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### A Prospective Study on How Symptoms in a Network Predict the Onset of Depression

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To explain the overt heterogeneous nature of major depressive disorder (MDD), it could be valuable to focus on individual symptoms [1]. Recent research, for example, showed that MDD symptoms differ in their underlying biology, risk factors and psychosocial impairments [for a review, see 2]. In addition, the presence of specific symptoms (e.g. psychomotor agitation) may have important clinical implications, such as expectations regarding the response to antidepressants [3].

The network approach is a conceptualization that specifically focuses on individual symptoms [4]. According to this approach, psychopathology results from the associations between symptoms, and each of these symptoms may have its unique set of associations with other symptoms. This information can be visualized into a network, in which symptoms are represented as nodes and the associations between them as lines.

In a recent study, we estimated the network of a large set of psychiatric symptoms, including those of MDD, and indeed found that symptoms differed in the number and strength of associations [5]. For example, depressed mood and fatigue were *central* in the network (i.e. having many and/or strong associations), whereas a decrease and increase in weight/appetite were not. Central symptoms are believed to have considerable impact on other symptoms and, consequently, more strongly predict the onset of MDD than symptoms that are less central.

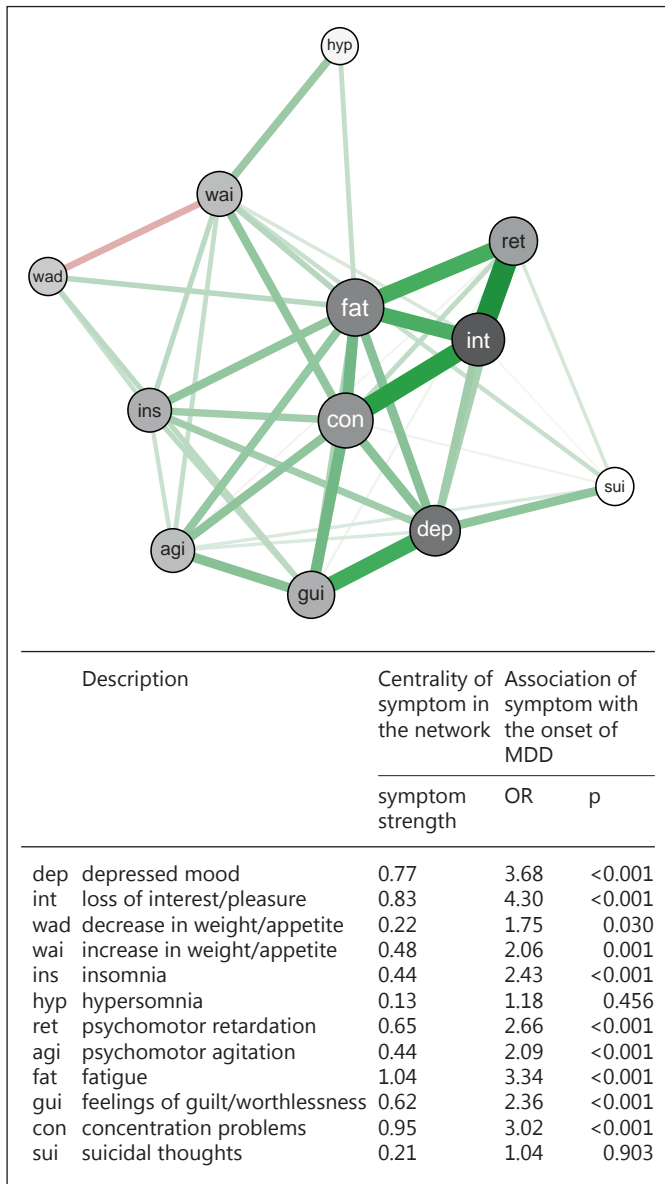
The present study aimed to test whether symptom centrality was indeed related to the risk of developing MDD. Therefore, we selected 501 adults with no lifetime DSM-IV depressive or anxiety disorder from the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA) [for a detailed description of the study design, see 6]. L1-regularized partial correlations were used to compute a sparse network of the 12 MDD symptoms as assessed with specific items of the Inventory of Depressive Symptomatology [for a detailed description of the procedures, see 7]. To determine the centrality of each of the symptoms in the network, *symptom strength* was calculated as the sum of all direct correlations with other symptoms.

Figure 1 shows the resulting network of baseline MDD symptoms. Symptoms differed substantially in both the number and magnitude of associations, but, overall, symptom strength was the highest for fatigue, concentration problems, loss of interest/pleasure and depressed mood. In contrast, hypersomnia, suicidal thoughts and a decrease in weight/appetite had the lowest symptom strength.

In this sample of healthy controls, we identified those who developed a DSM-IV MDD at the 2-, 4- or 6-year follow-up assessment ( $n = 79$ ) and those who did not ( $n = 422$ ). Univariable logistic regression analyses showed that loss of interest/pleasure, depressed mood, fatigue and concentration problems (i.e. those symptoms with the highest symptom strength in the baseline network) were the strongest predictors [all odds ratios (OR)  $\geq 3.02$ ], whereas suicidal thoughts, hypersomnia and a decrease in weight/appetite (i.e. those symptoms with the lowest symptom strength in the baseline network) were not or only weakly related to the onset of MDD (all OR  $\leq 1.75$ ). In general, symptoms that were central in the baseline network more strongly predicted the onset of MDD than symptoms that were less central ( $r = 0.87$ ,  $p < 0.001$ ).

Then, we tested whether information on the centrality of symptoms could improve the prediction of the onset of MDD. In addition to a conventional severity measure based on the sum of the 12 MDD symptoms (i.e. the unweighted severity measure), a new severity measure was calculated in which the 12 MDD symptoms were weighted for symptom strength (i.e. the weighted severity measure). Multivariable logistic regression analyses showed that the weighted severity measure more strongly predicted the onset of MDD than the unweighted measure (adjusted OR = 1.66,  $p = 0.043$  vs. adjusted OR = 1.00,  $p = 0.995$ ).

Our findings indicate that the risk of developing MDD depends on the type of subthreshold symptom that a person reports. Loss of interest/pleasure, depressed mood, fatigue and concentration problems were the most important risk factors, and these symptoms could, therefore, help clinicians (e.g. general practitioners) in identifying persons who are most vulnerable for MDD. These specific symptoms were also central in the MDD symptom network and may, consequently, be valuable targets in prevention strategies. By eliminating or reducing such a central symptom, it is hypothesized that activity within the whole network can be reduced (or prevented). For example, a strategy that encourages a person to engage in pleasant activities does not only have the potential to improve (or prevent) a person's ability to experience pleasure (symptom 'loss of interest/pleasure') but, subsequently, also his or her energy level (connected symptoms 'fatigue' and 'psychomotor retardation') and ability to concentrate (connected symptom 'concentration problems'). Although such strategies are already part of regular prevention programs and have proven to be effective [8], the network approach may offer a more empirical, data-driven basis that enhances even more focused interventions based on the role of specific symptoms within a network.



**Fig. 1.** Baseline MDD symptom network in persons with no lifetime depressive or anxiety disorder (n = 501). All lines represent positive correlations, except for the line between ‘wad’ and ‘wai’, which represents a negative correlation. Thicker lines represent stronger correlations. Larger nodes represent symptoms with a higher symptom strength and darker nodes represent symptoms with stronger associations with the onset of MDD during the 6 years of follow-up.

Strengths of our study were that we included a large sample of persons with no lifetime DSM-IV depressive or anxiety disorder (n = 501) and prospectively examined the onset of DSM-IV MDD during a 6-year follow-up. However, a limitation is that MDD symptoms were assessed at a single time point and, therefore, the temporal relationship between symptoms is unknown. Time series

analyses of longitudinal data from the experience sampling method could help to unravel the dynamics of symptom networks over time [9], which might also be a promising approach for examining therapeutic changes [for an interesting review on this topic, see 10].

In conclusion, subthreshold MDD symptoms were differentially associated with the prospective onset of MDD and these findings demonstrate the value of an approach focusing on individual symptoms. The network approach may be such an approach, as we showed that the risk of developing MDD depended on the centrality of a symptom in the network. This centrality may, therefore, inform clinicians on the symptoms that are likely to have the most prognostic impact when adapted by targeted treatment.

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