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The Small World of a Fear Memory

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Abstract

How are fear memories organized? In this issue of *Neuron*, Vetere et al. (2017) take a network-based approach to demonstrate the importance of highly interconnected hub regions in the consolidation of a fear memory. By doing so, they provide an elegant framework for predicting behavior from functional network properties.

Imagine booking a flight from San Francisco to Berlin. With few non-stop routes between these two cities, you will likely need to take a connecting flight through a major airport, such as Newark. But why fly into Newark, instead of the multitude of other airports that fall more directly along your flight path? The simple answer, as you may have already anticipated, is that of air traffic control: in order to accommodate a large number of flights in and out of many United States cities, airlines have created highly connected airport “hubs” that serve a much greater volume and diversity of flights than smaller airports. This system, often termed a hub and spoke distribution, has the main advantage of placing valuable economic resources in a few select airports, rather than building up expensive infrastructure at every airport.

It turns out an airline’s economic drive to minimize use of resources and maximize flight flexibility is analogous to the brain’s evolutionary drive to balance metabolic costs with information processing power. In graph theory, a mathematical approach to modeling complex systems such as the brain and air traffic, networks are composed of nodes and edges—again, similar to the hubs and spokes of a wheel. Brain areas, either as single neurons or groups of neurons, are represented as nodes, and edges signify connections between nodes: these can be excitatory, inhibitory, and uni- or bidirectional. Moreover, these

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edges may be based on anatomical connectivity between brain regions, or they may represent information about functional connectivity (based on readouts of neural activity). This approach has allowed researchers to interpret and model large datasets taken at various levels of analysis—from single-cell electrophysiology data to whole-brain fMRI recordings (van den Heuvel and Sporns, 2013).

There are a few emergent properties of a non-random, complex neural network that predict the occurrence of hub regions. These networks have non-Gaussian degree distributions, with few and sparse high-degree nodes (those with increased connectivity), as compared to the more common low-degree nodes (Barabási, 2009). These densely connected high-degree nodes are candidate hub regions, as simulations reveal they process more information and play a greater role on overall network function as opposed to low-degree nodes. In addition, neural networks exhibit a “small-world” architecture, with long-range connections that permit rapid transmission of information from one part of the network to another, while remaining in segregated, local clusters of interconnected nodes (Watts and Strogatz, 1998). Small-world networks allow for more efficient processing at both the local and global scale when compared to regular, lattice-like, or complete random connectivity patterns. Brain-wide mapping efforts have provided evidence of hub regions from *C. elegans* (Towlson et al., 2013) to humans (Bullmore and Sporns, 2009); however, a systematic interrogation of putative hubs and their importance to a specific behavior has been lacking. In this issue of *Neuron*, Vetere et al. (2017) provide compelling evidence for the role of hub regions in the consolidation of a fear memory and reveal the utility of network-level analysis for predicting behavior from large-scale neuronal activity.

Previously, using *c-fos* expression patterns in mice, this group identified networks of brain regions that were co-activated after recall of a fear memory (Wheeler et al., 2013). Two additional networks were generated for comparison to this fear memory network, one from a control group of mice, treated like the fear group with the exception that they did not receive a foot shock, and another based purely on anatomical connectivity data from the Allen Brain Atlas. The functional fear network showed a few highly interconnected areas (high-degree nodes), and these appeared as clusters in the thalamus, hippocampus, and cortex (Wheeler et al., 2013). This analysis indicated the presence of hub nodes and a small-world organization of the fear network.

In the current study, Vetere et al. (2017) interrogated this fear memory network, determining the effect of computational removal of high- and low-degree nodes. To do this, they used a disruption propagation model (DPM), which accounts not only for the initial removal of one node, but also a redistribution of connectivity among neighboring nodes. An example of this is the shutdown of a major hub airport like Chicago O’Hare, which would not only impact flights in the Midwest, but across the United States, as airlines begin redirecting traffic. This DPM simulation was contrasted with a simple node deletion model, in which neighboring nodes were not re-adjusted after removal. Deletion of high-degree, but not low-degree, nodes led to greater disruptions in global network efficiency, and the DPM had a larger effect on network function than a simple node deletion model.

The authors then tested whether this reduction of global processing power in silico would correlate with a functional deficit of memory retrieval in vivo if they targeted highly connected hub regions. To determine this possibility, they used a chemogenetic approach to silence 25% of the nodes from the fear memory network, corresponding to a sampling across the brain of both low- and high-degree nodes. Of the 21 sampled regions, independent inactivation in four high-degree nodes led to a robust decrease in freezing behavior, indicating impaired memory consolidation and retrieval. These areas were the CA1 region of the hippocampus (CA1), lateral septal nucleus (LSl), laterodorsal thalamic nucleus (LD), and reuniens thalamic nucleus (Re). Thus, inactivating these four hub regions in behaving mice recapitulated the simulated effects of silencing high-degree nodes in the DPM. Importantly, changes in global efficiency of the network after removing nodes in silico tightly correlated with freezing deficits after hub silencing in vivo. This is in stark contrast to in silico node deletion from either the control or anatomical networks, where global efficiency did not correlate with the strength of the fear memory after in vivo hub silencing.

Finding these four hub regions for a fear memory provides a novel perspective on the functional network required for recall of a fearful context. Both the CA1 and Re have been well described in their roles for initiating a fear response (Xu and Südhof, 2013). The LD is thought to participate in cortical-hippocampalthalamic reciprocal loops, and it has been shown to be critical for spatial learning (van Groen et al., 2002). The LSl has been linked to anxiety-related behavior and behavioral responses to social stress (Guzmán et al., 2013). These studies lay the groundwork for future experiments aimed at understanding the cell types and activity patterns that transmit fear-related information throughout this network. One limitation of the current approach is that *c-fos* integrates information over minutes to hours, and does not capture inter-regional interactions occurring on much shorter timescales. However, adapting these network based analytical approaches to methods such as large-scale calcium imaging, multisite fiber photometry, or whole-brain imaging in smaller organisms such a zebrafish may identify novel candidate hub regions that emerge during specific epochs of behavior.

Recent meta-analyses have indicated that hub regions are more likely to be impacted in a number of brain disorders, such as schizophrenia, frontotemporal dementia, and Alzheimer’s disease, with a subset of hubs similarly affected in multiple diseases, despite diverging pathogenesis (Crossley et al., 2014). It has been proposed that hubs may be especially vulnerable to dysfunction due to their high metabolic rate and involvement in connecting regions via fragile, long-range axonal projections. Since hubs play a greater role in network function, they may preferentially influence symptomatology in psychiatric and neurological disorders (Crossley et al., 2014). Future studies may interrogate these kinds of functional connectomes in animal models of disease to identify new vulnerable hub regions that, when disrupted, have a destabilizing effect on the larger network, possibly accounting for effects on cognition, mood, and behavior. These potential findings may be leveraged not only to provide clinical insight into the underlying anatomical abnormalities in brain disorders, but may also provide novel functional targets for interventions to treat the underlying behavioral symptoms, especially at early stages of illness.

The approach used by Vetere et al. (2017) builds upon recent use of inhibitory DREADDs in the rhesus macaque brain to identify the amygdala as a hub region that, when silenced, propagates effects throughout the entire network (Grayson et al., 2016). Both studies highlight the broad applicability of this methodology and suggest that this approach may be used to probe other functional networks, such as those that drive appetitive, instrumental, or motor learning, to name a few. Finally, Vetere et al. (2017) show that silencing a single hub can lead to deficits in fear recall, yet the *sufficiency* question is also intriguing: is a single hub, or two hubs, etc., sufficient to drive brain-wide activity and elicit specific aspects of a behavior? Are these hub neurons themselves gatekeepers of behavior, or simply highly connected relay stations? The work by Vetere et al. (2017) lays the groundwork for these studies and provides a new framework for understanding the neural circuits that generate fear memory.

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