The central nervous system (CNS) is composed of multiple layers of networks, physical, chemical, electrical, and molecular. The physical network, dubbed the 'connectome', describes the spatial organisation of billions of neurons, their interconnections, and their development and plasticity. The chemical network represents the subsets of the physical network that provide, amongst other things, positive and negative feedback systems of excitatory and inhibitory neurons. The electrical network describes the signal processing performed by collections of neurons over very short timescales and is ultimately regarded as the output or the activity of the brain. Finally, molecular networks are defined by the production and interaction of nucleic and amino acids within each of the cells of the CNS; complex pathways of often large numbers of interacting proteins define the state and function of each neuron and whose dysfunction underly almost all neuropathological conditions.

TABLE, FIGURE? Time vs. space

physical network: mostly spatial, some temporal (more at the beginning) but slower over long periods into adulthood
chemical network: mostly spatial (neurotransmitters/receptors), changes occur fast for electrical transmission, and fairly slowly (30mins?) for adaptation
electrical network: spatial and temporal (very fast!)
molecular network: spatial, temporal limited by transcription and translation (fairly slow, mins-hours)

At the finest level of resolution, these four layers of network all involve, in some way or another, the direct physical interaction of cells, chemicals, molecules, or electrons. However, due to the immense complexity of all of these component interactions, to make sense of it all we must generalise and abstract these. The most common method for achieving this is to construct networks of associations. For example, changes in blood flow measured by fMRI are associated with changes in brain activity, and two or more brain regions with similar patterns of blood flow can be thought of as having an association with each other. Similarly, measuring the expression/abundance of many thousands of RNA transcripts can reveal multiple correlated RNAs that we can then suppose are similar regulated by the cell, despite there being little or no evidence of a direct interaction between these molecules. Just as the fMRI signal can be correlated over regions of the brain, so too can the expression of RNA in order to try to identify larger regions of the brain (or collections of neurons) that are molecularly similar or that respond similarly to perturbation.

TABLE, FIGURE? Abstraction

physical: broad connections, connectome, brain regions/tissues
chemical: ?
electrical: proxy blood flow (fMRI) for activity, else activity measured electrically but both have poor resolution
molecular: co-expression, use the proxy of abundance for interaction/association

Mathematical networks are attractive representations for these abstract associations, in which the edges between nodes (which can represent individual genes, clusters of

genes, or groups of neurons) are a simple means of summarising an association that may in all likelihood actually involve multiple sets of physical interactions. Integration of multiple levels of measurement of cellular regulation of gene expression has been facilitated by the flexibility and generalisability that the network framework provides. However there has not been a wealth of complementary imaging and molecular data generated that would enable the integration, say, of the rich spatial and temporal information provided by PET with the underlying molecular activity in similar regions of the CNS.

One thing that is clear that the resolution of brain-wide studies of the CNS must increase dramatically before they can be of significant benefit to studies of neurodegeneration and disease. This increase in resolution of course includes increasing the spatial precision of fMRI and molecular profiling to assay single cell-types in the brain, but also relies on the tighter integration of these different, but highly complementary, data modalities. There exists significant advantages to the non-invasive monitoring of electrical and chemical activity in the mammalian CNS, but complementary molecular profiling is necessary for true mechanistic understanding of these signals.

Other topics (?):
- Redundancy in physical (e.g. rewiring after a stroke) and molecular networks - how to model this?