariance among symptoms must disappear if one makes them conditional on the presence of the latent factor. Clear examples where this assumption holds can be seen in medicine, or in neurodevelopmental disorders with a strong genetic component. For example, in Down syndrome, statistically controlling for the presence of a third copy of chromosome 21 eliminates the correlations between intellectual deficiencies, a crease across the palm, short stature and a protruding tongue (Borsboom et al., 2017). However, the situation is different for depression and most other psychiatric syndromes where obvious causal

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connections among the symptoms occur. For instance, a symptom that is part of depression such as insomnia inevitably causes sleep deprivation. Sleep deprivation would cause an increase in irritability, which causes a further increase in low mood and depressed feelings. Increases in depressed feelings would exacerbate an individual's initial insomnia. Thus, depressive symptoms are connected in the form of a causal chain that exhibits positive feedback. Causal relations abide among the symptoms of depression, which is a conclusion forbidden by the psychometric requirements of latent variable models. The same is true for many other psychopathological disorders.

The limits of our latent psychometric models relate directly to the ongoing clinical challenges faced by the DSM, such as the presence of arbitrary thresholds (Krueger & Eaton, 2015) and symptom overlap (Borsboom et al., 2011). In this regard, the reliance of the DSM on the concept of latent variables has likely impeded our attempts to uncover and understand the physiological markers and environmental risk factors for psychopathology (Cross-Disorder Group of the Psychiatric Genetics Consortium, 2013; Green et al 2010). This has led for calls to broaden the perspectives through which comorbid psychopathologies are understood.

Recently, the network approach is proving to be a useful alternative school of thought through which we can understand comorbidity. Cramer & Borsboom (2010; 2013) assert that a reason why central disease mechanisms (latent attributes) for common psychopathologies have remained elusive is because these mechanisms may not necessarily exist. For example in depression, symptoms such as slowness of movement, fatigue and diminished cognitive capacity may be caused by other symptoms such as a lack of sleep, instead of an underlying cause. Thus, symptoms from different psychopathological disorders are hypothesised to cause each other.

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Network theories of psychopathology

Networks represent the relationships between variables graphically: Nodes represent entities, and edges represent their relationships (Newman, 2018). In psychological networks, nodes are interpreted as variables, and single edges represent the association between two variables (Costantini et al., 2014). This perspective places emphasis on the conceptualization of disorders as networks of interconnected components, instead of latent constructs (Bringmann et al., 2019). Therefore, psychopathological disorders can be visualised as clustered groups of symptoms that are strongly associated with one another (See figure 1.)

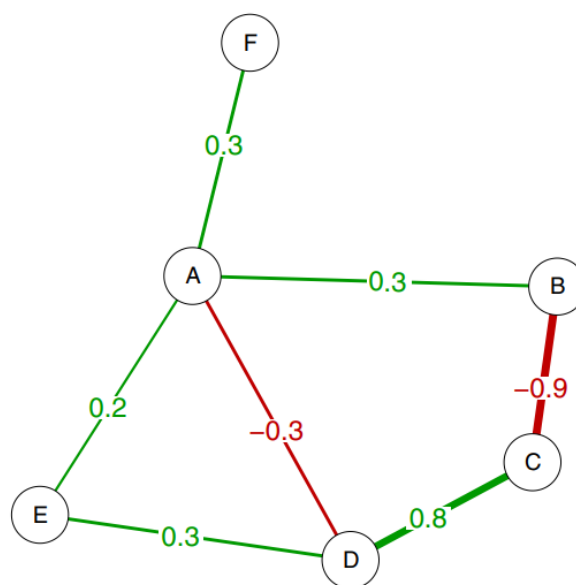


Figure 1. An example symptom network from Constantini et al., (2015). The network contains six symptom nodes and seven edges. Positive edges are green and negative edges are red. The letters identify the symptoms that each node represents. Numbers represent the weights associated with each edge. Darker edges represent higher correlations.

Borsboom (2017) propose the principle of Hysteresis. External risk factors such as life stress are proposed to activate symptom nodes in a network. These nodes (the initial symptoms presented by a patient) are then proposed to activate other related

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symptom nodes. As nodes in a network are interconnected, this causes a cascade of effects. In a strongly connected symptom network, symptoms can keep each other activated due to feedback relations. As a result the network becomes self-sustaining and may stay active long after external events have waned. During diagnosis, we recognize these activated symptom networks as psychopathological disorders.

It is likely the strength of connections between symptom nodes varies between individuals (Bringmann et al., 2019). What distinguishes individuals who develop psychopathology may be the connectivity of their symptom networks. Borsboom (2017) asserted that in weakly connected networks, serious triggers can still evoke strong reactions, but because the connections between symptoms are not self-sustaining, the network will gradually recover and return to its asymptomatic state. We propose it is possible that measurements of a general factor of psychopathology may allude to variations in the overall connectivity of symptoms between individuals. High latent scores on p - factor scales may indicate the presence of strongly interconnected symptom networks that are easily activated and perpetuate symptom activity.

One of the most novel features of Network Analysis is that it provides several centrality measures that allow researchers to identify symptoms with the greatest importance within the network structure (Rodrigues, 2018). By mapping the structure of symptom networks, we can begin to better portray and understand the relationships between individual symptoms. Network statistics allows us to quantify the importance of a symptom by both the strength of its connections, and position within the network. Doing so may reveal new perspectives on highly comorbid psychopathological symptoms.

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Symptom level comorbidities

The network approach has important implications for comorbidity. Even though symptom-to-symptom (henceforth referred to as ‘symptom-symptom’) connections may be most prevalent within disorders, by no means does this limit them to the borders of our diagnostic manuals. Research has consistently demonstrated that disorders across internalising (Curtiss & Klemanski, 2016; Bekhuis et al., 2016), externalising (Smith et al., 2016) attention deficit (Silk et al., 2019) and psychotic (Isvoranu et al., 2016) dimensions have symptoms-symptom connections that cross diagnostic boundaries. There are also symptoms that may not clearly belong to one disorder as they receive and send out effects to symptoms in multiple disorder groups (Contreras et al., 2019). Though the strength of these symptom relationships tend to be weaker than those within disorders, this does not mean that they are clinically irrelevant.

Identifying symptoms that have strong links to symptoms in other categories psychopathology may be important for the prediction and prevention of comorbid disorders (Contreras et al., 2019). These symptoms may act as “bridges” between disorder clusters, which contribute to rates of comorbidity by allowing for activation in one disorder cluster to spread to others. In individuals with strongly connected symptom networks, the likelihood of network activity spreading through these bridges would be higher (Borsboom, 2017). Bridging symptoms, by nature of their connections, are therefore likely to be located “closer” or more central within psychopathological networks. Thus the location of a node can therefore be an important indicator of its possible causal influence in a network (Bringmann et al., 2019).

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By mapping the structure of symptom networks, we can begin to understand how individual symptoms contribute to comorbidity between disorders. Doing so may reveal new perspectives on comorbid psychopathology.

Developmental psychopathological networks

As most psychopathologies emerge during childhood, mapping the network structure of symptoms during development may yield important insights into how and why psychopathologies develop (Kessler et al. 2005; McElroy et al., 2017). By viewing comorbidity as an emergent property of network activation, symptoms with high clinical importance to the development of later psychopathology can be identified early during development.

Many investigations of the network properties of psychopathology have been conducted in recent years. However, most current investigations of network psychopathology focus on mapping the structures of single disorders, or a small range of comorbid disorders (e.g. Bekhuis et al., 2016). To date, only three other studies have investigated psychiatric comorbidity across internalising and externalising disorder domains. Boschloo et al. (2015) examined the structure of 12 distinct DSM-IV disorders in the second wave of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, N = 34,653). They found that although symptoms clustered in a manner broadly consistent with the DSM structure, symptoms from all disorder groups included in the network were connected, either directly or indirectly. Each cluster of symptom nodes were connected to at least three others. Boschloo et al. (2016) then investigated the network structure of emotional and behavioural problems in a large sample of pre-adolescents. 95 symptoms were assessed using the Youth Self-Report, and the resultant network produced symptoms clustered in patterns that were

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reflective of the YSR domains. They found that connections were stronger within domains compared to between domains.

In both analyses, numerous symptom pairs were found to connect disorders. If latent variable models were accurate, all correlations between symptom pairs linking disorders should be roughly equivalent. Therefore, the defining factor differentiating latent variable models is that they assume all symptom correlations between disorder categories are homogenous. In contrast, the network approach can account for heterogeneous correlations between symptoms of different disorders (Boschloo et al., 2015, see figure 2.).

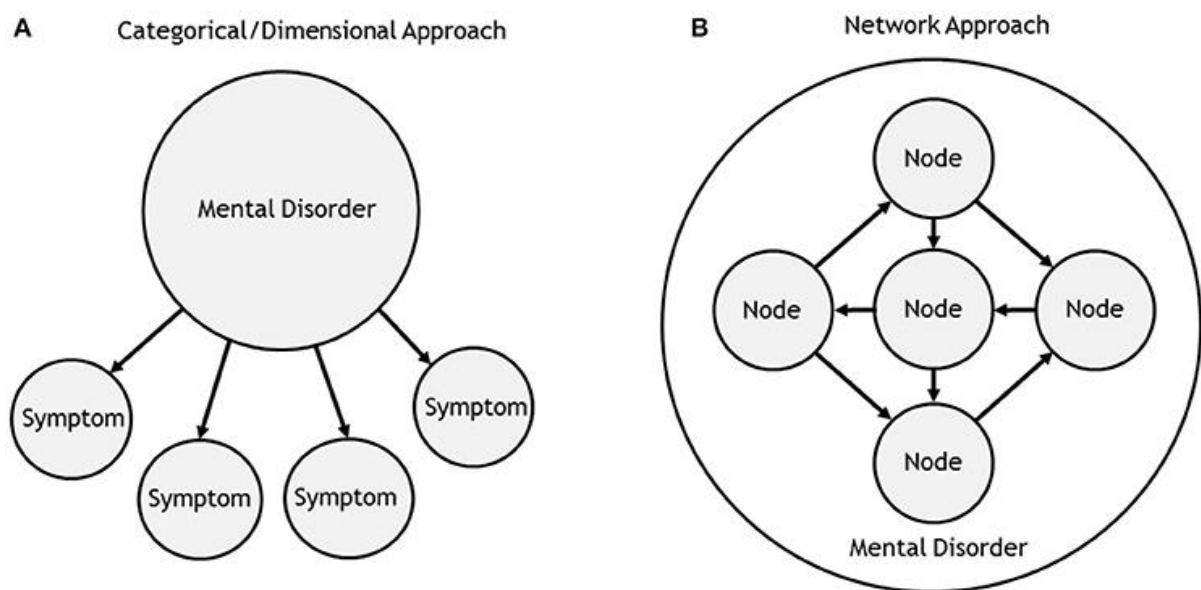


Figure 2. Latent vs. network approaches to Psychopathology. From Jones, Heeren & McNally, (2017). (A) Categorical and dimensional approaches to psychopathology assume that disorders are characterised by a latent entity that causes its symptoms. As a single causal factor is shared amongst all symptoms, thus correlations between symptoms would be homogenous. (B) Network approaches posit that symptoms exert causal influence over each other. Therefore, psychopathological disorders can be conceptualized as connections between interrelated nodes in a complex network. As no single cause is attributed to psychopathological symptoms, correlations between symptoms may be heterogeneous.

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A consistent issue raised within network analysis literature is the limited number of longitudinal studies investigating the consistency of network structures across time. An idea core to network theory is the attribution of causal relationships between nodes in a network. This cannot be done effectively using cross-sectional data. (Forbes et al., 2018). Due to the difficulty of measuring large numbers of symptoms over multiple periods of time, fewer network studies have investigated networks of symptoms across time. McElroy et al. (2017) investigated the network structure using data from the Avon Longitudinal Study of Parents and Children (ALSPAC, N = 4405), for children using maternal reports across three time periods, ages 7.5, 10.5 and 14 years. A network of eight DSM-IV disorders was mapped. A consistent network structure was found across all time points. They found that the network separated into two regions representing internalising and externalising disorders. Multiple disorder level connections were found between internalising and externalising disorders. However, their investigation did not investigate the symptom level connections between these disorders.

These studies emphasise the importance of studying the development of psychopathological networks, using large samples, across time. The same network structure was seen in McElroy et al.'s (2017) study between the ages 7.5 to 14. However, their network presents these relationships at a disorder level, and not on a symptom level. Consistency in a network of relationships at a disorder level does not imply that the symptom level connections that constitute these connections remain the same. As the transition between childhood and adolescence is a time of social, emotional and cognitive change, one would expect symptom level connections to change as an individual develops. Building on previous findings (the work of McElroy et al., 2017) it

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will be interesting to find out whether the constant network connection at the disorder level across development can be observed at a symptom level.

Aims and hypotheses

The aim of this study is to map the network of symptom relationships between frequently comorbid disorders in childhood. By doing this, we aim to first evaluate the effectiveness of DSM categories at describing symptom level data. We then aim to identify important symptom-symptom relationships that link comorbid disorders, as well as identify if and how these symptom bridges change as a child develops.

We therefore hypothesise that the following properties will be seen in our network model:

- 1) The clustering of symptom nodes in our network is anticipated to match the categories under the Diagnostic Systems Manual.
- 2) Nodes within our network are anticipated to cluster into groups of related symptoms, presumably representing latent factors and DSM disorder groups.
- 3) The network is expected to contain multiple trans-diagnostic symptom relationships.
- 4) Of these connections, we expect that the distribution of symptom correlations to be heterogeneous in nature.

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Method

Participants

Our sample consists of 7,635 Male, and 7,219 Female participants. This sample is drawn from the Avon Longitudinal Study of Parents and Children (ALSPAC) database, a study of children born in Bristol, UK, between 1990-92. The sample is broadly representative of the overall population of children in the UK (Golding et al., 2001). Data was collected using self-report postal questionnaires, and via yearly clinics for the study children from the age of 7.5 years. Only questionnaire responses by the mother about the child were be used in the current analysis. More information on this study and details of the data are available on an online data dictionary (<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary>).

Ethical approval for the ALSPAC study was granted by the ALSPAC Ethics and Law Committee, and informed consent was secured from parents. More detailed descriptions of the ALSPAC cohort, including recruitment and assessment procedures are available on the ALSPAC study website (Golding et al., 2001).

Materials

The maternal report versions of the Development and Well-Being Assessment (DAWBA) and Strengths and Difficulties Questionnaire (SDQ) were used in our analysis. The DAWBA is a structured clinical interview used to assign psychiatric diagnoses to 5-16 year olds. It is used to assess fourteen distinct symptom profiles corresponding to the ICD-10 and DSM-IV diagnostic criteria. The symptom profiles from DAWBA used in the present analysis are that of Attention-Deficit Hyperactivity (ADHD-H), Attention-Deficit Impulsivity (ADHD-IM), Attention-Deficit Inattention (ADHD-IN), Separation

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Anxiety (SPA), Social Anxiety (SA), General Anxiety (GAD), Obsessive Compulsive Disorder (OCD), and Awkward/Troubling behaviour – combined symptoms of Oppositional Defiant Disorder and Conduct Disorder (Externalising). The SDQ provided combined symptom measurements for mood and anxiety problems (Depressed Mood & Anxiety). Please refer to Table 1. for symptom labels and short codes. Please refer to appendix C for descriptive statistics, reporting frequency and unabridged questionnaire labels.

In total, 59 questionnaire items were mapped onto the network structure at the two time points: ages 6-7 and 13-14. Eighteen ADHD symptoms, six Separation Anxiety symptoms, eight Social Anxiety symptoms, seven GAD symptoms, five Depressive symptoms, and ten ODD symptoms were used. Symptoms are rated on three-point Likert scales (0 = not true; 1 = sometimes true; 2 = true/often).

Missing data

There is a lack of consensus on how to handle missing data in Network Analysis (Epskamp, 2016). The present study uses pairwise deletion, which is the current common practice. Complete data was available for 5827 maternal reports.

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Node	Disorder Category	Symptom
H.1	ADHD - Hyperactivity	<i>Compared to other children of her age, does she often fidget?</i>
H.2	ADHD - Hyperactivity	<i>Is it hard for her to stay sitting down for long?</i>
H.3	ADHD - Hyperactivity	<i>Does she run or climb about when she shouldn't?</i>
H.4	ADHD - Hyperactivity	<i>Does she find it hard to play or take part in activities without making noise?</i>
H.5	ADHD - Hyperactivity	<i>Is she is rushing about does she find it hard to calm down?</i>
IM.1	ADHD - Impulsivity	<i>Does she often blurt out an answer before she has heard the question?</i>
IM.2	ADHD - Impulsivity	<i>Is it hard for her to wait her turn?</i>
IM.3	ADHD - Impulsivity	<i>Does she often butt in on other people's conversation or games?</i>
IM.4	ADHD - Impulsivity	<i>Does she often go on talking even if she has been asked to stop?</i>
IN.1	ADHD - Inattention	<i>Does she often make careless mistakes or fail to pay attention?</i>
IN.2	ADHD - Inattention	<i>Does she often seem to lose interest in what she is doing?</i>
IN.3	ADHD - Inattention	<i>Does she often not listen to what people are saying to her?</i>
IN.4	ADHD - Inattention	<i>Does she often not finish a job properly?</i>
IN.5	ADHD - Inattention	<i>Is it often hard for her to get herself organised to do something?</i>
IN.6	ADHD - Inattention	<i>Does she often try to get out task such as homework?</i>
IN.7	ADHD - Inattention	<i>Does she often lose things she needs for school or PE?</i>
IN.8	ADHD - Inattention	<i>Is she easily distracted?</i>
IN.9	ADHD - Inattention	<i>Is she often forgetful?</i>
SPA.1	Separation Anxiety	<i>Not wanting to attend school fearing something nasty happening to parents</i>
SPA.2	Separation Anxiety	<i>Has she worried about sleeping alone?</i>
SPA.3	Separation Anxiety	<i>Has she come out of her bedroom at night to check on her caretakers?</i>
SPA.4	Separation Anxiety	<i>Has she worried about sleeping in a strange place?</i>
SPA.5	Separation Anxiety	<i>Has she been afraid of being alone in a room at home without her parents?</i>
SPA.6	Separation Anxiety	<i>Having repeated nightmares about being separated from her parents</i>
SA.1	Social Anxiety	<i>Degree to which child was afraid of meeting new people</i>
SA.2	Social Anxiety	<i>Degree to which child was afraid of meeting lots of people</i>
SA.3	Social Anxiety	<i>Degree to which child was afraid of speaking in class in past month</i>
SA.4	Social Anxiety	<i>Degree to which child was afraid of reading out loud before others</i>
SA.5	Social Anxiety	<i>Degree to which child was afraid of writing in front of others</i>
SA.6	Social Anxiety	<i>Degree to which child was afraid of eating in front of others</i>
G.1	General Anxiety	<i>Does she worry a lot about past behaviour?</i>
G.2	General Anxiety	<i>Expresses frequent fears about school work, homework or tests</i>
G.3	General Anxiety	<i>Expresses frequent fears about examinations</i>
G.4	General Anxiety	<i>Expresses frequent fears about disasters</i>
G.5	General Anxiety	<i>Expresses frequent fears about her own health</i>
G.6	General Anxiety	<i>Expresses frequent fears about Bad things happening to others</i>
G.7	General Anxiety	<i>Expresses frequent fears about The future</i>
C.1	Obsessive Compulsive	<i>Repeatedly cleaned his/herself excessively in past month</i>
C.2	Obsessive Compulsive	<i>Repeatedly taken other special measures to avoid dirt</i>
C.3	Obsessive Compulsive	<i>Repeatedly checked things in past month</i>
C.4	Obsessive Compulsive	<i>Repeatedly performed repeated actions</i>
C.5	Obsessive Compulsive	<i>Repeatedly touched things/people in particular ways</i>
C.6	Obsessive Compulsive	<i>Repeatedly arranged things symmetrically</i>
C.7	Obsessive Compulsive	<i>Repeatedly counted to lucky numbers / avoided unlucky numbers</i>
C.8	Obsessive Compulsive	<i>Frequency child has repeatedly done anything else</i>
D.1	Mood / Anxiety	<i>She has often complained of headaches, stomach aches or sickness</i>
D.2	Mood / Anxiety	<i>She has many worries, often seems worried</i>
D.3	Mood / Anxiety	<i>She is often unhappy, down-hearted or tearful</i>
D.4	Mood / Anxiety	<i>She is nervous or clingy in new situations, easily loses confidence</i>
D.5	Mood / Anxiety	<i>She has many fears, is easily scared</i>
E.1	Behavioural / Conduct	<i>Compared with other children has she had severe temper tantrums?</i>
E.2	Behavioural / Conduct	<i>Has she argued with grown-ups?</i>
E.3	Behavioural / Conduct	<i>Has she taken no notice of rules, or refused to do as she is told?</i>
E.4	Behavioural / Conduct	<i>Has she seemed to do things to annoy other people on purpose?</i>
E.5	Behavioural / Conduct	<i>Has she blamed others for her own mistakes or bad behaviour?</i>
E.6	Behavioural / Conduct	<i>Has she been touchy and easily annoyed?</i>
E.7	Behavioural / Conduct	<i>Has she been angry and resentful?</i>
E.8	Behavioural / Conduct	<i>Has she been spiteful?</i>
E.9	Behavioural / Conduct	<i>Has she tried to get her own back on people?</i>

Table 1. Table of symptom short codes. Abbreviated symptom descriptions, symptom node labels and corresponding disorder categories. Symptoms are rated on three-point Likert scales (0 = not true; 1 = sometimes true; 2 = true/often).

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Statistical analysis

Network estimation

Analysis of the data proceeded in three steps. First, network graphs were visualised using R (R Core Team, 2019; version 3.61) with the package “*qgraph*” (Epskamp et al., 2012). Within each graph, symptoms were represented as nodes and edges represent partial correlation coefficients. Each edge represents the relationship between two symptoms controlling for all other relationships in the network. Green edges represent positive associations, red edges represent negative associations. The thickness of edges indicates the strength of their association. Since our measurements are ordered-categorical, all calculations were based on polychoric correlations.

To control for false positive edges, the least absolute shrinkage and selection operator (lasso) is used (Tibshirani, 1996). By using a graphical lasso (or glasso), the sum of the absolute partial correlation coefficients within the network is limited, shrinking all correlation estimates. As a result, very small edges (i.e. very small correlations) were set to zero. This calculation is based on a tuning parameter (called a hyper-parameter) that sets the stringency of lasso regularization (Mazumder & Hastie, 2012). The value of this hyper-parameter influences how the optimum connective structure of a network is selected. To determine this hyper-parameter, a minimization function is executed comparing 100 different possible sets of networks with the aim of minimizing an Extended Bayesian Information Criterion (EBIC), allowing the selection of a tuning parameter that optimally fits the final estimated partial correlation network (Epskamp, Borsboom and Fried 2017). This procedure removes spurious links while retaining important connections within the network, and is termed the *EBIC-glasso*.

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The graphical layout of nodes in each network was determined using a Fruchterman-Reingold algorithm. This method iteratively computes the optimal layout of a graph by organising nodes within the graph based on the number and strength of their adjacent connections (Fruchterman & Reingold, 1991). This layout was computed for the structure of nodes at time point 1. For visual clarity, subsequent networks graphs are fitted to this node layout, but retain all their initial properties.

To estimate the number of latent clusters within our symptom network, a further network analysis technique termed Exploratory Graph Analysis was used, with the R package “*EGAnet*” (Golino & Christensen, 2019). This technique first estimates a network using the *EBIC-glasso*. To further identify community structures of nodes, known as clusters, a *clustering-walktrap* algorithm was then applied to the regularized correlation matrix. This algorithm captures the community structure of subgroups of nodes within a network by generating and comparing random walks. These random walks consist of a series of varying probability distribution patterns which are used to estimate the likelihood of transitioning between clusters of associated nodes in the network (Golino & Epskamp, 2017). This process is used to identify densely connected clusters of nodes within our network. As densely connected node clusters are believed to represent latent psychometric variables, each cluster approximates an extracted latent “factor” in classic factorial analyses (Golino & Christensen, 2019). Therefore, comparing the data-derived clusters of symptom nodes identified through this exploratory graph method against their corresponding categories under the DSM allows us to evaluate how traditional classifications used in diagnosis translate into the location of nodes within a symptom network.

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Network statistics & centrality indices

The second step is to determine which symptoms within the network are most important. To do this, we estimated the centrality of all symptoms in our network. In psychopathological networks, centrality represents the connectedness of a given symptom with all other symptoms in a network (Fried et al., 2016). Our main focus in this report is node betweenness and expected influence. Node betweenness was calculated for each node in the network by summing the number of times that each node lay on the shortest path between two other nodes (figure 3.b). Nodes that are high in betweenness are important for bridging unconnected nodes, and thus are likely to be responsible for comorbidity between disorders (Borsboom et al., 2017).

As our network contains a high proportion of both positive and negative edges, and betweenness centrality does not distinguish between these, another centrality estimate termed “Expected Influence” was used as a secondary index of node centrality to estimate the cumulative influence of all a nodes connections and its effect on activation within the network (Robinaugh et al. 2016). A node’s one-step expected influence (EI_1) is calculated by computing the sum of both its positive and negative edges (figure 3.c). A node’s influence relevant to its position in the network can then be calculated by using two-step expected influence (EI_2), which is the sum of the node’s EI_1 value plus the EI_1 values of its neighbours (see figure 3.d, and refer to Robinaugh et al., 2016 for further information).

In addition to betweenness centrality and expected influence, the strength (absolute sum of edge weights connected to a node) (figure 3.e) and closeness (The inverse of the sum of the number of connections of the focal node from all the other nodes in the network) (figure 3.f) was also calculated (Everett & Borgatti, 2005).

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Strength, closeness and betweenness centrality for all nodes in the network were then averaged to create global descriptive statistics for both networks at each time point.

A summary of centrality indices described above and used within our analyses can be found in table 2. Alternatively, refer to figure 3. for illustrations of centrality indices within a sample network.

Centrality Index:	Definition:
Betweenness:	The number of times a node lies on the shortest path between two other nodes in the network.
Strength / Degree:	The absolute sum of edge weights connected to a node
Closeness:	The inverse of the sum of the number of connections of the focal node from all the other nodes in the network.
<u>Expected Influence</u>	
One-Step (EI₁):	The sum of a node's positive and negative edges.
Two-Step (EI₂):	The sum of a node's positive and negative edges, plus the EI ₁ values of its adjacent nodes.

Table 2. Summary of definitions for centrality indices. Please refer to Rodrigues, (2018) for detailed definitions of Betweenness, Strength and Closeness centrality. Refer to Robinaugh et al., (2016) for detailed definitions of EI₁ and EI₂ centrality.

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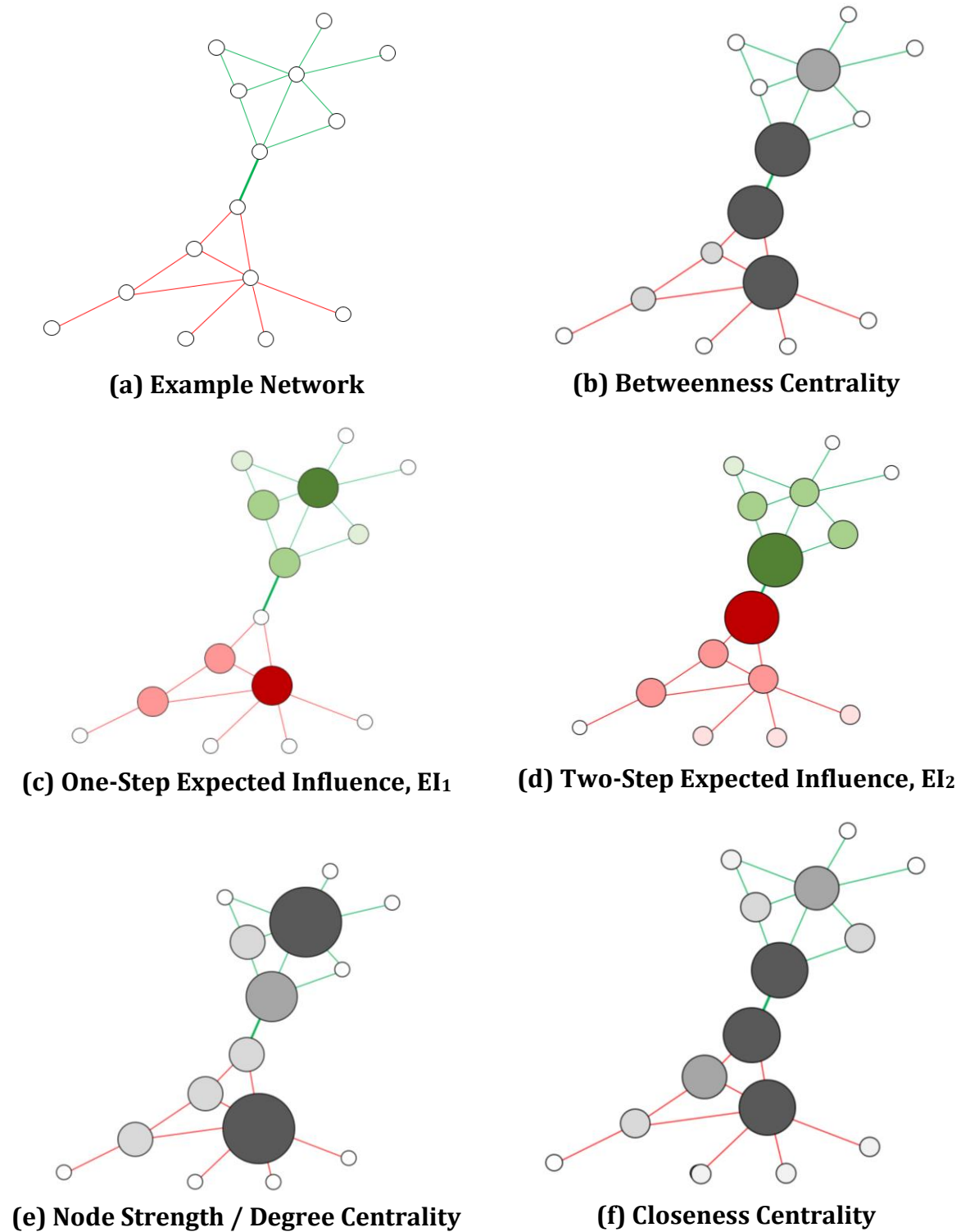


Figure 3. Comparison of centrality measures. (a) An example network containing nine positive and eight negative correlations. Green lines represent positive edges, and red lines represent negative edges. The thickness of each line corresponds to its edge weight. (b) Betweenness centrality, (c) degree centrality, (d) closeness centrality, (e) one-step expected influence, (f) two-step expected influence. In figures (b) to (f), the size and darkness of each node are proportional to its centrality measure. In figures (c) and (d), the colour of each node corresponds to the direction (positive or negative) of its influence within the network.

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Identifying and highlighting comorbid symptom bridges using filters

To identify important bridging nodes, each edge in the network was labelled and compared. Nodes containing edges that did not connect different clusters of disorders were ignored. Nodes that connected different clusters were then ranked according to the strength of their strongest edge (their highest partial correlation value). This information was then used to highlight nodes with high strength bridges across disorders in the network.

This metric in particular was used because node strength (the average of all edges connected to a node) cannot be used as a measure of a symptom's comorbid influence for our analyses. This is because it includes connections to other symptoms within the same disorder group during calculation. Furthermore, a symptom may bridge multiple disorders. Thus, the importance of each edge in connecting disorder clusters must be evaluated on a case-by-case basis

For further analysis, a filter was applied to the network that hid (but not removed from the model) edges that did not bridge disorder clusters. To allow for better visibility, another filter is applied which selectively displays only edges which connect to a certain population. Within these graphs, all other edges connecting unrelated clusters are hidden. This method is used to generate three graphs, showing bridging edges connected to internalising, externalising and compulsive disorders respectively. This method was applied to the network at time 1, and repeated again at time 2.

Full documentation, including code used for this statistical analysis can be found online at https://github.com/Auclstudent/BSC_PSY_DIS_2020.

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Results

Demographic characteristics

The 15,444 participants included in the final sample were between 6-7 years old at the first time point, and between 13-14 years old at the second time point. 49.4% of the sample was male. Table 1 provides an overview of all 59 symptoms used at both time points. Descriptive statistics for each symptom can be found in appendix 3.

Research question 1: Latent factor vs. DSM comparison

In our first step, a psychopathological network consisting of 59 symptoms from the DAWBA and SDQ questionnaires were created for time point 1, representing individuals between 6 to 7 years old (figure 4.A).

	Time point 1		Time point 2	
	DSM grouped network	Latent (EGA) grouped network	DSM grouped network	Latent (EGA) grouped network
Significant edges	693 / 1711 (40.5%)		756 / 1711 (44.1%)	
Avg. edge strength	Mean = 2.022, SD = 0.772 *		Mean = 2.260, SD = 0.742 *	
Avg. Node Betweenness	Mean = 50.068, SD = 71.726		Mean = 47.881, SD = 48.770	
Avg. Node Closeness	Mean = 0.0112, SD = 0.002		Mean = 0.0112, SD = 0.002	

Table 3. Table of global network descriptive statistics across time points.

* The difference between the average edge strength between networks was significant, $t(58) = -3.590, p < .0001$

Externalising, ADHD (Hyperactive, Impulsive & Inattentive) as well as compulsive symptoms seemed to visually cluster separately from other symptoms in the network. Conversely, internalising symptoms consisting of Mood, Social Anxiety, Separation Anxiety and General Anxiety clustered together. Exploratory Graph Analysis was then conducted on this network. The factors extracted correspond to seven of the nine DSM categories of symptoms within the data (see figure 4.B). These groups include

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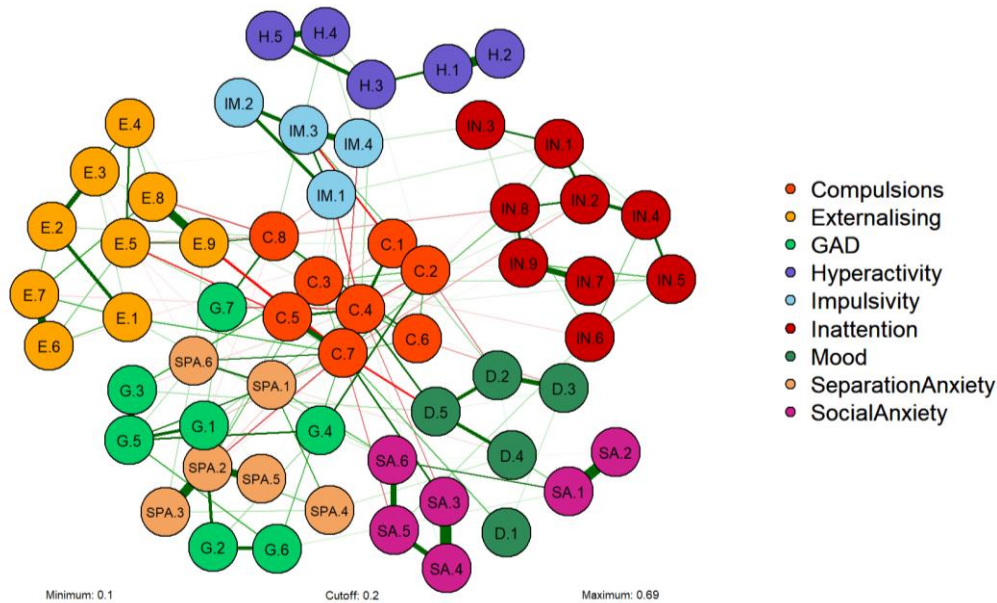
Mood/General Anxiety, ADHD-Hyperactivity/Impulsivity, Compulsions, Social anxiety, Separation Anxiety, ADHD-Inattention and Externalising problems. Mood disorders and General Anxiety Disorder were grouped under the same latent factor. ADHD - Hyperactivity and ADHD – Impulsivity was also grouped under the same latent factor. In line with existing DSM classifications, each cluster within the network comprised of symptoms that corresponded with their respective DSM disorder category.

A similar psychopathological network was created with the same symptom nodes at time point 2, representing the same individuals between 13 to 14 years old (figure 5.A). The layout of nodes in this network was determined by the network structure at time point 1. At the second time point a 4% increase in the number of connected nodes is seen. Between time point 1 and time point 2, the average betweenness centrality of each node decreased. The average closeness centrality of the network did not change (see Table 3). A paired sample t-test indicated the average edge strength of the network increased significantly between time point 1 (*Mean* = 2.022, *SD* = 0.772) to time point 2 (*Mean* = 2.260, *SD* = 0.742), $t(58) = -3.590, p < .0001$. This indicates that associations between symptoms (in general) strengthened over time.

Exploratory Graph Analysis was then conducted again. Overall the factors extracted correspond to eight of the nine DSM symptoms categories. A key difference between the network at time 1 and the new network at time 2 is that the clustering walk-trap algorithm now distinguished General Anxiety symptoms as belonging to a different cluster to Depression (see figure 5.B). This represents an increase in the distinctiveness of our diagnostic boundaries. ADHD-Hyperactivity and ADHD-Impulsivity were still categorised under the same cluster. Similar to time 1, no other symptoms were extracted as part of factors from different diagnostic categories.

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A: Symptom network with DSM category labels



B: Symptom network with latent EGA category labels

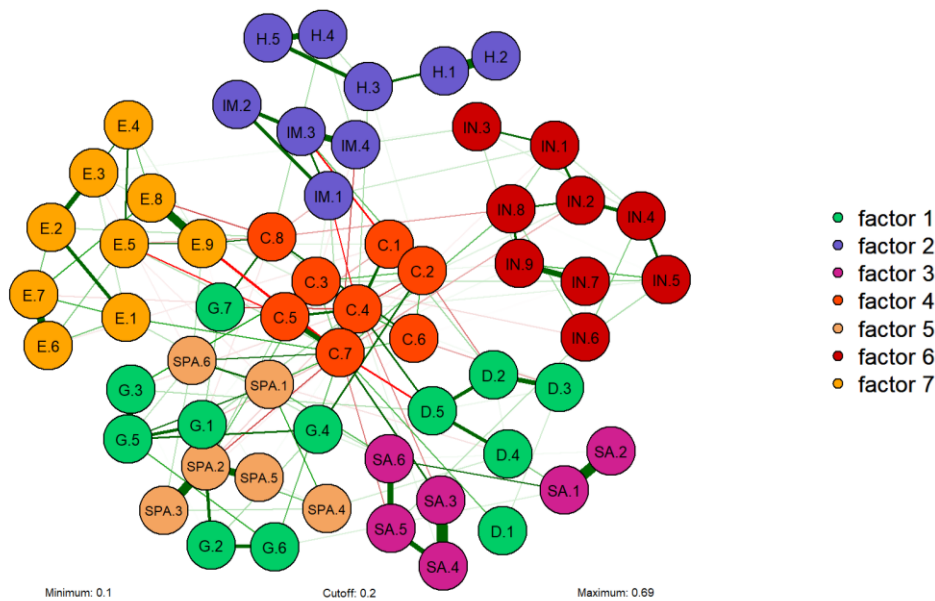
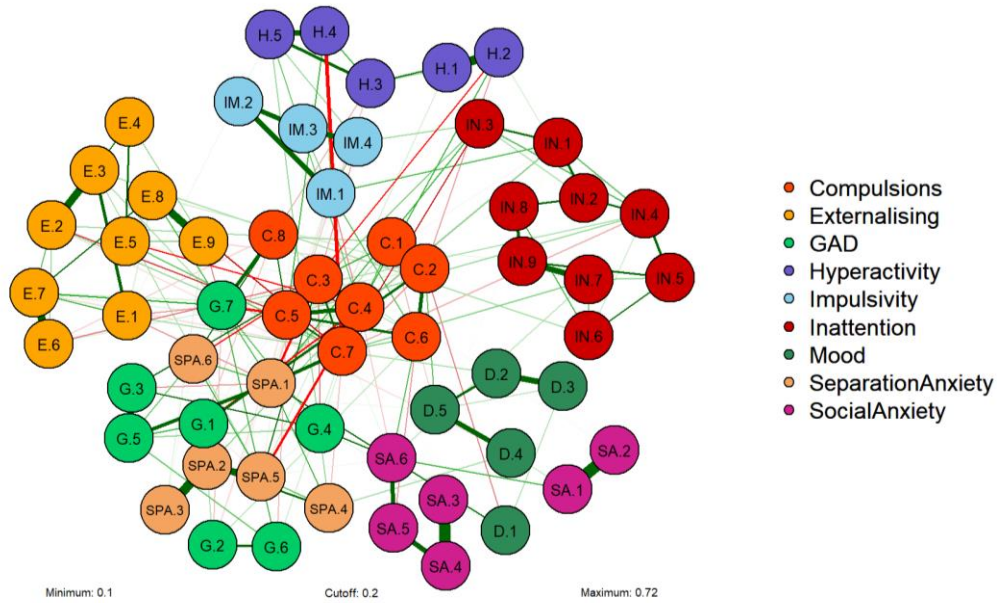


Figure 4. DSM and EGA networks at time point 1. (C) For compulsions, (E) for conduct and disruptive behaviour, (G) for general anxiety disorder, (H) for ADHD-Hyperactivity, (IM) for ADHD-Impulsivity, (IN) for ADHD-Inattention, (D) for Mood and Anxiety, (SPA) for Separation Anxiety, and (SA) for social anxiety. The numbers adjacent to these letters correspond to symptom short-codes in Table 1. The network layout is based on a Fruchterman-Reingold algorithm, which places nodes with stronger connections together, and more central nodes in the centre. Green lines represent positive associations, red lines represent negative ones. “Minimum” represents the smallest edge shown in this network. “Cutoff” represents the point at which edges begin to be faded to white on the graph. “Maximum” represents the highest displayed correlation in the network.

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A: Symptom network with DSM category labels



B: Symptom network with latent EGA category labels

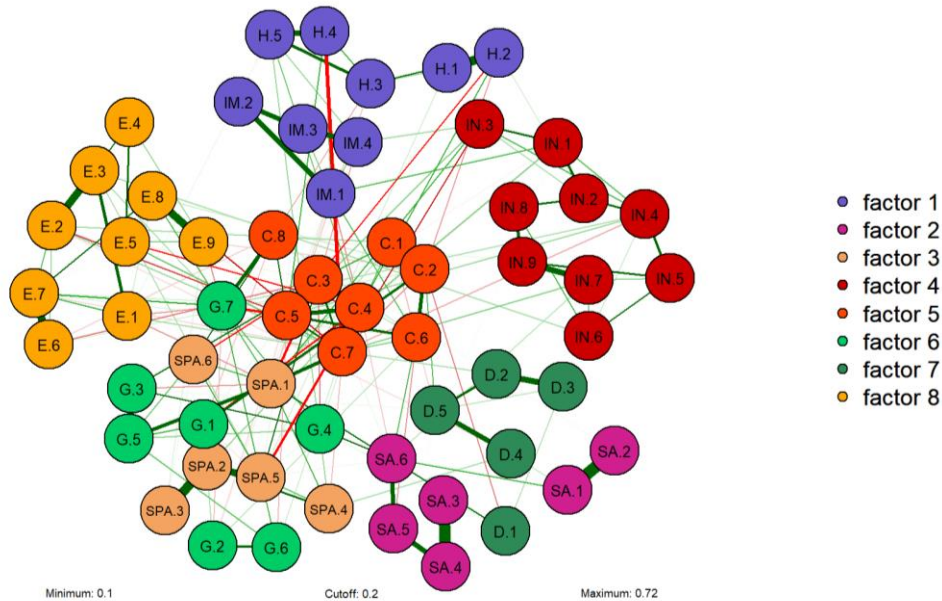


Figure 5. DSM and EGA networks at time point 2. (C) For compulsions, (E) for conduct and disruptive behaviour, (G) for general anxiety disorder, (H) for ADHD-Hyperactivity, (IM) for ADHD-Impulsivity, (IN) for ADHD-Inattention, (D) for Mood and Anxiety, (SPA) for Separation Anxiety, and (SA) for social anxiety. The numbers adjacent to these letters correspond to symptom short-codes in Table 1. The layout has been fitted to the layout generated by a Fruchterman-Reingold Algorithm for symptom nodes at time 1. Green lines represent positive associations, red lines represent negative ones. “Minimum” represents the smallest edge shown in this network. “Cutoff” represents the point at which edges begin to be faded to white on the graph. “Maximum” represents the highest displayed correlation in the network.

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Research question 2: Identification of comorbid “bridge” symptoms

Analysis of symptom bridges at time point 1

To investigate the importance of individual symptoms within the network, nodes were re-coloured by the weight of their strongest connection to an outside cluster (Figure 6). In the network at time 1, a total of 27 nodes had a connection one standard deviation above the mean weight, 17 had a connection two standard deviations above the mean, and two nodes had a connection three standard deviations above the mean.

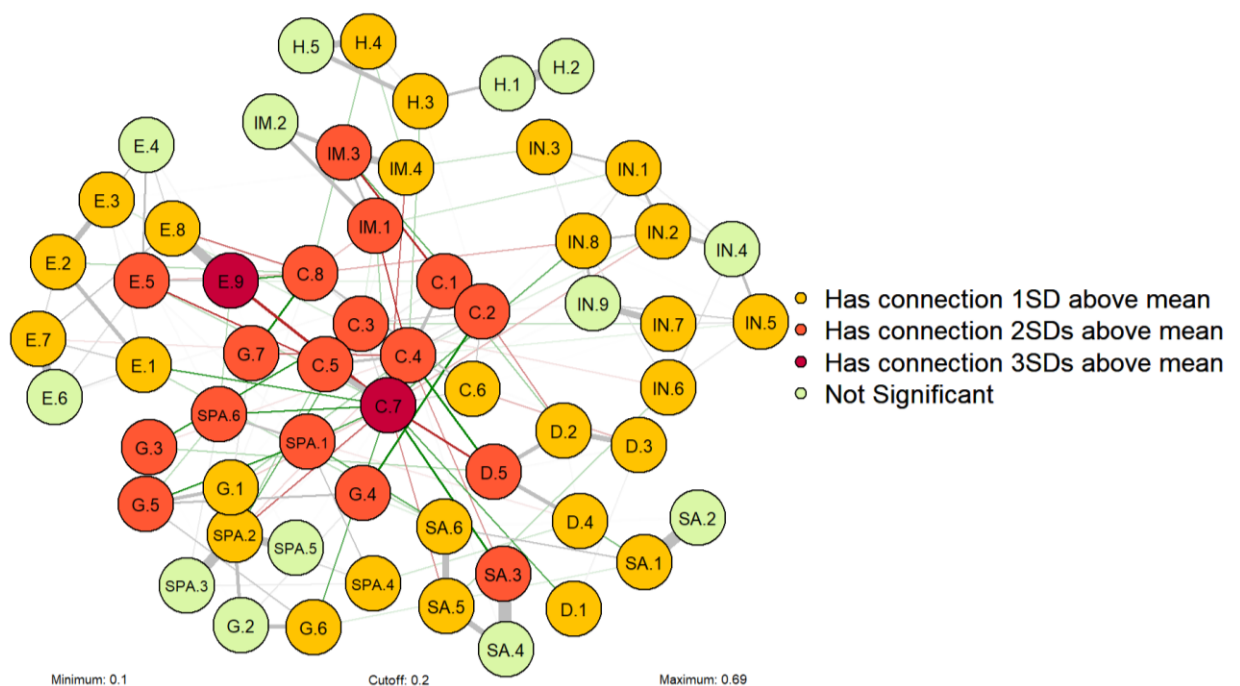


Figure 6. Diagram of trans-diagnostic connections coloured by standard deviations away from network mean at time 1. (C) For compulsions, (E) for conduct and disruptive behaviour, (G) for general anxiety disorder, (H) for ADHD-Hyperactivity, (IM) for ADHD-Impulsivity, (IN) for ADHD-Inattention, (D) for Mood and Anxiety, (SPA) for Separation Anxiety, and (SA) for social anxiety. The numbers adjacent to these letters correspond to symptom short-codes in Table 1. Green lines represent positive associations, red lines represent negative ones. Greyed lines represent correlations within symptom clusters (connections within symptoms from the same disorder). “Minimum” represents the smallest edge shown in this network. “Cutoff” represents the point at which edges begin to be faded to white on the graph. “Maximum” represents the highest displayed correlation in the network.

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We found that at time 1, a large proportion of bridging nodes between disorders clusters were compulsive symptoms. One connection, between E.9 (“Has she tried to get her own back on people?”) and C.7 (“Frequency child has repeatedly counted to lucky numbers”) was found to have a negative correlation 3 standard deviations away from the network mean, indicating it’s strong inhibitory role in the network. Only two notable connections existed between internalising and externalising disorder clusters that did not include compulsions symptoms. These were (1) a connection between IN.5 (“Is it often hard for her to get herself organised to do something?”) and SA.5 (“Degree to which child was afraid of writing in front of others in past month”) and (2) a connection between E.1 (“Compared to other children has she had severe tantrums recently?”) and SPA.6 (“Has she had repeated nightmares about being separated from her family?”).

All betweenness centrality scores were scaled to have mean of zero and a standard deviation of one. After scaling betweenness scores to a normal distribution, these z-scores were plotted on a probability distribution. *p* values under 0.05 were considered to be significant. Using these criteria, five nodes were found to be highly central at time 1. Notably, of these nodes, two were obsessive-compulsive symptoms (Table 4). The importance of compulsive symptoms in bridging disorder clusters in our network has been visualised by arranging the disorder symptoms in the network by group, and by then hiding all edges that were not connected to a compulsive symptom (figure 7.) This same process was also repeated for externalising and internalising disorder groups respectively (Please refer to appendices 1 and 2 for these visualisations).

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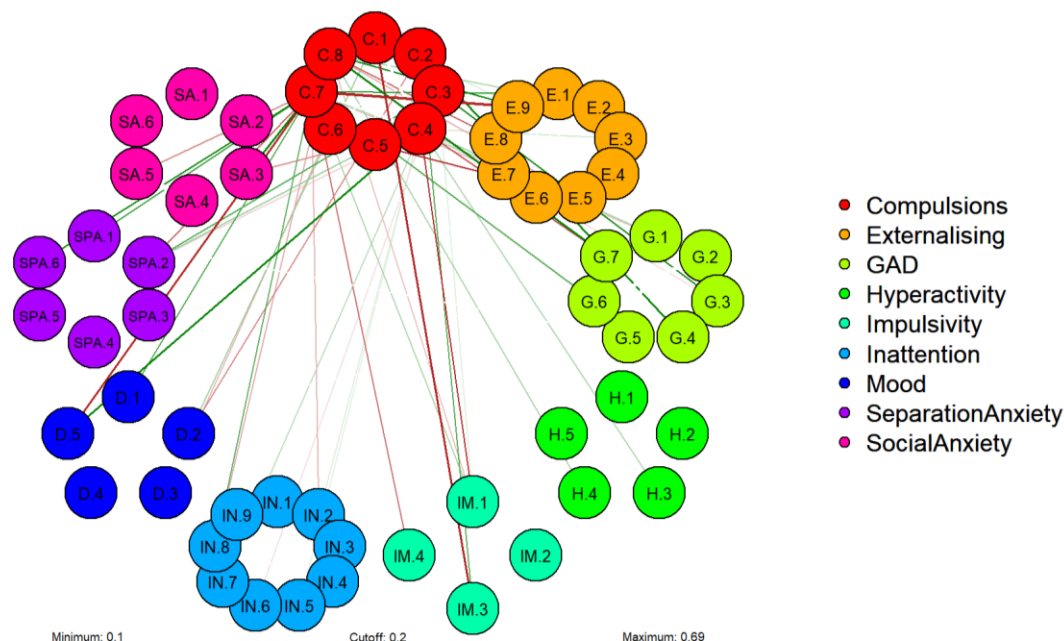


Figure 7. A filtered network of bridging connections from compulsions at time 1. The symptoms have been arranged by disorder group. Numbers adjacent to letters correspond to symptom short-codes in Table 1. A filter has been applied, hiding (1) connections between symptom nodes of the same disorder, and (2) connections between symptom nodes that are not part of obsessive-compulsive disorders. Green lines represent positive associations, red lines represent negative ones.

Node	Disorder category	Questionnaire Item	z-score	p
C.7	Compulsions	<i>Repeatedly counting to Lucky Numbers</i>	6.05	< .0001
C.4	Compulsions	<i>High frequency of performing repeated actions</i>	2.93	< .0001
D.5	Mood/Anxiety	<i>Having many fears or being easily scared</i>	1.27	< .0001
H.3	ADHD Hyperactivity	<i>Running and climbing inappropriately</i>	1.15	< .0001
SPA.2	Separation Anxiety	<i>Worries about sleeping alone</i>	1.15	< .0001

Table 4. Betweenness centrality z-scores and significance values for time 1

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Analysis of symptom bridges at time point 2

At time 2, the network overall becomes more densely connected as the average number of connections to each node increases. The average strength of these connections between symptoms also increases. At this time, 26 nodes had a connection one standard deviation above the mean, 14 had a connection two standard deviations above the mean, and six nodes had a connection three standard deviations above the mean (See figure 8). A higher proportion of nodes within the network now contain significant connections with weights more than three standard deviations away from the network mean.

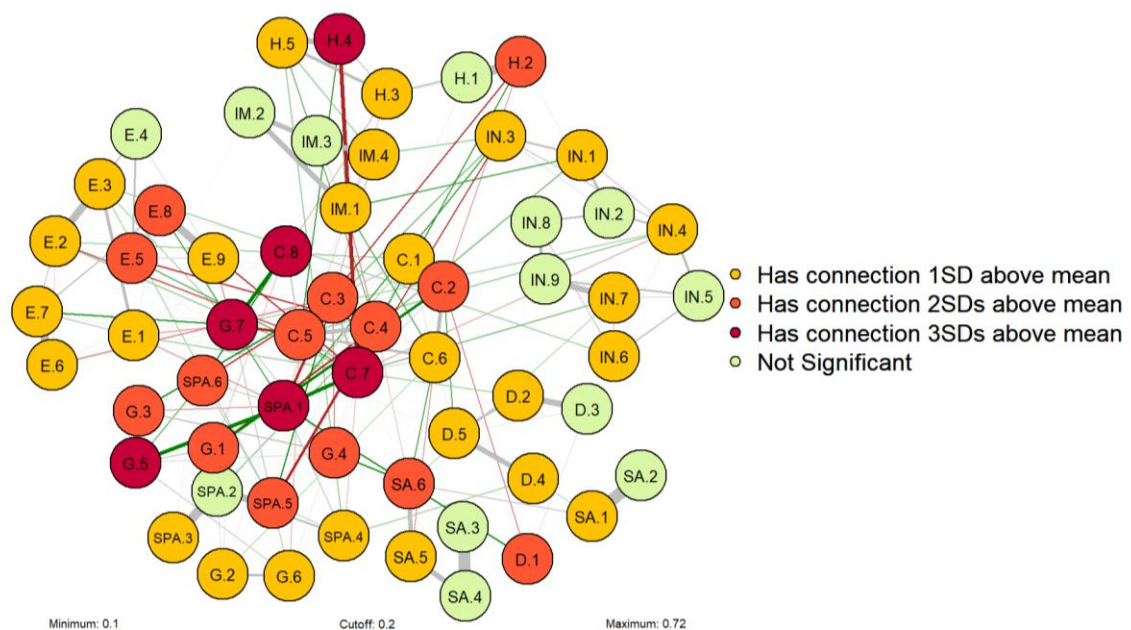


Figure 8. Diagram of trans-diagnostic connections coloured by standard deviations away from network mean at time 2 containing 59 DAWBA/SDQ symptoms of Obsessive Compulsive Disorder (C), Conduct & disruptive behaviour (E), General Anxiety Disorder (G), ADHD – Hyperactive (H), ADHD – Impulsive (IM), ADHD – Inattentive (IN), Mood & Anxiety (D), Separation Anxiety (SPA) and Social Anxiety (SA). Numbers adjacent to these letters correspond to symptom short-codes in Table 1. Green lines represent positive associations, red lines represent negative ones. Greyed lines represent correlations within symptom clusters (connections within symptoms from the same disorder). “Minimum” represents the smallest edge shown in this network. “Cutoff” represents the point at which edges begin to be faded to white on the graph. “Maximum” represents the highest displayed correlation in the network.

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Four new significant bridging connections were found at time 2. These include, (1) G.5 (“Worries about her own health”) and SPA.1 (“Has she often not wanted to go to school in case something nasty happened whilst she was there to a person she is attached to?”), (2) SPA.1 and C.7 (“Frequency child has repeatedly counted to lucky numbers / avoided unlucky numbers in past month”), (3) G.7 (“Worries about the future”) and C.8 (“Frequency child has repeatedly done anything else in the past month”), (4) C.7 and H.5 (“Is she rushing about and does she find it hard to calm down?”). The aforementioned connections were not found to be significant at time 1. No significant bridges at time 1 remained at the same level of significance (>3 SDs from the mean) at time 2. Despite this change in connectivity, compulsive symptoms still comprise many of the shortest paths connecting internalising and externalising disorder clusters. This has been visualised in figure 9. in the same manner as before in figure 7.

A change in the distribution of central nodes can also be seen in the network at time 2. Only two central nodes at time point 1 remain highly central at time point 2. These are nodes C.7 (Compulsions counting to lucky numbers) and C.4 (Compulsions to perform repeated actions). New nodes which have high betweenness only at time point 2 are nodes SPA.1 (Unwillingness to go to school for fear of harm of parents), C.5 (“Frequency child has repeatedly touched things/people in particular ways”) and SA.6 (“Degree to which child was afraid of eating in front of others in past month”) (Please refer to table 5).

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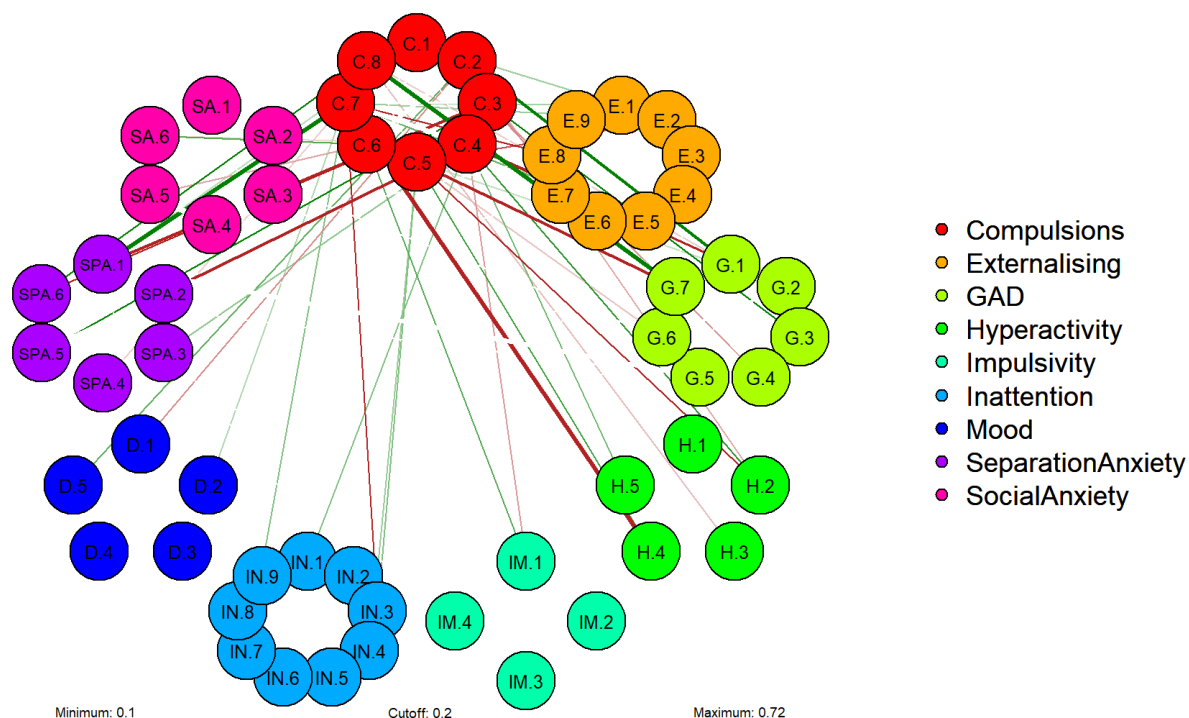


Figure 9. A filtered network of bridging connections from compulsions at time 2.

The symptoms have been arranged by disorder group. Numbers adjacent to letters correspond to symptom short-codes in Table 1. A filter has been applied, hiding (1) connections between symptom nodes of the same disorder, and (2) connections between symptom nodes that are not part of obsessive-compulsive disorders. Green lines represent positive associations, red lines represent negative ones.

Node	Disorder category	Questionnaire item	z-score	p
C.7	Compulsions	<i>Repeatedly counting to Lucky Numbers</i>	3.76	< .0001
C.4	Compulsions	<i>High frequency of performing repeated actions</i>	3.14	< .0001
SPA.1	Separation Anxiety	<i>Not wanting to go to school for fear of a disaster at home</i>	2.46	< .0001
C.5	Compulsions	<i>Repeatedly touching things in particular ways</i>	2.00	< .0001
SA.6	Social Anxiety	<i>Fear of eating in front of others</i>	1.86	< .0001

Table 5. Betweenness centrality z-scores and significance values for time 2

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Across both time points, compulsive symptoms have the highest mean betweenness centrality amongst all disorder symptoms (See figure 10). The average centrality of compulsive symptoms drops between time 1 ($M = 142.6$, $SD = 184.7$) and time 2 ($M = 107.6$, $SD = 76.9$), indicating that a greater number of alternative paths are present at time 2. A high variation is seen in the betweenness centrality across all disorders, indicating each category only contains a few highly central nodes (figure 11).

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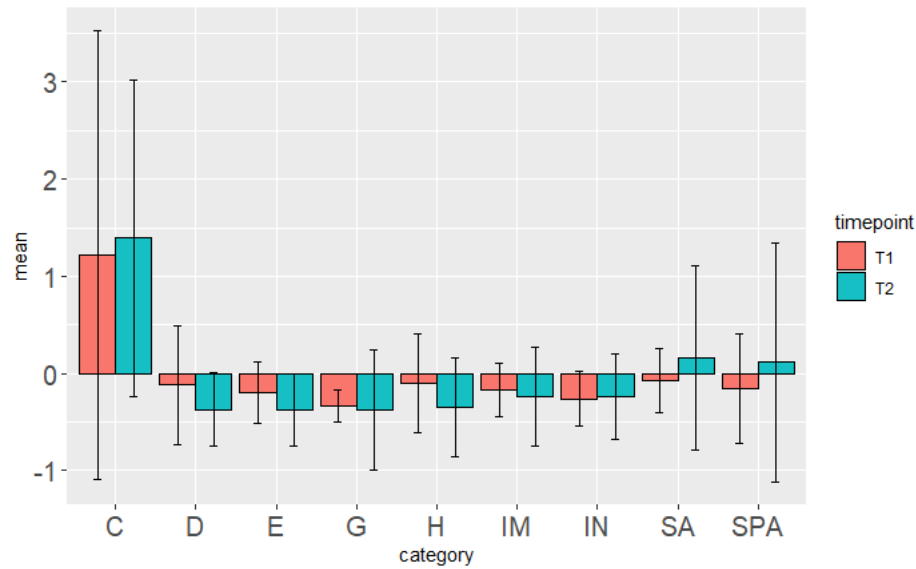
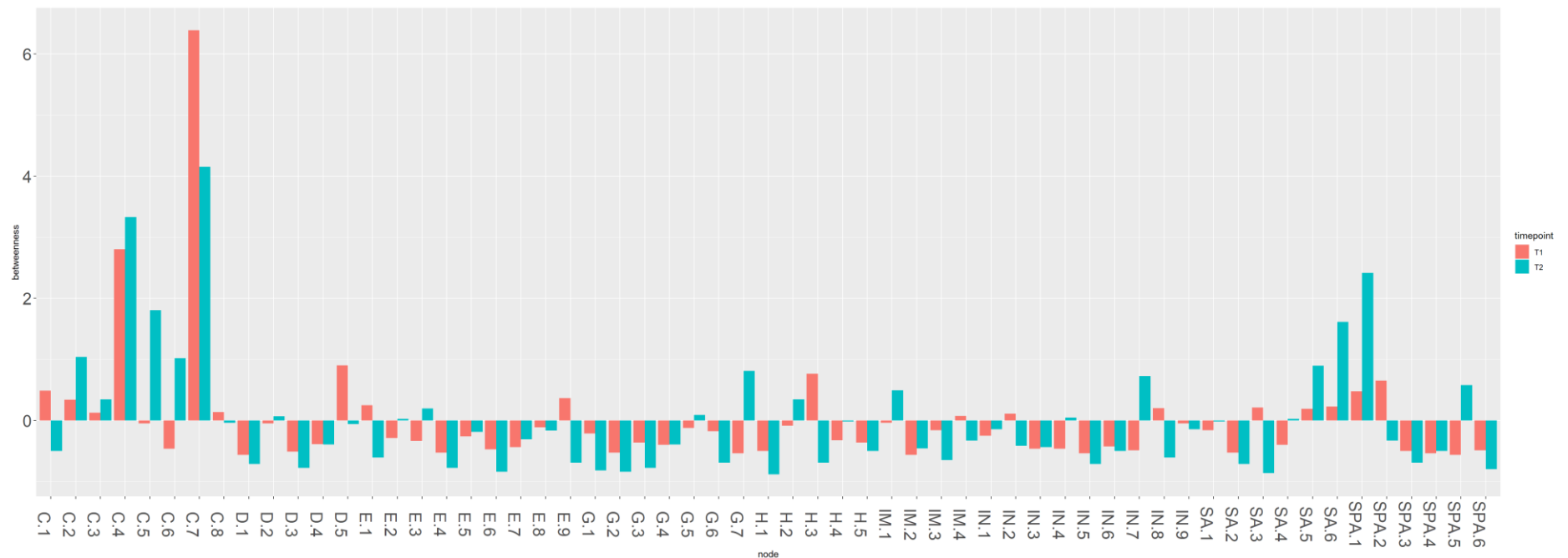


Figure 10 (left): Scaled average and standard deviation of node betweenness centrality organised by DSM disorder categories of Compulsions (C), Depression/Anxiety (D), Conduct Problems (E), General Anxiety Disorder (G), ADHD-Hyperactivity (H), ADHD-Impulsivity (IM), ADHD-Inattention (IN), Social Anxiety (SA) and Separation Anxiety (SPA).

Figure 11 (Below): Standardized node betweenness centrality estimates (z-scores, Mean = 0) of the 59 DAWBA/SDQ symptoms for time point 1 and time 2. Please refer to Table 1. For symptom short-codes.



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Compulsive symptoms as bridging nodes:

Based on our initial analysis, it is clear that obsessive-compulsive symptoms are highly central within our network. This therefore warrants further investigation into their role as bridging symptoms between internalising and externalising dimensions.

A by-node analysis of compulsive symptoms shows that at time point 1, the two nodes that had the highest betweenness centrality were nodes C.7 (compulsions counting to lucky numbers) and C.4 (compulsions to perform repeated actions). Both these nodes have multiple significant connections to both internalising and externalising disorders (See table 6.).

At time 2, the average betweenness of compulsive nodes decreases. The centrality of nodes C.7 and C.8 (Other associated compulsive behaviours) decrease, however, the centrality of nodes C.2 ("Frequency child has taken special measures to avoid dirt"), C.3 ("Frequency child has repeated checked things"), C.4, C.5 ("Frequency to repeatedly touch things or people in particular ways") and C.6 ("Frequency child has arranged things symmetrically") increase. All of these nodes gain new connections at time 2.

Regardless of a change in network connectivity overall, nodes C.7 and C.4 still remain the two most central nodes within the symptom network, this property makes them likely bridging nodes key for spreading activation within the network. Importantly, all (except one) compulsive nodes across both time points have significant connections to at least one externalising and internalising disorder, making the compulsive disorder cluster an important focal point for spreading activation within the symptom network.

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Node	Betweenness		Mean absolute edge weight		Connections to				Total connections	
	Time 1	Time 2	Time 1	Time 2	Externalising symptoms		Internalising symptoms		Time 1	Time 2
C.1	0.488	-0.502	0.162	0.133	1	1	2	1	3	2
C.2	0.338	1.042	0.187	0.176	2	1	1	3	3	4
C.3	0.125	0.344	0.144	0.198	3	1	2	5	5	6
C.4	2.802*	3.327*	0.143	0.179	6	5	6	4	12	9
C.5	-0.050	1.804*	0.169	0.176	1	5	1	2	2	7
C.6	-0.463	1.021	0.135	0.150	0	1	1	3	1	4
C.7	6.393*	4.153*	0.175	0.187	7	7	9	3	16	10
C.8	0.138	-0.037	0.159	0.197	7	1	1	3	8	4

*Table 6. Node Betweenness, Edge weight and connection descriptive statistics for compulsive symptoms across time points 1 and 2. * Centrality values significantly different from network mean, ($p < .05$)*

Betweenness centrality and two-step expected influence comparisons

A secondary index of centrality (Two-step expected influence) was also calculated. Significance levels for expected influence were computed by converting expected influence scores to z-scores and placing them on a probability distribution ($\alpha = 0.05$). We found that overall within our network, measures of node betweenness centrality corresponded poorly with measures of expected influence. This was true for centrality measures at both time points (See figures 12.A and 12.B).

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At time point 1, no nodes that had significant betweenness centrality had significantly positive expected influences, and vice versa. Interestingly, despite having an extremely high betweenness centrality, C.7 (Compulsions counting to lucky numbers) had a negative expected influence on the network, indicating that it correlated negatively, or suppressed the activation of many other symptoms within the network. This was the same for all but one central node at time point 2.

To further investigate how centrality values within our network changed between time points, Spearman's rank order correlations were calculated between node centralities at time 1 and time 2. This showed that a node betweenness centralities at time 1 weakly correlated with betweenness centralities at time 2 ($r_s = .351, p = .007$). This indicates that between both time points each nodes betweenness centrality did not change greatly. However, no correlation was found between node expected influence scores at time 1 and time 2 ($r_s < .0001, p = .997$), indicating a notable change in expected influence centralities between time points.

The exception to these trends was the node SPA.1 ("Not wanting to go to school for fear of a disaster at home"). It had a significantly high betweenness centrality and positive expected influence at time 2. This points strongly towards its causal role in spreading activation within the network at time 2 (see table 7).

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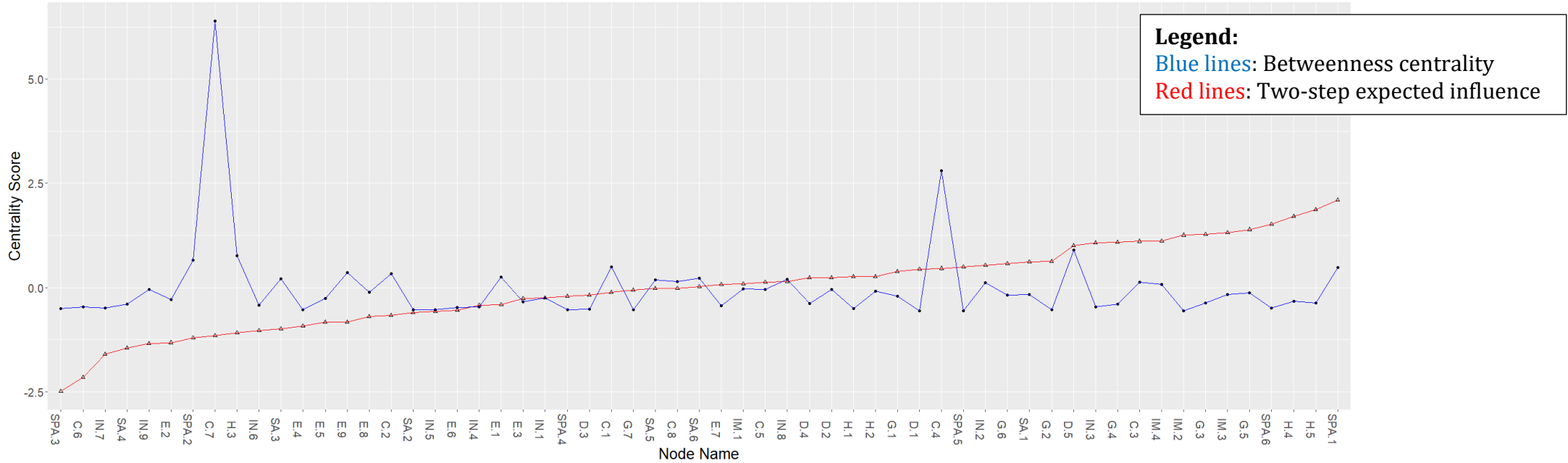
Node	Disorder group	Time point	Centrality (z-scores) * $p < .05$	
			Betweenness	Two-step expected influence
C.7	Compulsions	T1	6.39*	-1.16
C.7	Compulsions	T2	4.15*	0.22
C.4	Compulsions	T2	2.80*	-1.04
C.4	Compulsions	T1	3.33*	0.46
SPA.1	Separation Anxiety	T2	2.46*	2.77*
C.5	Compulsions	T2	2.00*	-1.49
SA.6	Social Anxiety	T2	1.86*	1.57
D.5	Mood/Anxiety	T1	1.27*	1.00

Table 7. Expected influence values of nodes with significant betweenness centrality

Therefore, based on our centrality analyses and network plotting, three symptoms across two time points were identified as important bridging symptoms within our psychopathological network. According to betweenness centrality measurements across time points 1 and 2, nodes C.7 (Compulsions counting to lucky numbers) and C.4 (Compulsions to perform repeated actions) are likely bridge symptoms. According to expected influence and betweenness centrality at time 2, node SPA.1 (Unwillingness to attend school for fear of parents being hurt) may also be a bridging symptom. These three symptoms play an important role in spreading activation between comorbid disorders within the network, and may have a causal influence in the development of comorbid psychopathology during development.

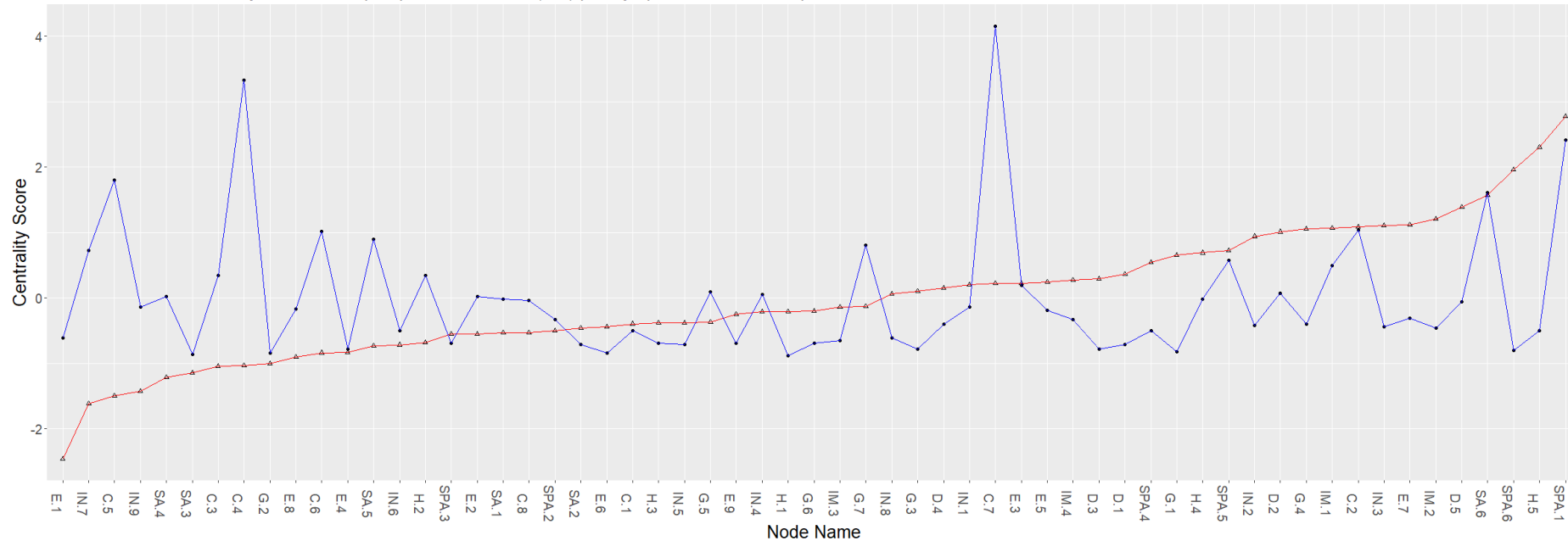
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A. Betweenness Centrality and Two-Step Expected Influence (EI2) per Symptom node at Time point 1



Figures 12.A& 12.B: Node betweenness centrality and two-step expected influence

B. Betweenness Centrality and Two-Step Expected Influence (EI2) per Symptom node at Time point 2



Discussion

Aim of the present study

The present study sought to map the network of symptom relationships of frequently comorbid disorders in childhood. We aimed to evaluate the effectiveness of DSM categories at describing symptom networks. We then aimed to identify comorbid symptoms that bridged internalising and externalising disorders, and ascertain if these symptom bridges were affected by developmental changes. To our knowledge, this is the first study to apply a network approach to modelling internalising and externalising disorders at a symptom level.

Evaluating the application of DSM categories to symptom networks

A coherent network organisation was found at ages 6 to 7 and ages 13 to 14. Externalising, internalising and hyperactive symptoms clustered into independent domains. Of the nine DSM-diagnostic categories of symptoms included in our network, exploratory graph analysis consistently returned seven complete factor solutions in childhood which increased to eight during early adolescence. In both childhood and adolescence, no symptoms were extracted as part of factors from different diagnostic categories. For example, the disorder cluster corresponding to Social Anxiety disorder consisted only of symptoms originally intended as diagnostic measures of Social Anxiety. The same is true for all other disorder categories in our network. This suggests that symptoms in the DAWBA and SDQ are valid measurements of their respective disorders. The close-to-perfect replication of the categories in the DSM diagnostic manual within the network support that the symptoms used are valid measurements of different types of psychopathology. An increase in the specificity of diagnostic categories is seen between childhood and adolescence, in particular in mood and

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general anxiety symptoms. This finding was expected, as symptoms in the diagnostic manual were initially derived from adult populations (Goodman et al., 2010). Therefore, one would expect the diagnostic validity of symptoms to increase with age.

Network analyses of comorbid symptoms

Previous findings from factor analysis studies suggest that all forms of psychopathology are attributable to a latent p – factor. This latent p – factor may capture the highly interrelated symptom structure present in psychopathological networks. Therefore, high scores on p – factor scales may correspond to patterns of dense, strongly connected networks of symptoms in mentally unwell individuals. Our findings show that if modelled as a network, traditional measurements of psychopathology are reflected in clusters of highly associated nodes (Borsboom et al., 2017). This shows the utility of network analysis for investigating comorbidity on a symptom level.

Betweenness centrality is the sum of the number of times a node lies on the shortest path between two nodes in a network. Observations of the consistency of node betweenness centrality within networks at different time points measure the stability of network structures as a whole. McElroy's (2017) investigation of the ALSPAC dataset found that the betweenness centralities of disorder nodes correlated across time points, suggesting a stable network structure. Our results partially support their findings. Node betweenness centrality at time 1 was moderately correlated ($r_s = .351$) with node betweenness at time 2. Therefore, central nodes which lie on the shortest path between disorder clusters remain central in connecting different network regions. This indicates a consistency in overall network structure, as most nodes retain their position and number of connections within the network between times 1 and 2.

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However we also found that the number, type and strength of connections between symptom nodes differed significantly between middle childhood and early adolescence. Our second measure of centrality, two-step expected influence (EI_2), is a measure of the sum of a node's positive and negative edges, plus the sum of the positive and negative edges of its neighbours. Importantly, EI_2 is a valence measure of a node's connective importance, whereas betweenness is a magnitude measure. Within our network, much unlike betweenness centralities when compared, node EI_2 between time points 1 and 2 were not correlated ($r_s < .0001$).

Our finding a correlation of betweenness, but not EI_2 centralities across time is consequential. Notably, McElroy's (2017) investigation focused on the connections within a network of disorders, whilst our investigation focused on the connections of (the same set of) disorder symptoms. Therefore, our results suggest that while the overall connections between disorders in the network may appear homogenous when observed at a disorder level, heterogeneity across time can be found within the connections at a symptom level.

Observing a stable correlation between disorders does not necessarily imply that the symptom level correlations that constitute these connections remain stable over time. Our network analysis instead demonstrates that symptom level connections are heterogeneous and exhibit developmental changes. This interpretation is supported by the fact that expected influence is a measure of a node's contribution to activation within the network. Furthermore, our investigation also uses a longitudinal data set. Therefore, while a symptom's position in the psychopathological network may remain constant, the dynamics of its connection to its neighbours change across time.

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Based on their findings, McElroy et al. (2017) proposed that the dimensions of internalising and externalising are correlated due to certain disorders acting as bridges between these broad spectra. Our results build upon this interpretation further at the symptom level. In our network a large number of symptoms were found to have trans-diagnostic connections, indicating the presence of multiple bridging symptoms per disorder. We therefore propose within disorder level connections, certain symptoms may be especially important comorbid bridges.

Anxious-aggressive symptom bridges for network activation

Our results highlight certain symptom bridges that may make good clinical indicators for detecting comorbidity during early childhood. Specifically, two unique comorbid bridges during early childhood were found to connect externalising and inattentive symptoms to anxiety. A comorbid bridge between E.1 (“In the last 6 months and compared with other children has she had severe temper tantrums?”) and SPA.6 (“Has she had repeated nightmares or bad dreams about being separated from any of these people?”) and a bridge between IN.6 (“Does she often try to get out of things she would have to think about, such as homework?”) and SA.5 (“Degree to which child was afraid of writing in front of others in past month”) were identified. Therefore, the presence these comorbid pairs of symptoms means that children with ADHD who report difficulties in completing homework may be further vulnerable to the development of anxiety. Likewise, children whose oppositional behaviour comprises heavily of temper tantrums may have unaddressed fears related to separation anxiety.

Relatively little research has investigated the co-occurrence for comorbid symptoms of anxiety and aggression. Explanations such as comorbidity due to chance, symptom overlap or sampling bias may not fully explain comorbidity between anxiety

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and disruptive behavioural disorders (Bubier & Drabick, 2009). Frustration derived from anxiety, may confer risk for the development of reactive aggression (Polman et al., 2007; Kellam, 1994). This relationship may be based on an individual's trait "anxious impulsivity" which fosters a tendency amongst anxious individuals to respond impulsively in adverse situations (Newman & Wallace, 1993). Research has found a relationship between childhood aggression at age 3 and anxious depressive symptoms at age 12 (Pihlakoski et al., 2006).

Early aggressive behaviour has also been linked with the development of later anxiety. Community based studies show that at least 7.6% of children diagnosed with ODD, ADHD or ODD & ADHD were then diagnosed with a second comorbid anxiety disorder 2 years later (Speltz et al., 1999). The "failure model" of developmental psychopathology suggests that externalizing behaviour and internalising problems are causally connected (Capaldi, 1991; 1992). A child's problems with attention, or their disruptive behaviour leads to negative responses from their teachers, parents or peers. These frequent negative responses distress the child, and eventually lead to the manifestation of an internalizing disorder, such as anxiety (Ostrander & Herman, 2006).

These symptom bridges may capture an important aspect of the early development of anxious impulsive behaviours. Therefore, the presence of such pairs of inattentive & anxious or disruptive & anxious symptoms in clients may be important early indicators for comorbid anxiety with ADHD or behavioural problems.

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Obsessive-compulsive symptom bridges for network activation

All compulsive symptoms were closely linked to multiple disorder symptoms in both internalising and externalising dimensions. In particular, nodes C.7 (“Frequency child has repeatedly counted to lucky numbers / avoided unlucky numbers in past month”) and C.4 (“Child has repeatedly performed repeated actions in past month”) were highly central within the psychopathology network. The high centrality of this symptom may relate to its significance in affecting a patient’s quality of life. Research shows that individuals affected by OCD report increasing levels of distress with the number of comorbid diagnoses (Welkowitz et al., 2000). Therefore, our results suggest compulsions surrounding “counting to lucky numbers” or “performing repeated actions” are related to the development of comorbid distress or anxiety in an individual.

The strong connectivity of compulsive nodes to internalising and externalising disorders also support findings from factor analytic studies showing heterogeneity in the presentation of obsessive compulsive symptoms as well as its comorbid disorders (Bloch et al., 2008). Research has found that the first psychopathological manifestation in OCD patients is associated with the development of different comorbid psychiatric disorders (De Mathis et al., 2012). OCD patients had different outcome trajectories depending on their first diagnosis of a comorbid disorder. Patients with antecedent symptoms of separation anxiety were more likely to develop other anxious disorders (Manicavasagar et al., 2000), whilst those who presented first with ADHD symptoms were more likely to develop substance abuse disorders (Sihvola et al., 2011).

Comparing connections within our network between childhood and adolescence provides information on the developmental pathways of psychopathology. A strong relationship was found between node C.7 (Compulsions counting to lucky numbers) and

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SPA.1 (“Has she often not wanted to go to school in case something nasty happened whilst she was there to a person she is attached to?”) that strengthened over time. This was found in conjunction to correlations with other anxiety disorder symptoms alongside a strong negative relationship to an externalising disorder symptom, node E.9 (“Has she tried to get her own back on people?”). This may indicate that such repetitive behaviour may be predictive of these later problems, or of a comorbid developmental path that hinges on this form of compulsion. Our network showed that the presence of these connections matches the developmental timing of initial separation anxiety diagnoses, which peak between the ages of 5-8 (De Mathis et al., 2012).

A similar comparison can be drawn with OCD comorbid with ADHD. From the ages of 13 to 14, new positive connections can be found from ADHD symptoms to a different set of obsessive-compulsive symptoms, which include nodes C.4 (compulsions to perform repeated actions) and C.8 (“Frequency child has repeatedly done anything else in past month”). These symptoms have weaker – but still statistically significant – negative correlations with internalising disorders, and positive correlations with conduct and behavioural symptom nodes. Importantly, the developmental timing of the formation of these symptom links matches the increase in diagnoses of comorbid ADHD in OCD patients (De Mathis et al., 2012). These compulsive symptom nodes may therefore be associated with a distinct developmental path between hyperactive and externalising disorders. Therefore, groups of connected symptoms in OCD may reflect different developmental trajectories. This may result in OCD patients with comorbid disorders developing with distinct developmental trajectories.

Connectivity in our network may also be influenced by variables not included in our network model, for instance, genetic vulnerabilities. It is clear that genetic factors

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are important in the aetiology of obsessive compulsive symptoms, with heritability estimated at around 40% (Taylor, 2011; Matthews et al., 2014). The genetic basis for OCD is most probably influenced by large numbers of common genetic variants, likely at the level of single nucleotide polymorphisms (SNPs).

Investigations of polygenic risk scores show that through genome wide association studies in clinical samples, an individual's risk for the development of psychopathology can be predicted. Polygenic risk scores for major depression, schizophrenia and clinical OCD have been found to significantly predict the presence of sub-clinical obsessive compulsive symptoms. This finding of a shared association between polygenic risk for depression and subscale OCD suggests that the two disorders share genetic variance (Zilhao et al., 2018). While schizophrenic symptoms were not included in our network, node C.7 (Compulsions to repeatedly count to lucky numbers) was nevertheless found to be significantly correlated with symptoms of disrupted mood and anxiety within our network. Similarly, Node C.4 (Compulsions to perform repeated actions) was also correlated with mood and anxious symptoms. Therefore, the early high centrality of these symptom nodes, and their large range of early connections with associated comorbid disorders could relate to individuals within our sample population with a high genetic risk for the development of subscale OCD or depression.

The presence of obsessive or compulsive symptoms may therefore be important indicators for the presence of, or possible capability for development of other comorbid disorders. As these symptom nodes bridge multiple disorders, measuring OCD symptoms in individuals with externalising disorders may inform clinicians of a patient's risk of developing comorbid internalising disorders. Therefore, subscale

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measures of central symptoms within compulsions may have clinical applications as an early intervention tool to prevent the development of comorbidities.

Separation anxiety and internalising symptom bridges

Another central symptom node within the network identified based on high expected influence and betweenness centrality was node SPA.1. During early adolescence, this symptom was found to have strong positive correlations with GAD, depression and OCD. Previous research has identified separation anxiety as a risk factor for the development for psychopathological disorders during young adulthood, in particular, panic disorder and depression (Lewinsohn et al., 2008). Research has also identified that OCD patients with a history of separation anxiety disorder were significantly younger, and had a more severe onset of OCD alongside other comorbid diagnoses of social phobias (Mroczkowski et al., 2011). In conjunction with our findings, this symptom may also have clinical significance as a diagnostic marker for the development of comorbidity within internalising disorders.

Strengths and limitations

The strengths of our study are its large sample size, which provides sufficient statistical power to perform the *EBIC-glasso* with the number of symptom nodes used. Two networks from the same sample of participants are also compared across development, and two indices of centrality are used to verify the centrality of symptoms within our network. Therefore, while causality cannot be assumed in our model, we can draw strong inferences from which further work can be done.

Our study however, has limitations. Importantly, our network is an undirected acyclic graph. This means all edges represent bidirectional correlations. Therefore,

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these relationships cannot, and must not be interpreted as causal. Thus many of the interpretations, such as those given above, remain speculative.

The network presented is constructed from an amalgamation of individuals with and without diagnoses of psychopathology. It is possible that the frequency of reporting may have affected the significance of correlations shown within the network.

Compulsive symptoms were rarely reported, and their low frequency may have artificially inflated their correlations with other symptoms. Future research should investigate this possibility further, and seek to separate the plotting of network structures between disordered, and mentally well participants in their sample population.

There is also a lack of agreement on the interpretation and use of centrality statistics in psychopathological network analysis. As the field is relatively new, centrality estimates have been borrowed from other fields; no current consensus exists on which centrality estimates – or how exactly – to use such measures as accurate descriptors of relationships between psychopathological nodes (Bringmann et al., 2019). Betweenness centrality was used in our network as we think it was the most appropriate to investigate bridge symptoms. Our analysis also attempted to compensate by using a secondary index of centrality: Two-step expected influence. However, it should be noted EI_2 does not account for external influences on nodes, nor does it take into account self-feedback loops within the network (Robinaugh et al., 2016).

The generalisability of our network is also unclear. While the possibility for spurious connections has been limited, it is unclear how effective current regularisation techniques are at truly increasing the generalisability of data (Borsboom et al., 2018). Furthermore, no network bootstrapping or confidence interval analysis was conducted

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for edges in the finalised network. Little research has been conducted on the topic of how stable or accurate network parameters such as edge weights and centrality estimates are (Fried and Cramer, 2017).

A further issue in the burgeoning field of network analysis is the replication of network structures across studies. Separate investigations of networks from the same dataset do not necessarily yield the same results (Borsboom & Cramer, 2013; Forbes et al., 2017; Borsboom et al., 2017). While some of this variation can be attributed to either the use of statistical analyses of samples with insufficient power, a lack of consensus on statistical methodology, or the use of cross sectional datasets, it is undeniable that the structure of psychopathological networks in individuals changes over time as well (Epskamp et al., 2017).

Future directions

The field therefore, is ripe for future research. The creation of network analysis techniques for causal inference is essential to the development and application of psychopathological networks in clinical settings. A fruitful starting point would be to apply techniques from cross-lagged panel analysis to network data. This technique appears to be a promising avenue to allow for the plotting of causal networks between large numbers of symptom nodes. (Rhemtulla, Bork & Cramer, in press). Alternatively, time series data would allow the construction of personalised temporal networks that could detect symptom fluctuations, and other time sensitive phenomenon within individuals (Epskamp et al., 2017).

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Concluding remarks

Overall, our findings demonstrate the utility of network techniques for studying psychopathological disorders. We found that a network of symptoms organised into a structure that matched their diagnostic categories. This network was densely connected, and contained multiple significant symptom-symptom associations between disorders. Multiple, clinically relevant bridging symptoms were identified. Of these, Anxious, Obsessive-Compulsive and Separation-Anxiety symptoms were found to be important bridging symptoms for activation to spread across the network. In particular, Obsessions and Compulsions were highly influential within the network. It is likely that the organisation of symptom level connections holds deeper meaning, and may reflect either differing developmental trajectories, or underlying genetic vulnerabilities. Network analysis holds great promise in being able to shine a light, and focus our search on the connections and mechanisms underlying psychopathological comorbidity.

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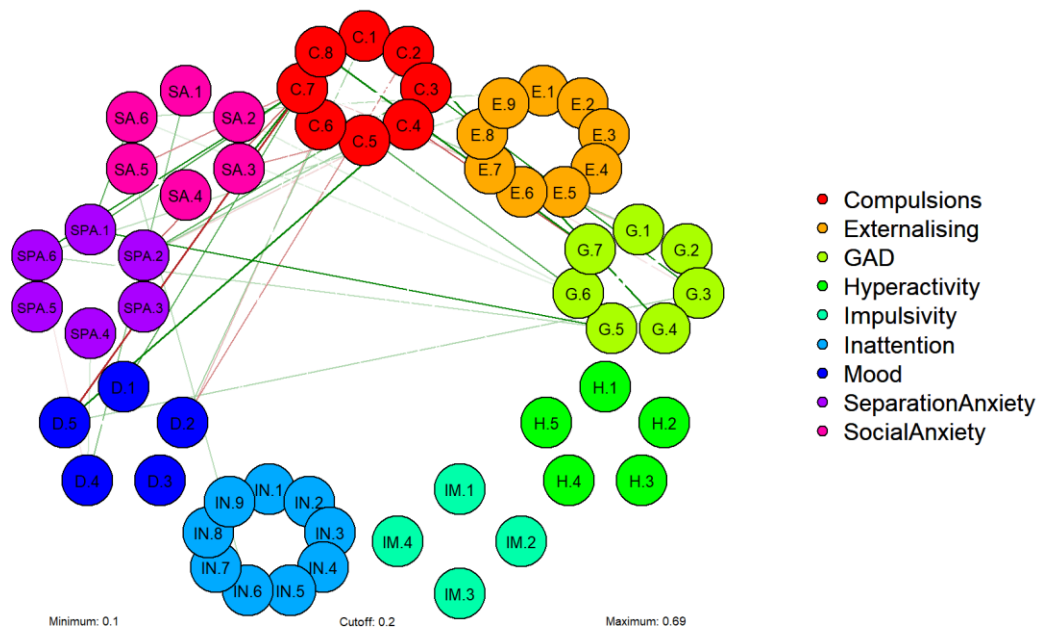
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Appendix 1:

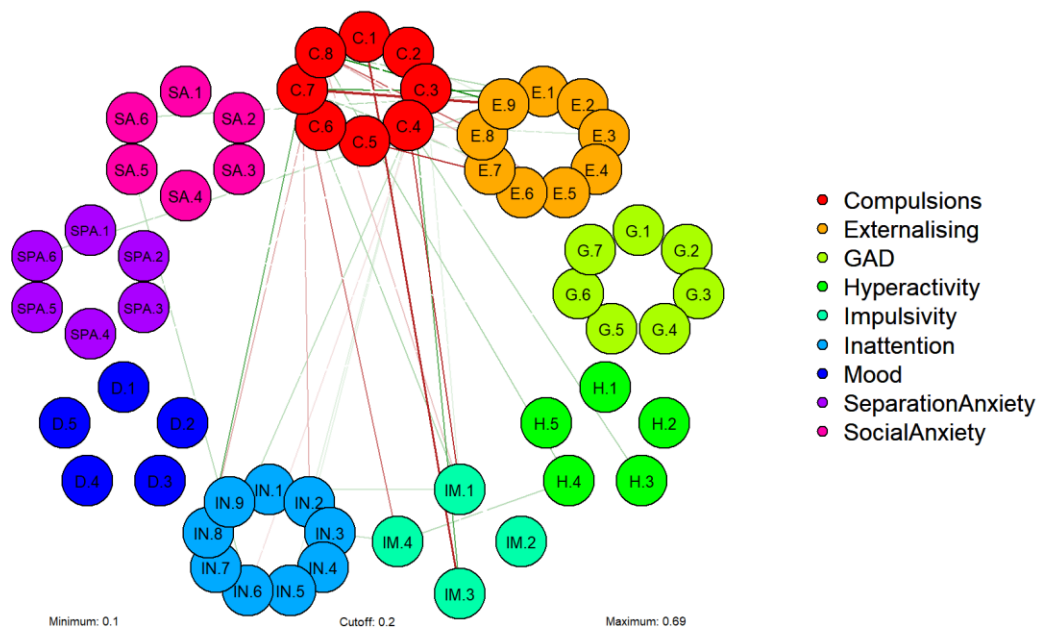
Network of Internalising Symptoms at Time Point 1

0.5



Network of Externalising Symptoms at Time Point 1

0.5

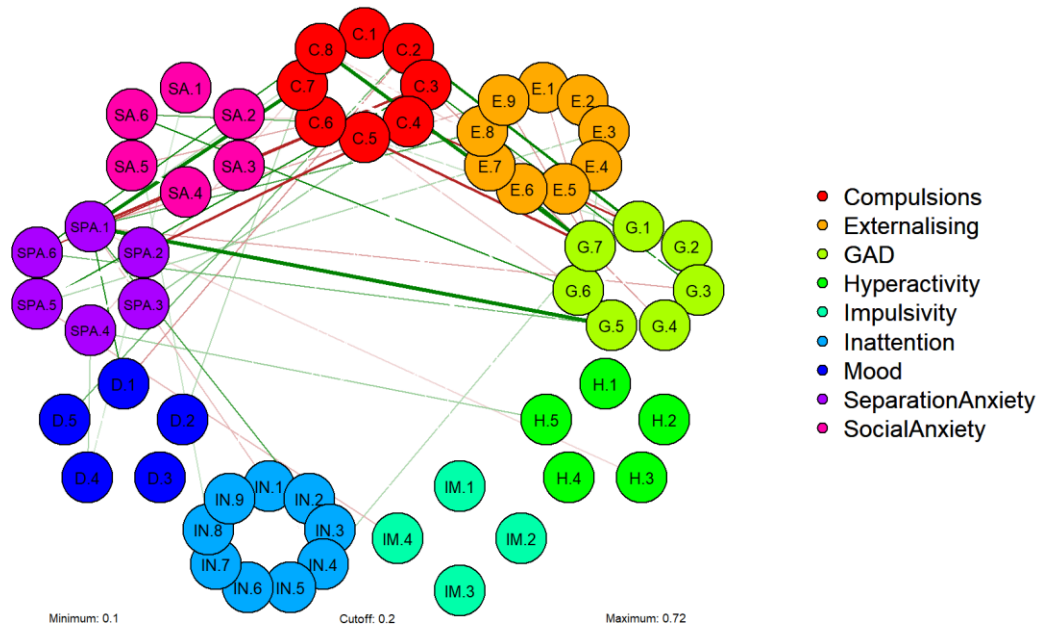


NETWORKS OF COMORBID CHILDHOOD PSYCHOPATHOLOGY

Appendix 2:

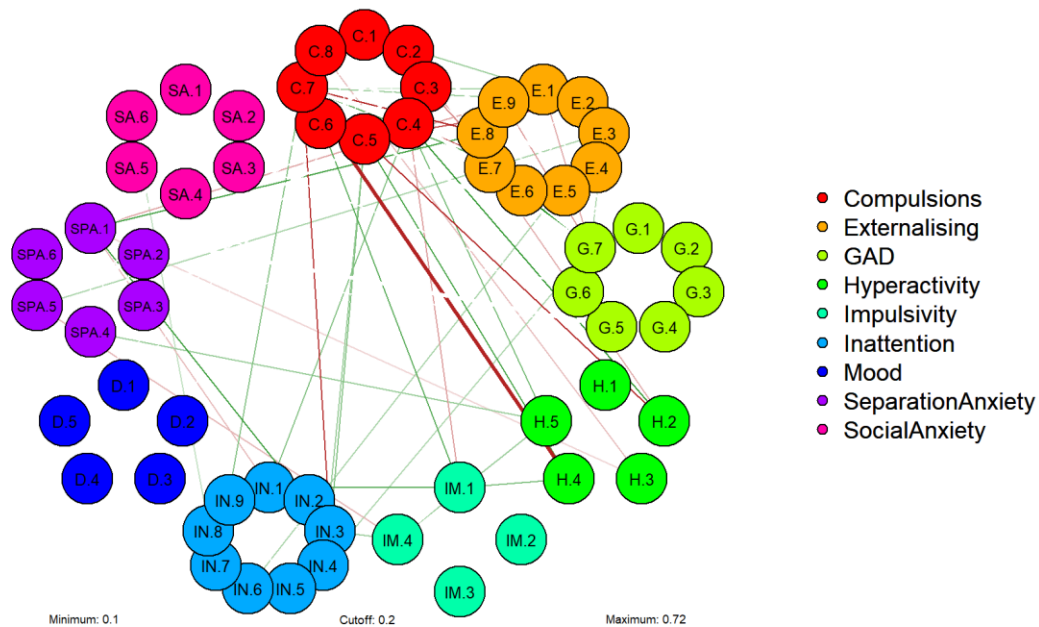
Network of Internalising Symptoms at Time Point 2

0.5



Network of Externalising Symptoms at Time Point 2

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NETWORKS OF COMORBID CHILDHOOD PSYCHOPATHOLOGY

Appendix 3

Table X: Symptom labels and Descriptive; Means & SD for DAWBA & SDQ nodes at Time Points 1 (6-7 years) and Time 2 (13-14 years).

Node	Names	Time Point 1		Time Point 2:	
		Mean (SD)	N	Mean (SD)	N
H.1	Compared to other children of her age, does she often fidget	0.316(0.566)	8121	0.227(0.501)	7009
H.2	Is it hard for her to stay sitting down for long?	0.277(0.545)	8131	0.159(0.437)	7015
H.3	Does she run or climb about when she shouldn't?	0.234(0.503)	8126	0.066(0.292)	7013
H.4	Does she find it hard to play or take part in other leisure activities without making a noise?	0.201(0.479)	8139	0.104(0.355)	7014
H.5	If she is rushing about does she find it hard to calm down when someone asks her to do so ?	0.24(0.510)	8119	0.111(0.363)	7000
IM.1	Does she often blurt out an answer before she has heard the question properly?	0.206(0.461)	8123	0.159(0.418)	7021
IM.2	Is it hard for her to wait her turn?	0.24(0.498)	8132	0.132(0.393)	7022
IM.3	Does she often butt in on other people's conversation or games?	0.357(0.567)	8113	0.224(0.481)	7017
IM.4	Does she often go on talking even if she has been asked to stop or no one is listening?	0.398(0.598)	8115	0.261(0.524)	7020
IN.1	Does she often make careless mistakes or fail to pay attention to what she is supposed to be doing?	0.322(0.550)	8107	0.295(0.532)	6996
IN.2	Does she often seem to lose interest in what she is doing?	0.22(0.490)	8123	0.193(0.460)	6997
IN.3	Does she often not listen to what people are saying to her?	0.344(0.566)	8105	0.301(0.538)	6994
IN.4	Does she often not finish a job properly?	0.269(0.516)	8089	0.294(0.532)	6989
IN.5	Is it often hard for her to get herself organised to do something?	0.264(0.520)	8090	0.321(0.562)	6980
IN.6	Does she often try to get out of things she would have to think about, such as homework?	0.294(0.544)	8091	0.343(0.587)	6980
IN.7	Does she often lose things she needs for school or PE?	0.181(0.445)	8112	0.268(0.539)	6997

NETWORKS OF COMORBID CHILDHOOD PSYCHOPATHOLOGY

Node	Names	Time Point 1		Time Point 2:	
		Mean (SD)	N	Mean (SD)	N
IN.8	Is she easily distracted?	0.357(0.587)	8099	0.338(0.583)	6988
IN.9	Is she often forgetful?	0.247(0.506)	8109	0.292(0.547)	6989
SPA.1	Has she often not wanted to go to school in case something nasty happened whilst she was there to a person she is attached to?	0.029(0.195)	7586	0.024(0.186)	6411
SPA.2	Has she worried about sleeping alone?	0.167(0.445)	7606	0.062(0.277)	6432
SPA.3	Has she come out of her bedroom at night to check on, or to sleep near any of her caretakers?	0.168(0.455)	7579	0.054(0.265)	6398
SPA.4	Has she worried about sleeping in a strange place?	0.092(0.335)	7565	0.073(0.293)	6418
SPA.5	Has she been afraid of being alone in a room at home without one of the people she is attached to?	0.12(0.380)	7571	0.041(0.224)	6416
SPA.6	Has she had repeated nightmares or bad dreams about being separated from any of these people?	0.039(0.218)	7533	0.022(0.163)	6406
SA.1	Degree to which child was afraid of meeting new people in past month	0.247(0.732)	8162	0.335(0.871)	7039
SA.2	Degree to which child was afraid of meeting lots of people in past month	0.327(0.880)	8168	0.442(1.040)	7029
SA.3	Degree to which child was afraid of speaking in class in past month	0.298(0.720)	8109	0.478(0.848)	6977
SA.4	Degree to which child was afraid of reading out loud before others in past month	0.382(0.828)	8106	0.511(0.886)	6979
SA.5	Degree to which child was afraid of writing in front of others in past month	0.201(0.684)	8119	0.282(0.818)	6987
SA.6	Degree to which child was afraid of eating in front of others in past month	0.049(0.348)	8153	0.087(0.443)	7027
G.1	Does she worry a lot about Past behaviour?	0.204(0.424)	8153	0.408(0.529)	3964
G.2	School work, homework or tests	0.394(0.564)	8168	0.912(0.515)	3992
G.3	Examinations	0.157(0.391)	8156	0.295(0.487)	3963
G.4	Disasters	0.094(0.310)	8151	0.318(0.517)	3963

NETWORKS OF COMORBID CHILDHOOD PSYCHOPATHOLOGY

Node	Names	Time Point 1		Time Point 2:	
		Mean (SD)	N	Mean (SD)	N
G.5	Her own health	0.269(0.483)	8152	0.479(0.558)	3959
G.6	Bad things happening to others	0.182(0.419)	8143	0.478(0.566)	3958
G.7	The future	0.109(0.382)	8171	0.253(0.544)	2665
C.1	Frequency child has repeatedly cleaned self excessively in past month	0.02(0.165)	8104	0.035(0.220)	6947
C.2	Frequency child has repeatedly taken other special measures to avoid dirt in past month	0.015(0.137)	8101	0.017(0.156)	6945
C.3	Frequency child has repeatedly checked things in past month	0.015(0.142)	8102	0.036(0.220)	6951
C.4	child has repeatedly performed repeated actions in past month	0.017(0.153)	8099	0.015(0.149)	6940
C.5	Frequency child has repeatedly touched things/people in particular ways in past month	0.021(0.171)	8099	0.019(0.168)	6939
C.6	Frequency child has repeatedly arranged things symmetrically in past month	0.041(0.225)	8092	0.039(0.230)	6942
C.7	Frequency child has repeatedly counted to lucky numbers / avoided unlucky numbers in past month	0.004(0.072)	8095	0.012(0.129)	6932
C.8	Frequency child has repeatedly done anything else in past month	0.038(0.264)	8105	0.051(0.299)	5997
D.1	She has often complained of headaches, stomach aches or sickness	0.338(0.565)	8390	0.486(0.743)	7063
D.2	She has many worries, often seems worried	0.293(0.521)	8360	0.356(0.935)	7056
D.3	She is often unhappy, down-hearted or tearful	0.171(0.409)	8404	0.211(0.709)	7050
D.4	She is nervous or clingy in new situations, easily loses confidence	0.435(0.607)	8384	0.352(0.786)	7061
D.5	She has many fears, is easily scared	0.269(0.507)	8363	0.265(0.943)	7063
E.1	In the last 6 months and compared with other children has she had severe temper tantrums?	0.112(0.373)	8097	0.506(0.564)	6957
E.2	Has she argued with grown-ups?	0.201(0.471)	8125	0.174(0.450)	6997
E.3	Has she taken no notice of rules, or refused to do as she is told?	0.181(0.456)	8114	0.14(0.416)	6973
E.4	Has she seemed to do things to annoy other people on purpose?	0.188(0.456)	8098	0.158(0.421)	6975

NETWORKS OF COMORBID CHILDHOOD PSYCHOPATHOLOGY

Node	Names	Time Point 1		Time Point 2:	
		Mean (SD)	N	Mean (SD)	N
E.5	Has she blamed others for her own mistakes or bad behaviour?	0.183(0.442)	8103	0.135(0.396)	6968
E.6	Has she been touchy and easily annoyed?	0.222(0.473)	8108	0.221(0.475)	6991
E.7	Has she been angry and resentful?	0.155(0.422)	8090	0.156(0.428)	6971
E.8	Has she been spiteful?	0.079(0.305)	8071	0.062(0.277)	6926
E.9	Has she tried to get her own back on people?	0.075(0.302)	8074	0.061(0.276)	6934