Reconstructing Neuronal Signaling Pathways With the Potential for Disruption in Schizophrenia

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Objectives

Schizophrenia (SCZ) is a poorly characterized disorder. Using a network-based technique, we hoped to:

- Further explore the syndromicity of schizophrenia using a topological approach
- Reproduce well-known signaling proteins and proteins related to SCZ
- Link together previously disparate neuronal signaling pathways
- Find proteins that could be good candidates for future physiological experimentation

Introduction

- Genomic studies have yielded several highly-associated genes [1]
- Finding rare but collectively frequent mutations is statistically difficult
- We use PathLinker to look at a pathway model of disruption
- PathLinker reconstructed signaling proteins, SCZ-related proteins, and protein candidates for future studies

PathLinker Method

We are given a directed graph $G = (V, E)$ describing an *interactome*, where nodes represent proteins and edges represent interactomes among proteins. The interactome G has an associated *cost* for each edge $e \in E$ [2]. Given a source set of nodes $S \subseteq V$ and a target set of nodes $T \subseteq V$, Pathlinker efficiently calculates the k shortest paths from any source node in S to any target node in T [3].In this work, we run PathLinker using iterative pairs of targets and receptors; i.e., for every receptor in the source set $S = s_1, s_2, ...s_x$ and every transcription factor in the target set $T = t_1, t_2, ...t_y$, PathLinker computed the k=100 paths between each possible pair (s_x, t_y).

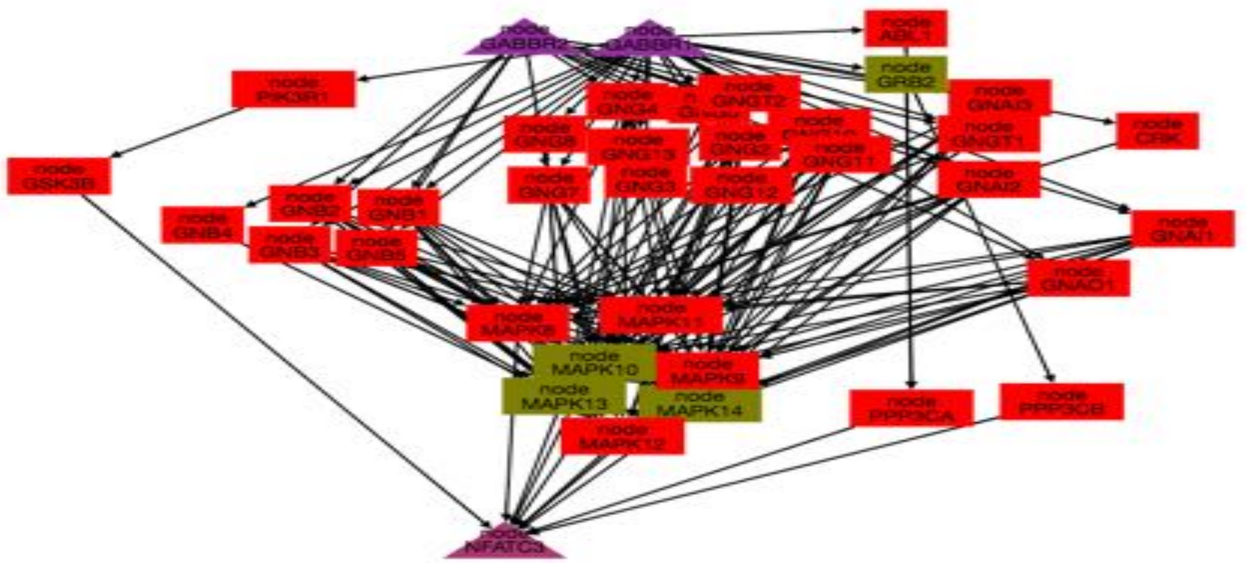

Figure 1: Metanetwork that combines two of the 170 networks, including GABBR1 and GABBR2 receptors connected to NFATC3 transcription factor, found in the GWAS set [1]. Purple triangles are from the hand-curated dataset. Red nodes are in both datasets, and brown nodes are only present in one.

Reconstructed Proteins

PathLinker reconstructed MAPKs and G proteins, well-known signaling proteins. PIK3R1 is known to be associated with SCZ [4]. ABL1 is implicated with neuronal death in mice, but has not been studied in SCZ context [5].

Metanetworks

The PathLinker method resulted in 170 networks, which were compared by total node overlap percentage (Fig. 2). Networks with high enough overlap were combined into metanetworks.

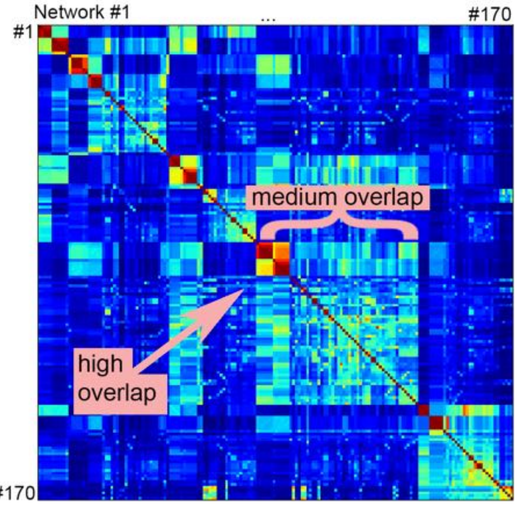

Figure 2: Pairwise node overlap percentage of 170 networks.

Topology

SCZ networks were found to have a significantly higher edge overlap than a random sampling, but not a significantly different node overlap. This might suggest the presence of more interconnected hubs in neuronal signaling pathways.

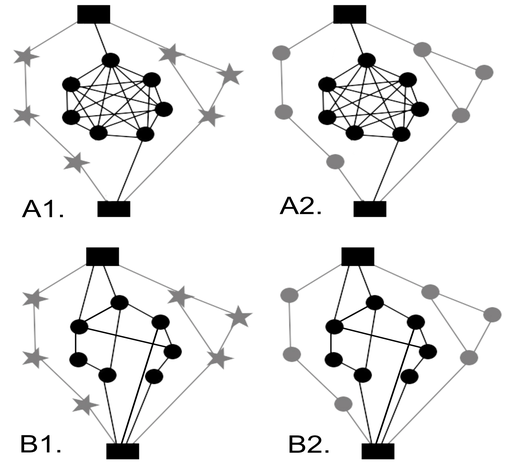

Figure 3: (A1, A2) and (B1, B2) have the same node overlap, but (A1, A2) have a higher edge overlap.

Inputs

- **Sources:** Receptors were hand-curated from the literature using GWAS data, drug targets, and other associations to SCZ. Sources were expanded to include families and different isoforms.
- **Targets:** Transcription factors were similarly hand-curated from the literature.
- **Interactome:** Described in [3]

Conclusion

Network analysis offers a powerful tool to use in conjunction with genomic results. This method reconstructs well-known signaling pathways, proteins known to be involved in schizophrenia etiology, and offers good hypotheses for future biomolecular studies.

References

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