Tracking Neuropsychiatric Symptom Progression in Dementia Through Time-Varying Conditional Dependency Networks

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Abstract

Neuropsychiatric symptoms such as agitation, anxiety, depression, irritability, and hallucinations frequently co-occur in individuals with cognitive impairment and dementia, yet the direct relationships among these symptoms—and how they evolve over time—remain poorly understood. Since simple co-occurrence patterns can obscure whether symptoms are directly or indirectly related, we model symptom interactions using conditional independence networks, where a link between two symptoms represents a direct relationship that remains even after accounting for all other symptoms—that is, when knowing one symptom still provides new information about another beyond what the remaining symptoms already explain. Using data from the Mayo Clinic Study of Aging (MCSA), we estimate conditional independence networks for dementia and non-dementia cohorts across multiple time bins and compare their trajectories at the network and symptom levels. Our symptom-level analyses consistently identify depression, anxiety, hallucinations, and delusions as key symptoms whose direct connections strengthen and expand over time in dementia patients, indicating their increasing structural influence within the neuropsychiatric system.

1 Introduction

Neuropsychiatric symptoms (NPS), also referred to as behavioral and psychological symptoms of dementia, are a core component of the clinical presentation of dementia alongside cognitive impairment [19]. These symptoms—including agitation, anxiety, depression, irritability, and hallucinations—are highly prevalent, affecting a substantial majority of individuals with dementia [22, 23]. Despite their clinical importance, research has historically emphasized cognitive decline over NPS [20, 21], even though the presence of NPS has been consistently linked to disease progression, functional decline, and reduced life expectancy [24–27]. Importantly, NPS rarely occur in isolation; rather, they tend to co-occur, fluctuate over time, and follow heterogeneous trajectories with varying intensities as dementia progresses [27]. Understanding how these symptoms relate to one another beyond simple co-occurrence is therefore essential for characterizing clinical trajectories and for distinguishing direct symptom–symptom relationships from associations driven by shared underlying factors.

Conventional analyses [12, 13] often rely on correlations to describe associations among symptoms. While correlations quantify overall co-occurrence, they cannot distinguish between direct symptom–symptom relationships and spurious associations driven by third variables. Such spurious associations may arise when predictor variables are correlated with one another (collinearity) or when a confounding variable jointly influences multiple symptoms, thereby obscuring their true relationships. To illustrate this, consider the toy example in Figure 1: anxiety and hallucinations may appear positively correlated in a cohort of patients, but this association may be entirely explained by their shared relationship with depression. Once depression is accounted for, anxiety may provide no additional information about hallucinations—they may be *conditionally independent* given depression. Identifying these conditional independence relationships is essential for isolating the direct pathways through which symptoms co-vary.

Probabilistic graphical models [14] provide a principled framework for characterizing conditional dependencies among symptoms. In a conditional independence (CI) graph, each symptom is represented as a node, and an edge is included only when two symptoms remain related after adjusting for all others. This representation aligns naturally with clinical intuition, viewing symptoms as components of an interconnected system. Importantly, this perspective differs

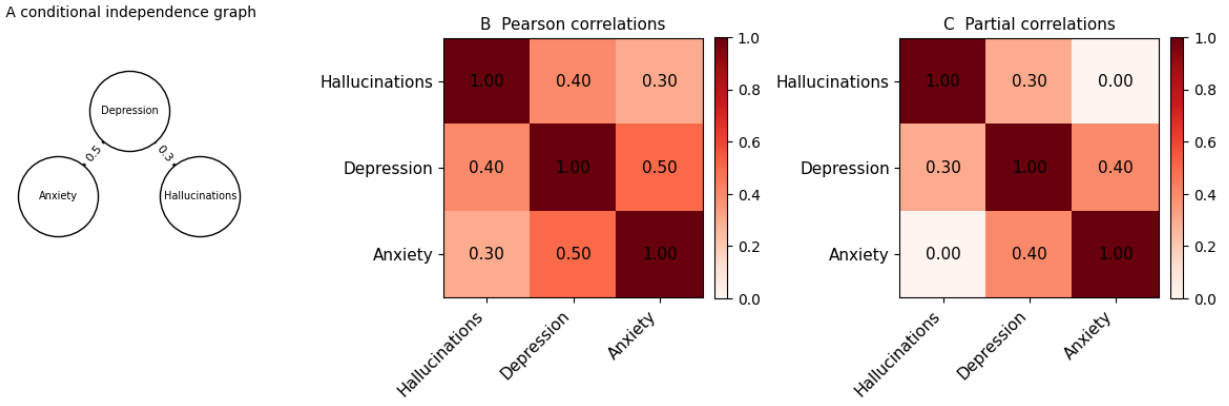


Figure 1: Illustration of how depression can create a false link between anxiety and hallucinations. **Panel A**: the true pattern, where depression is directly connected to both symptoms but anxiety and hallucinations are not directly related. **Panel B**: simple correlations incorrectly suggest a connection between anxiety and hallucinations because both tend to occur with depression. **Panel C**: once depression is taken into account, the apparent link disappears, revealing the correct underlying relationships.

fundamentally from graph-based deep learning approaches such as graph neural networks (GNNs), which treat the graph as a computational structure for prediction rather than as an explicit probabilistic model of the data-generating process [31].

Although static symptom networks provide valuable insight, they cannot capture the dynamic nature of symptom progression. NPS evolves over months and years, and their interaction structure may shift as patients transition through stages of cognitive decline [15, 16]. To study how symptom relationships change over time, we adopt **time-varying** models that allow the underlying CI network to evolve.

Estimating a sequence of networks from longitudinal clinical data is statistically challenging: the number of observations within each time window may be limited, and naively estimating networks at each time point leads to unstable or noisy results. To address these challenges, we adopt a time-varying Ising modeling algorithm proposed in [1] that combines sparsity with temporal regularization to produce stable, interpretable networks across time. The Ising model is an appropriate graphical model for capturing pairwise conditional dependence for binary features (e.g., presence or absence of NPS). Using this algorithm, we analyze data from the MCSA [32] to compare the evolution of NPS networks in dementia and non-dementia cohorts.

Contributions..

- We incorporate a time-varying Ising modeling pipeline tailored to NPS progression in dementia.
- We compare network trajectories between dementia and non-dementia groups, highlighting connectivity patterns.
- We provide a reproducible statistical framework that can support future studies of symptom progression and other longitudinal binary clinical features.

2 Related Work

Prior work on NPS in dementia has primarily relied on epidemiological and neuroimaging methodologies to characterize symptom burden and progression. Large-scale systematic reviews and meta-analyses have quantified the prevalence of depression, anxiety, and apathy across stages of Alzheimer's disease and mild cognitive impairment using standardized clinical rating scales [2–5, 10]. Longitudinal cohort studies have examined associations between affective symptoms and disease trajectories, often linking symptom measures to structural brain changes using neuroimaging biomarkers [3, 6]. Additional studies have investigated anxiety and depressive symptoms using cross-sectional clinical assessments, comorbidity analyses, and experimental animal models [7–9].

Prior longitudinal and cross-sectional studies [15, 16] have shown that NPS are highly prevalent in dementia and follow

heterogeneous progression patterns over time, with apathy, agitation, irritability, and sleep and eating disturbances generally worsening as dementia advances, while delusions and depressive symptoms may decline. These studies also report sex-specific differences in symptom trajectories, but primarily rely on symptom prevalence and severity measures rather than modeling interactions among symptoms.

[18] examined stage-specific co-occurrence patterns of NPS in dementia using large cross-sectional cohorts, identifying distinct symptom clusters associated with disease severity. These studies report that anxiety and restlessness tend to co-occur in earlier stages, while in moderate to severe dementia, delusions and hallucinations cluster with sleep disturbances.

Recent work [17] explored GNNs for modeling longitudinal cognitive impairment data by constructing a variable graph based on pairwise correlations and using GNNs to predict disease progression outcomes. In contrast, our work adopts a probabilistic graphical modeling perspective, in which we assume the existence of an underlying probability distribution governing symptom co-occurrence and aim to infer its conditional-dependence structure from finite observational samples [31].

3 Study Design

The data used in this study come from the MCSA [32], a large longitudinal cohort comprising both cognitively normal and cognitively impaired participants. The analytic subset includes 4,978 cognitively normal individuals and 981 cognitively impaired individuals, with the impaired group contributing a higher average number of clinical visits (6.49) compared with the cognitively normal group (4.43). Sex is evenly distributed across groups.

Our analysis focuses on two groups—those with dementia and those without—each evaluated on a shared set of twelve neuropsychiatric symptoms: agitation, anxiety, apathy, appetite changes, delusion, depression, hallucinations, euphoria, disinhibition, irritability, and motor behavior. Each symptom is recorded as a binary indicator (1 = present, 0 = absent).

We used a cumulative time-binning strategy based on each patient's diagnosis date. Clinical visits were grouped into time windows defined by increasing temporal distance from diagnosis:

- **Pre-1-year bin**: visits occurring within one year before diagnosis.
- **Pre-3-year bin**: all visits within three years before diagnosis (including the pre-1-year window).
- **Pre-5-year bin**: all visits within five years before diagnosis.

Thus, each successive bin contained all observations from the earlier bins, resulting in nested time windows that capture progressively longer pre-diagnostic histories.

4 Methodology

4.1 Graphical Models and the Ising Model

A graphical model arises when a probability distribution is associated with a graph $G = (V, E)$, where V is a set of vertices and $E \subseteq V \times V$ is a set of edges. Each vertex represents a random variable and the edges encode the conditional independence structure among them.

Let $\mathbf{X} = (X_1, X_2, \ldots, X_p)^\top \in \{-1, +1\}^p$ denote a p-dimensional binary vector representing NPS (where p is the number of symptoms). An Ising model specifies a joint probability of the form:

$$P(\mathbf{X} = \mathbf{x}) = \frac{1}{Z(\Theta, \mathbf{h})} \exp\left(\sum_{1 \le i < j \le p} \theta_{ij} x_i x_j + \sum_{i=1}^{p} h_i x_i \right), \tag{1}$$

where $\Theta = \{\theta_{ij}\}$ is a symmetric interaction matrix, $\mathbf{h} = (h_1, \ldots, h_p)$ represents external symptom-specific potentials, and $Z(\Theta, \mathbf{h})$ is the normalizing constant (partition function). Each nonzero entry $\theta_{ij} \neq 0$ corresponds to an edge between symptoms (X_i, X_j), representing a conditional dependence between these symptoms given all others. The sparsity pattern of Θ thus encodes the conditional independence structure of the neuropsychiatric symptoms.

In practice, direct maximum-likelihood estimation of Eq. (1) is computationally expensive since evaluating the partition function scales exponentially with p. A common and efficient alternative is the node-wise pseudolikelihood approach,

which estimates each node's conditional distribution given all others via a logistic regression model. For node u:

$$P(X_u = 1 \mid \mathbf{X}_{-u}) = \sigma\left(h_u + \sum_{v \neq u} \theta_{uv} X_v\right), \tag{2}$$

where $\sigma(z) = 1/(1+e^{-z})$ is the logistic function. The coefficients θ_{ij} from node-wise regressions collectively recover the graph structure of the underlying Ising model.

4.2 The Time-Varying Ising Model

As NPS evolve over the course of disease progression, the dependencies among them are unlikely to remain static. Symptoms that are conditionally independent at one stage may become tightly linked later, while early interactions may weaken or disappear altogether. We employ the TV-ISING algorithm [1] to estimate evolving conditional dependencies across discrete time points.

Given binary feature matrices $\{\mathbf{X}_t\}_{t=1}^T$, where each $\mathbf{X}_t \in \{+1, -1\}^{n_t \times p}$ represents the observed nodal states at time t, the algorithm jointly estimates a sequence of Ising networks $\{\theta_t\}_{t=1}^T$ through a temporally regularized node-wise pseudo-likelihood formulation:

$$\min_{\{\theta_t\}_{t=1}^T} \sum_{i=1}^{n_t} \log\left(1 + e^{-y_{it}\, \theta_t^\top \mathbf{x}_{it}}\right) + \lambda_1 \sum_{t=1}^{T} \|\theta_t\|_1 + \lambda_{\mathrm{TV}} \sum_{t=1}^{T-1} \|\theta_{t+1} - \theta_t\|_1, \tag{3}$$

where λ_1 controls sparsity within each time-specific network, and λ_{TV} encourages smooth transitions in the interaction structure across consecutive time points. The optimization decouples across nodes, allowing scalable estimation via parallel node-wise fused-logistic regressions.

To obtain the final edge set, the method first estimates asymmetric pairwise parameters from node-wise regressions and then applies symmetrization. After symmetrization, an edge is included only if its absolute parameter value exceeds a threshold τ. The regularization parameter λ_1 is selected using the Bayesian Information Criterion (BIC). Algorithm 1 summarizes the procedure.

Algorithm 1 Time-Varying Ising Model (TV-ISING) [1]

Require: Binary feature matrices $\mathbf{X}_1, \ldots, \mathbf{X}_n$; regularization parameters λ_1, λ_{TV}; thresholding parameter τ
Ensure: Edge sets $\{E_t\}_{t=1}^n$

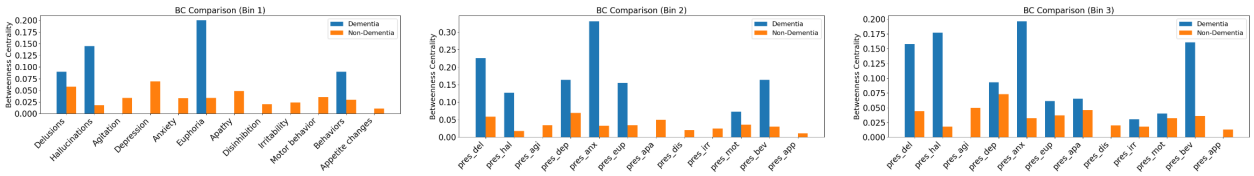
```
for each node u do
    Fit node-wise fused-logistic regression across all time windows to estimate {h_u, θ_uv,t}
    Solve fused-lasso optimization in Eq. (3) to impose sparsity within each time window and temporal smoothness across time
end for
Symmetrize pairwise parameters
for each time t and node pair (u, v) do
    Include edge (u, v) ∈ E_t if |θ_uv,t| ≥ τ
end for
return {E_t}_{t=1}^n
```

5 Experimental Results

We present our results from three complementary perspectives. The non-dementia CI network remains largely stable over time, whereas the dementia CI network becomes progressively denser, reflecting increased conditional dependencies among symptoms.

5.1 Global CI Network Evolution

We employ three metrics to characterize structural changes across time bins:



(a) Bin 1 (b) Bin 2 (c) Bin 3

Figure 2: Betweenness centrality comparison between dementia (blue) and non-dementia (orange) networks across the three time bins.

- **Jaccard Similarity**: $|E_1 \cap E_2|/|E_1 \cup E_2|$, measuring edge-set overlap between two networks.
- **Hamming Distance**: counts edges appearing in one network but not the other.
- **Edge Density**: proportion of all possible edges that appear in the network.

Across all metrics, the non-dementia edge set showed minimal structural change over time; we therefore report only dementia cohort results. Edge densities were: Bin 1 = 6.06%, Bin 2 = 12.12%, and Bin 3 = 19.7%. Jaccard similarities between consecutive bins were 0.50 (Bin 1→2) and 0.62 (Bin 2→3), and the corresponding Hamming distances were 4 and 5, respectively.

5.2 Betweenness Centrality

Betweenness centrality measures how frequently a node appears on the shortest path between other nodes in the graph. If symptom C lies on the shortest path between symptoms A and B, this indicates that A and B are conditionally independent once C is accounted for—i.e., C mediates the conditional-dependence relationship between A and B. Throughout this paper, we use *betweenness centrality* and *centrality* interchangeably, always referring to this shortest-path-based notion in the CI network.

Comparison across dementia and non-dementia networks.. NPS including **delusions, anxiety, depression, behavioral disturbances, and hallucinations** show increasing betweenness centrality over time among dementia patients, while remaining largely unchanged among non-dementia patients (Figure 2). Across all three time bins, dementia networks exhibit higher and more variable betweenness centrality than non-dementia networks. In the first bin, several dementia symptoms already display modest betweenness (≈0.03–0.04), whereas non-dementia values are near zero. In the second bin, betweenness for multiple dementia symptoms increases further (≈0.07–0.12). By the final bin, delusions and anxiety exceed 0.30, and depression, behavioral disturbances, and hallucinations exceed 0.15.

Betweenness centrality trajectories per symptom (dementia).. Figure 3 shows symptom-specific betweenness centrality trajectories for dementia patients across the three time bins. **Delusions, anxiety, and depression** show clear and consistent increases: delusions from ≈0.03 → 0 → 0.37, anxiety from 0 → 0 → 0.33, and depression from 0 → 0 → 0.25. **Euphoria** also shows a steady rise (≈0.04 → 0.12 → 0.19), while **irritability** increases from 0 → 0 → 0.15. This pattern suggests progressive reorganization of the symptom structure in dementia, where a small subset of symptoms becomes central to how other symptoms are conditionally related over time.

5.3 Degree Trajectories

Degree trajectories per symptom (dementia).. Figure 4 shows degree trajectories for dementia patients. **Delusions, euphoria, and irritability** show increasing degree over time, rising from 0–1 in the first bin to degree 3 by the final bin. **Depression** and **anxiety** show moderate increases from degree 1 to 2, while **disinhibition, agitation, appetite changes, and motor behavior** increase from 0 to 1. Symptoms with zero degree remain structurally isolated throughout. Consistent with the betweenness results, symptoms such as delusions and depression that exhibit rising betweenness centrality also show increasing degree, reflecting systematic changes in how conditional independence relationships among symptoms are organized as dementia progresses.

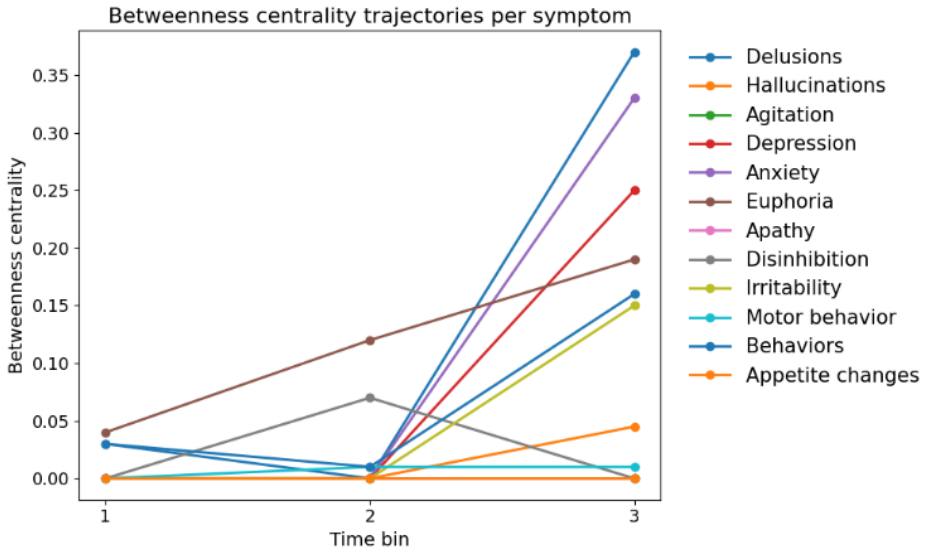


Figure 3: Betweenness centrality values over time for all neuropsychiatric symptoms in the dementia cohort, showing symptom-specific trajectories across the three time bins.

6 Discussion and Limitations

Discussion.. A key observation from our analysis is the increasing centrality of depression, anxiety, hallucinations, and delusions within the dementia CI network over time. Increasing centrality means that these symptoms increasingly lie on the shortest conditional-dependence paths between other symptom pairs, such that more symptom relationships become conditionally independent once these symptoms are accounted for. Importantly, increasing centrality does not reflect symptom onset or severity, but rather changes in how symptoms are conditionally related to one another over time.

This pattern is consistent with prior clinical findings. Brodaty et al. [28] reports that overall NPS association increases over time, with delusions, hallucinations, agitation, anxiety, apathy, disinhibition, irritability, and aberrant motor behavior showing significant progression. Fuller et al. [29] and Liew [30] shows that the presence of NPS is associated with progression to more severe dementia in Alzheimer's disease; symptoms including depression, anxiety, apathy, delusions, hallucinations, irritability, and motor disturbances are linked to progression in Alzheimer's disease, whereas in non-Alzheimer's dementias, only hallucinations and delusions exhibit such associations.

Our results for hallucinations and delusions are also consistent with established evidence. Rockwood et al. [18] note that hallucinations and delusions tend to emerge more frequently in later disease stages, aligning with our finding that these symptoms gain centrality over time within the dementia CI network. Together, these converging lines of evidence indicate that the symptoms identified by our model as central are also those repeatedly emphasized in the broader neuropsychiatric literature.

Limitations.. A key limitation of the time-varying Ising framework is its reliance on sufficient sample sizes within each time bin; when data are sparse, the recovered network structure may become unstable or sensitive to noise. Incorporating more NPS would require proportionally larger samples per time bin. The method also relies on regularization and thresholding choices that introduce an element of subjectivity and may affect the comparability of networks across time bins.

From a study design perspective, the analysis is based on observational data drawn from a single cohort, which may limit generalizability to other populations, and unmeasured confounders cannot be ruled out. Finally, the Ising model assumes pairwise interactions and does not capture higher-order dependencies among symptoms, which may limit its ability to represent more complex multivariate relationships present in real-world clinical data.

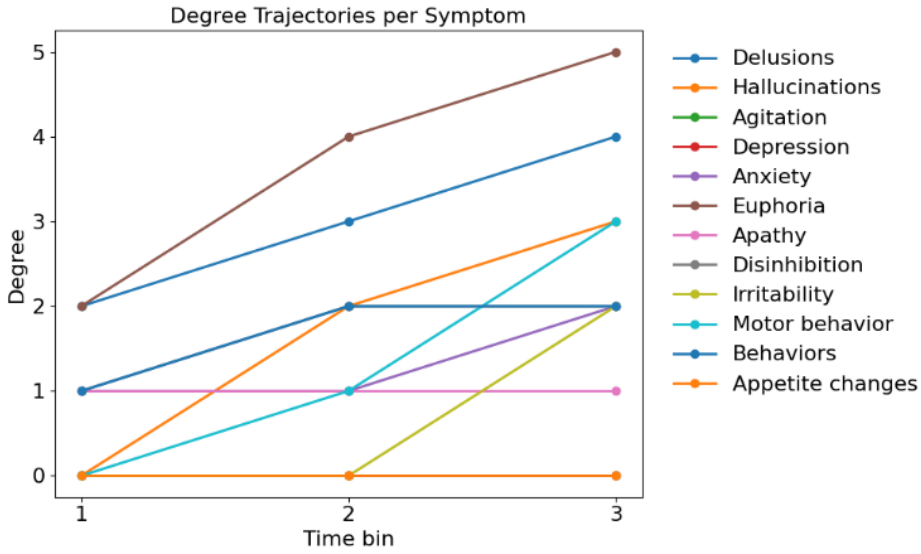


Figure 4: Degree values over time for all neuropsychiatric symptoms in the dementia cohort, showing symptom-specific trajectories across the three time bins.

7 Conclusion

In this study, we applied a time-varying Ising modeling framework to characterize how direct relationships among neuropsychiatric symptoms evolve in dementia and non-dementia populations. Across multiple complementary perspectives—including CI network recovery, global structural trajectories, and symptom-level dynamics—we observed a clear divergence between the two groups. The CI network of the non-dementia cohort remained stable over time, suggesting relatively consistent symptom interactions. In contrast, the dementia CI network became progressively denser, indicating that symptoms increasingly develop direct associations as the condition advances. Together, these results underscore the potential of time-varying graphical models to capture clinically meaningful changes in symptom interdependencies and to provide a statistical foundation for future research on longitudinal neuropsychiatric progression in populations affected by dementia.

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