18th May
Morning
Session I

Statistics and geometry of neuronal connections

Questions
- The statistics of the cortical connections: long-range axonal connections and micro-circuits
- The mini-architecture of the cerebral cortex. The on-board micro-circuitry, dendritic growth, trees bifurcations and plasticity

Topics
1. Bring together functional and anatomical connectivity
2. Species comparison and bridging (human, monkey, rodent)
3. Exploring different spatial levels of connectivity (area to area, micro-circuitry, etc.) and structures (area, column, layer, etc.)
4. Integration of long-distance and intrinsic connections
5. Formation and plasticity of neural connections

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Brain connectivity shows important characteristics that enable efficient information transfer, yet it has been difficult to evaluate the relation between this capacity and the actual functional networks that are observed. We attempt to bring anatomy and function together by using neuroimaging to define a functional network, and then evaluating the connections to ascertain the computational structure of this network.

**Methods:**
Regional Maps & Connectivity: Kötter & Wanke [1] defined a Regional Map (RM) that relates human and non-human primate brains. The RM is linked to the CoCoMac database of primate brain connectivity [2] to extract the connections between 38 cortical and thalamic areas in the RM.
Computational Structure: Based the connections of RM elements, we calculated three network participation indices [NPI,3]: Density, the number of connections for an area relative to the total possible; Transmission, the number of efferents from a region relative to its afferents and efferents; and Symmetry, the proportion of symmetrical entries versus symmetrical and asymmetrical entries in the connectivity matrix.
Regional Selection: The estimation was done for a PET rCBF study on auditory-visual learning where data were extracted in two groups of subjects based on functional connectivity of the hippocampus [4]. One group learned with awareness while the other group did not, but the hippocampal activity was related to behaviour in both groups. The regions showing the strongest functional connectivity with the hippocampus were defined within each group using the MNI305 coordinate system. The coordinate was then translated to the equivalent RM area, defining the subset of areas that formed the functional network. For each region, we determined how likely the observed NPIs occurred compared to a large random sampling of other sets of regions for the particular subset size (minus one).

**Results & Conclusion:**
The figures show a (rectangular) multidimensional scaling plot of the RM areas for each group with respect to the location of the three
NPIs. Obvious from the plots is the great distance of primary visual cortex (V1) from the rest of areas in the unaware group, suggesting the connectivity structure of V1 is set up for receiving information from more areas than it emits. The aware group showed greater structural capacity for V1, resulting from the added recruitment of visual association cortices (VACv&d). Moreover, the functional network in the aware group shows more asymmetric configurations (lower symmetry) of temporal and prefrontal areas.

The representation of functionally-defined regions in terms of their computational structure appears to provide key insights into information integration capacity. As a complement to multivariate image analysis, this helps to interpret neuroimaging data based on the computations/information exchange that is supported by the anatomy.

References
Macaque cerebral cortex contains ~100 distinct areas interconnected by ~1,000 distinct pathways that vary greatly in strength. Despite many advances, our understanding of cortical organization and connectivity in the macaque remains fragmentary. A consensus partitioning scheme has yet to be achieved for most regions of cortex, and connectivity data are mostly qualitative. Neuroimaging approaches, including fMRI, DTI, and functional connectivity analyses, provide good prospects for accelerating progress on these fronts.

Human cerebral cortex, with its 10-fold greater surface area, presumably contains many more cortical areas than the macaque. Individual variability in the pattern of cortical convolutions, which is one of many impediments to accurately charting the layout and connectivity of these areas, can now be more effectively addressed by registering individual surface reconstructions to a surface-based atlas. Functional connectivity analyses provide a promising approach to identifying cortical areas and inferring connectivity patterns.

Humans and macaques differ greatly in their pattern of cortical convolutions, probably reflecting connectivity differences that impact a tension-based mechanism for cortical folding. Comparisons across species can best be made using interspecies surface-based registration to evaluate hypotheses about functional similarities as well as regions of divergence in functional organization.
Long-Range Axonal Connections

Area interactions depend on combinations of long-distance and intrinsic connections, originating from multiple cell types and participating in specific microcircuits. Long-distance connections have been the more difficult to investigate; and for any single axon, we usually don't know: the full axonal configuration (branches; intrinsic and extrinsic terminations), postsynaptic targets, and/or exact parent neuron. Rapid progress in all these areas may soon become feasible with network-appropriate tools, such as cell type specific inactivations, or controlled transneuronal tracers capable of revealing input populations to identified neurons.

In my talk, I will try to review briefly what has been learned about cortical connectivity from single axon analysis (light microscope). One set of data concerns quantitative specifics, such as arbor size, bouton numbers, and divergence factors. The same observations provide a window on broader issues, such as reciprocity, cell types, columnar organization, area diversity, and mutualistic interactions. The anatomical organization looks messy, even in the primary areas; and I will propose as an interesting question, the apparent discrepancy between organized functional columns and what looks to be a less organized anatomical connectivity.

Relevant background:
Local and Long-Range Connectivity in Neocortical Microcircuits

The pyramidal cells (PCs) in layer V constitute the main output layer of the neocortex, projecting to various sub-cortical brain areas including the striatum, brainstem nuclei, and spinal cord. The subpopulation of thick tufted PCs have dendrites that span across all cortical layers, enabling integration of inputs from all cortical layers. The distal portions of their apical and tuft dendrites are targeted by top-down and multi-modal afferents from other cortical areas, whereas synaptic connections from neighboring PCs are formed mainly on the basal dendrites. We studied the local connectivity within this PC subpopulation, as well as pathways for regulation of long-range input to their distal dendrites. Morphological considerations predict very high connectivity between neighboring PCs, yet electrophysiological recordings show only sparse connectivity (10-15 %) between them. We analyzed the connectivity between these PCs and showed that while axo-dendritic touches are formed without preference between all neighboring PCs, only a small fraction is functionally connected. In a different study we demonstrate for the first time a disynaptic inhibitory feedback pathway targeting the distal portions of PC dendrites. We describe the morphological and electrophysiological properties of this pathway, and discuss its function in the neocortical microcircuit.