

Functional Neural Systems (or what we can study with fMRI)

- I. Overview of the anatomy of the brain relative to the size of a voxel.
- II. Cortical anatomy
 - A. Functional zones
 - Primary sensory/motor areas- in blue
 - auditory (A1), motor (M1), somatosensory (S1), visual (V1)
 - Secondary or unimodal association areas- in yellow
 - auditory (AA/ST) contains Wernike's area, motor (MA) contains Broca's area, somatosensory (SA), visual (VA, IT, PS, MT)
 - Higher order or heteromodal association areas- in red
 - Paralimbic areas- in green
 - B. Laminar organization
 - Neocortex
 - Archicortex
 - C. Intrinsic cortical circuitry
 1. Pyramidal cells comprise 70-85% of all cortical neurons. They use EAAs (glutamate and aspartate) as neurotransmitters. They are mostly spiny.
 2. Interneurons make up the remaining 15-30% of neurons and are divided into many categories based on morphology and neurochemical content (e.g. GABA or ACh only or in combination with one or more neuropeptides and or calcium binding proteins).
 - Morphological types:
 - Large basket cells- synapse on pyramidal cell bodies and apical dendrites
 - Double bouquet cells- synapse onto distal dendrites and spines
 - Chandelier cells- synapse onto axon initial segments
 - D. Efferent circuitry (where does information from the cortex go?)
 - Corticocortical- from layers II/III to layers II/III
 - Corticosubcortical (brainstem, spinal cord)- primarily from layer V and a few from VI
 - Corticothalamic- primarily from layer VI a few from V
 - E. Afferent circuitry (what information enters cortex from where)
 - Thalamocortical- primarily onto layer IV, a few to layers III and V; asymmetric (excitatory) synapses 85% of which are onto dendritic spines; marked specificity between thalamic nuclei and cortical target.
 - Corticocortical- from layers II/III to layers II/III

Brainstem (e.g. monoamines)

The adult pattern of monoamine innervation shows a high degree of specificity in terms of the exact brain regions (even down to which cortical areas and which layer within the cortex) and density. For instance, there is a high density of 5-HT innervation of somatosensory cortex, but not motor cortex. In both humans and non-human primate the highest density of NE in cortex is in primary motor and somatosensory cortex and the sparsest innervation is to the exposed surface of the inferior temporal gyrus. The inferior temporal cortex is one of the major components of the ventral system of higher visual processing that deals with object properties such as shape and color. In visual cortex, the primary sensory region V1 (Brodmann's area 17) has moderately high levels of NE in all layers except layer IV (thalamic input layer) where NE is very sparse. At the border of V1 and V2 (Brodmann areas 17 and 18), innervation changes sharply with a dramatic increase in layer IV. Other areas rich in NE fibers include the parietal lobe (Brodmann area 7), certain thalamic nuclei including the pulvinar-lateral posterior complex, and superficial layers of the superior colliculus. This anatomy has prompted others to suggest that tasks involving spatial analysis and visomotor response rather than those involved in feature extraction and pattern analysis will be more likely to be influenced by changes in NE release.

Basal forebrain (ACh)

F. Summary comments

Each human cortical neuron receives between 5,000- 60,000 synapses. Organization in many areas is columnar in that close pyramidal cell neighbors excite one another and inhibit those more distant via intervening interneurons.

III. Chemical organization of the brain (specific neurotransmitter systems)

- A. Amino acid neurotransmitters activate ligand gated channels to produce rapid point-to-point communication. This type of pathway precisely preserves maps (e.g. retinal, somatic) of the world and are the connections largely responsible for defining the response properties (e.g. receptive fields and optimal stimuli) for a given neuron.

Excitatory amino acids (EAAs)- glutamate/aspartate

Examples of neurons that use EAA neurotransmitters include cortical pyramidal neurons, thalamic relay neurons, olfactory bulb mitral cells, hippocampal neurons, colliculi neurons, cerebellar granule cells (parallel fibers).

Inhibitory amino acids - GABA/glycine

These types of neurons can be divided into two groups based on whether their axons project to distant target sites or ramify locally. Inhibitory projection neurons are found in the caudate nucleus, putamen,

nucleus accumbens, septal nucleus, substantia nigra pars reticulata, and cerebellum (purkinje cells). The vast majority of GABAergic neurons have axons that project in the within the near vicinity of the cell body to “sculpt or shape” the local response to inputs. These interneurons can be found everywhere in the brain. They are further subdivided on the basis of the details of their axonal morphology and the neuropeptides they express.

- B. Monoamine projections derive from a small number of cell bodies in the brainstem tegmentum and project widely. A single neuron may project to multiple functionally unrelated cortical areas or even to cortical and subcortical brain regions. These transmitter systems act primarily via G-protein linked receptors to produce global changes in the firing patterns of cortical and subcortical neurons. For example, norepinephrine (NE) and serotonin (5-HT) inputs partially control the change in thalamic neurons from rhythmic burst firing to repetitive single spike activity with greatly increased responsiveness to excitatory synaptic inputs that occurs in the shift from slow wave sleep to waking and attentiveness.

Tremendous heterogeneity in monoamine transmitter receptors has been demonstrated. The receptors for each neurotransmitter type may be found pre- or post synaptically and indeed it is thought that monoamines may be released from non-synaptic sites (volume neurotransmission).

Serotonergic neurons are contained within the raphe nuclei. 5-HT projections from the brain stem raphe nuclei are the most extensive of all the monoamines. Unlike the noradrenergic locus coeruleus, which is relatively compact and uniform, the raphe nuclei are nonuniform with 5-HT cell bodies overlapping, but not entirely congruent with the anatomic nuclei.

Serotonergic neurons display a distinctive slow (1 to 5 spikes per second) and regular rate of spontaneous activity that varies with behavioral state. Endogenous 'pacemaker' ion channels in serotonergic neurons are responsible for this regular rate of firing which occurs in the absence of excitatory input. This tonic activity means that serotonin is nearly always being released, but that the amount or concentration of serotonin changes based on state changes such as the phase in the sleep wake cycle, level of arousal and timing of the circadian cycle. One important consequence of this arrangement is that those serotonin receptors with a high affinity for 5-HT will be tonically activated while those with a lower affinity will only be phasically activated during times of increased firing. Serotonergic neurons have inhibitory autoreceptors such that increased serotonin release negatively feeds back on them, slowing the firing rate.

Noradrenergic neurons are located in the locus coeruleus (LC) and nearby lateral tegmental noradrenergic nuclei. Physiologic experiments using microelectrodes to record from individual LC neurons in whole animals show that the firing rate of these noradrenergic neurons is relatively synchronized. LC neurons express ion channels responsible for generating the pacemaker

currents underlying a slow tonic firing rate. The rate of LC firing can be increased or decreased by changes in the afferent input to the LC. Importantly, stimulation of alpha2 autoreceptors and/or opiate receptors slows the firing rate while glutaminergic inputs speed the firing rate.

It is largely held that regulation of the firing rate of noradrenergic neurons, and hence release of NE, is responsible for the regulation of the level of behavioral arousal and vigilance. In rat, spontaneous LC firing rate (range 0-20 spikes/sec) covaries consistently with stages of the sleep-wake cycle. In both rats and monkeys LC neurons fire fastest during vigilant waking, slower during relaxed alertness, slower still during slow wave sleep and are virtually silent during rapid eye movement (REM) sleep. Thus, there is tonic release of NE at all times except during REM sleep. LC neurons are most strongly activated by phasic noxious stimuli. The firing rate in LC neurons is also increased by threat, fear conditioning, chronic stress, hypotension, elevated CO₂, blood loss, hypoglycemia; these same conditions increase NE turnover/release in forebrain sites.

Changes in LC firing rate are temporally correlated with changes in not only behavior but also with measures of cortical electrical activity as measured by electroencephalographic (EEG) recordings. This effect may be, at least in part, mediated by NE actions in thalamus; NE activates *in vitro* thalamic and cortical neurons and changes their discharge patterns from burst firing to single spiking, analogous to changes that occur in the switch from slow wave sleep to arousal.

Numerous single unit recording studies in rats, cats and monkeys have focused on the question of how NE, or stimulation of the LC, alters spontaneous and sensory evoked discharge patterns of cortical neurons. The most consistent findings indicate that the primary functional consequence of NE in the cortex is to enhance the robustness or precision of cortical neuronal responses to defined sensory input (e.g. mediated by EAA transmitters) while reducing or not affecting background cortical activity.

Investigators have hypothesized that activity in the LC and other NE containing neurons is important for determining whether an individual directs attention toward the external stimuli or internal cues. Given the strategic position as gatekeeper for autonomic efferent and afferent information to the entire CNS it is no wonder that dysfunction of this system has been hypothesized to underlie the pathophysiology of many anxiety disorders including PTSD and Panic.

Dopaminergic neurons are found within the Substantia nigra pars compacta (SNc) and Ventral tegmental area (VTA) as well as the hypothalamic nucleus infundibularis.

Mesencephalic and diencephalic DA projections are more restricted in their terminal fields than

the other monoamine projections. Dopaminergic projections from the SNc innervate the striatum. Dopaminergic projections from the VTA innervate the limbic forebrain (mesolimbic projections) and cerebral cortex (mesocortical projections). Dopaminergic innervation is densest in the superficial layers of the anterior cingulate and prefrontal areas of cortex. It has been hypothesized that dopamine is needed to enable motor systems and motivation. In the striatum, motivation and sensory inputs are integrated to produce action.

Cholinergic projection neurons are found in predominately in the basal forebrain. ACh neurons from the nucleus of the diagonal band and the nucleus basalis of Meynert project to the cortex; septal ACh neurons project via the fimbria/fornix to the hippocampal formation (important in the generation of theta rhythm) and the medial habenula. The ACh neurons in the dorsolateral tegmental area project to the thalamus (important in regulating the sleep/wake cycle). Local ACh interneurons are found predominately in the caudate/putamen/accumbens and in the cortex and brainstem.