Language and Behavioral Function

The distinction between speech and language
Although lay people often consider the terms “speech” and “language” as analogous, they are truly distinct from the neurological viewpoint. Speech or speaking is the production of audible sounds, which may or may not be used to communicate. Speech consists of phonation and articulation. **Phonation** is sound production by the moving vocal cords, the muscles of which are innervated by branches of the vagus nerve, which is controlled by its upper motor neurons. Abnormal phonation or **dysphonia** often sounds hoarse, whispering, or breathy. **Articulation** is sound production by actions and varied positions of the lips, tongue, palate, and pharynx, which are innervated by cranial nerves VII, IX, X, and XII, and controlled by their associated upper motor neurons. Connections with the cerebellar and extrapyramidal systems also provide the motor coordination needed for precise, clearly understood enunciation. Abnormal articulation or **dysarthria** often sounds slurred, choppy and indistinct. Both phonation and articulation depend on moving air from the lungs and thus requires a normally functioning respiratory system.

**Language**, neurologically speaking, is communication by means of symbols, and is not limited to production of audible sounds. Reading and writing are other means of communication, as are gestures, pictures, signing, Braille, and Morse code. Comprehension and expression or execution of language are functions of specific areas of cerebral cortex in the dominant hemisphere. The left cerebral hemisphere is dominant in almost all right-handed people and more than half of all left-handed people. The major language centers are in the vascular territory of the left middle cerebral artery.

Abnormal language or aphasia may thus occur from an ischemic infarction, but may also be due to hemorrhage, tumor, trauma, or dementia. **Aphasia** is therefore a disorder of previously acquired language ability due to a lesion in a critical language center. A newborn infant born with a severely maldeveloped brain is not considered "aphasic" in the purest sense, since they may never learn to communicate. Although some aphasic patients may speak and produce sounds, certain aspects of their ability to communicate are impaired, and these same aspects are present to some degree in whichever method they communicate, such as reading and writing. Other patients may lose the ability to speak, as after extensive surgical removal of laryngeal cancer, but communicate normally by reading, writing, or other means, and thus have normal language function. A deaf person may be mistakenly considered unable to understand at first, but may exhibit normal comprehension by signing, reading and writing.

Clinical examination of language
Language function is tested in several ways to ensure that deaf or visually impaired patients or those unable to speak are not erroneously considered aphasic. Usually the patient is first engaged in spontaneous conversation. More directed testing would include naming items, repeating phrases, following spoken and written commands, reading passages, and writing to dictation. Speech therapists use standardized tests of language that can be graded or scored.

- **Fluency** refers to the ease, facility, and quantity of speech regardless of content or meaning.
- **Comprehension** should be evident when verbal or written commands are followed.
- **Repetition** is intact only if a phrase from the examiner is perfectly repeated by the patient. One of the most time-honored test phrases to repeat is: "no ifs, ands, or buts." Imperfect repetition occurs with a lesion in either perisylvian language center (Broca or Wernicke area) or the connecting arcuate fasciculus.
- An aphasic patient may utter a **paraphasia**, which is an abnormal word or syllable substitution. Paraphasias are more common with lesions in the posterior perisylvian language region, particularly with Wernicke aphasia. The substitution errors may involve phonemes or syllables ("Open the boor" instead of "Open the door") or full words ("The grass is blue" instead of "The grass is green"). The most extreme type of paraphasia is a **neologism**, which sounds like a nonsensical or foreign-sounding word or phrase ("That is a blastorale" instead of "That is a ham sandwich").
Types of aphasia
Different types of aphasia are associated with lesions of specific language centers. Since several aspects of language may be affected, the old simplified terms of "expressive or motor aphasia" and "receptive or sensory aphasia" proved inaccurate, and Broca and Wernicke aphasia are best named after the physicians who first described them, Figure 1.

- **Broca aphasia** is caused by a posterior inferior frontal lobe lesion in the dominant hemisphere. Fluency is very impaired, so speaking or reading aloud is very laborious and effortful. Few words are slowly spoken, often in telegraphic fashion. (In the old days of the telegram, wordier messages were costlier, so frugal customers sent very succinct, brief statements over the wire.) The patient may struggle to say over several minutes, "I . . . up early," intending to say, "I have to get up early tomorrow morning." Comprehension is relatively preserved and may be further evidenced by overt frustration in a patient aware of his language deficit. Repetition is imperfect. Attempts to read or write show these same difficulties. There often is an accompanying right hemiparesis since the lesion may also involve the primary motor cortex, which is just posterior to Broca's area.

- **Wernicke aphasia** is caused by a posterior superior temporal lobe lesion in the dominant hemisphere. Fluency is preserved such that the patient often speaks long phrases which make little sense, containing paraphasic errors and gibberish. The patient may say, "If you saw it, redness would schlodder over the galls anyway. I don't think it would much matter tweetch since fries are never made by keeters." Comprehension is very impaired and may instill paranoia in the patient who is unable to communicate with those around him. Repetition is imperfect. Reading and writing should likewise display these same difficulties, although the patient may not understand a request to read or write. In the absence of hemiparesis or other common stroke deficit, the diagnosis of Wernicke's aphasia may be difficult to make, and the patient is often considered drugged or intoxicated or beset with a psychiatric illness.

- **Conduction aphasia** occurs with a lesion of the arcuate fasciculus, the pathway connecting Broca and Wernicke areas. This aphasia has characteristics in-between those of Broca's and Wernicke, although more closely resembles the features of Wernicke. Fluency is relatively intact with some milder impairment of comprehension but repetition remains imperfect. Some paraphasias are present.

- **Global aphasia** occurs with an extensive lesion that virtually damages the entire perisylvian language region. The patient may appear awake but is unable to speak or communicate otherwise, follows no commands or gestures, and usually has a severe hemiplegia. Other types of aphasia may occur with lesions in the thalamus or in cortical areas just outside the perisylvian language centers. Lesions in posterior parts of the dominant hemisphere may affect specific aspects of language such as alexia or agraphia. **Alexia** refers to the impairment of reading when visual cortex is disconnected from language centers critical for reading. **Agraphia** occurs when a lesion disconnects the motor cortex for the dominant hand from language centers critical for writing.

Language and the nondominant cerebral hemisphere
The analogous "mirror images" of language centers in the nondominant hemisphere are concerned with a more subtle aspect of spoken language called prosody. **Prosody** refers to the semantic and emotional meaning of language as conveyed by changes in vocal pitch, inflection, melody or tone. For example, the rising pitch or stress at the end of a spoken question ("You gave this to me?") distinguishes it from a spoken statement ("You gave this to me."). More
complex changes in the prosody of spoken words can convey the affect or mood of fear, anger, sadness, joy, or surprise. Nondominant cortical lesions may create aprosodia, where these features are impaired.

- A lesion in the nondominant posterior superior temporal lobe, opposite to Wernicke’s area, produces a sensory ("receptive") aprosodia. Here the patient has trouble understanding the emotional content in the words spoken by others, and cannot repeat or mimic the elements of prosody that they hear. When that patient speaks, however, normal prosody and gesturing is present.
- A lesion in the nondominant posterior inferior frontal lobe, opposite to Broca’s area, produces a motor ("expressive") aprosodia. Here the patient may fail to incorporate elements of prosody when speaking and is unable to repeat or mimic the elements of prosody that they hear. However, he or she is able to understand the emotional content or mood in the speech of others.

**Behavioral Functions**

**Memory** is the ability to learn and then recall information after different periods of time. "Immediate" memory is somewhat of a misnomer, as it pertains to the pre-requisite state of attentiveness required for learning something. A patient should be alert and awake enough to immediately repeat or recite a sequence of 5 numbers spoken out loud. Patients too inattentive for this task may be excessively sleepy, sedated from medications, have a systemic illness diffusely inhibiting cortical function, or have lesions affecting the reticular activating system more directly. Impaired attention precludes any reliable testing of recent or remote memory as well as other cortical functions. Recent or short-term memory is the ability to recall information after several minutes of retention. A patient would be given 3 items to repeat out loud and instructed to repeat them 5 minutes later. Remote or long-term memory is the ability to recall past events hours, weeks, or even years afterward. The examiner could ask about a prior address or anniversary date for which the correct answer is known.

Memory function depends on bilateral circuits or pathways involving the temporal lobe and thalamus, specifically the hippocampus fornix/mammillary body/anterior thalamic nucleus. Amnesia is caused by bilateral thalamic and mammillary body lesions in Wernicke-Korsakoff syndrome, a state of thiamine deficiency often seen in malnourished alcoholics. Bilateral hippocampal lesions cause amnesia as sequelae of anoxia (cardiac arrest survivors) or Herpes simplex encephalitis. A milder memory impairment of gradual onset may occur with normal aging or represent the earliest symptom of dementia and thus is one of the most common complaints of elderly patients seeking medical attention.

**Apraxia** is the inability to conceptualize and perform a skilled, learned, motor act on command. There must be no existing significant or severe impairments of sensation, strength, comprehension or attention to prevent performance of the task. On request, an apraxic patient would be unable to follow commands such as "comb your hair" or "salute the flag" but may spontaneously carry out these actions at another time.

It is as if a computer file containing all the elements to execute a task exists but cannot be opened or accessed. A patient with a prefrontal lobe lesion may exhibit gait apraxia, the inability to walk on command as if both feet were "glued to the floor" or "stuck in the mud." Posterior cortical lesions, especially involving the parietal lobe, may cause constructional apraxia, where the patient cannot "draw a house" or copy a simple drawing, and dressing apraxia, where the patient cannot put on and button a shirt.

**Agnosia** is the impaired recognition of perceived stimuli caused by lesions of sensory association cortex. The same familiar object not identified solely by one sensory modality often is recognized by different sensory stimuli or characteristics. In visual agnosia, a patient cannot identify a "bell" by seeing it but does recognize it by hearing it rung.
or touching it. Tactile agnosia is the inability to recognize objects solely by "feel" or "with eyes closed," although accurate visual identification of the same objects is normal. Tactile agnosia can thus be considered a severe degree of astereognosis.

**Focal cerebral “syndromes”**
Lesions of lobes of the cerebral hemispheres often involve head trauma, stroke, tumor, or dementia. **Syndromes of the prefrontal or frontal lobe** are listless, apathetic, and unconcerned, with poor hygiene and incontinence. Poor judgment and disinhibition lead to impolite outbursts, rude humor, and inappropriate sexual behavior. **Executive functions** are impaired, with poor planning and performance of multistep or novel tasks, lack of creative thinking and creativity, limited attention, and motor perseveration (aimless repetition of simple motor acts). **Gait apraxia** may be present. **Gegenhalten or paratonia** may be found on examination, manifested as increased limb tone or resistance felt as the examiner moves the patient's limb more rapidly. There may be the abnormal reappearance of **frontal lobe release signs**, which were previously normal findings during infancy when myelination of descending inhibitory pathways was incomplete. (Stroking lightly around the mouth causes the lips to "suck" and "snout," or seek out and "root" to the stimulus. Palmar and plantar grasp responses consist of the fingers or toes "latching onto" the examiner's finger when the palm or sole is rubbed.)

**Syndromes of the temporal lobes** may include **amnesia** (bilateral hippocampal lesions), **cortical deafness** (bilateral auditory cortex lesions), and the **Klüver-Bucy syndrome**. A unilateral lesion of the superior-posterior dominant temporal lobe produces Wernicke aphasia.

**Parietal lobe syndromes** affecting sensory cortex produce astereognosis, agraphesthesia, and extinction on double simultaneous stimulation. Lesions of the nondominant parietal lobe cause impairment of spatial relationships between the body and its surroundings. A patient with anosognosia is unaware of his or her hemiparesis, which in its extreme form consists of a "denial" of that half of the body, or hemispatial neglect. Patients with a right parietal infarction may fail to dress or groom the left side of the body, even ignoring injuries or harm there. Spatial confusion may also be exhibited as dressing apraxia or constructional apraxia.

**Occipital lobe syndromes** may involve enough bilateral visual cortex to produce cortical blindness, which is sometimes accompanied by a denial or unawareness of visual loss, **Anton’s syndrome**. Bilateral temporo-occipital lesions may produce **visual agnosia**, a subtype of which is **prosopagnosia**, the inability to recognize previously known faces. A dominant temporo-occipital lobe lesion may cause **color anomia**, the inability to name colors.

**Neurobehavioral Syndromes from Diffuse or Multiple Cerebral Lesions**

**Acute confusional state (delirium)**
Global, extensive cognitive impairment, abnormal behavior, and cortical dysfunction occur if several lobes of the cerebral hemispheres are simultaneously or progressively affected. If this occurs abruptly over a short period of hours to days, it is known as the **acute confusional state or delirium**, a common clinical problem in neurology. Typical here are fluctuating levels of attention and motor activity, with the patient alternating from overly-excitable agitation and often purposeless hyperactivity "as if high on drugs" to periods of obtundation and stupor. Moods and emotions may vary, and hallucinations are often reported. Other prominent findings include tremulousness, asterixis, myoclonus, ataxia, and dysarthria.

There are multiple causes of the acute confusional state, many of which are treatable or reversible if diagnosed early. The brain may be directly involved, as in viral encephalitis or the post-ictal state after a seizure, or it is indirectly
involved, as from systemic illness like kidney failure, metabolic abnormalities, or the effects of medications or illicit drugs. Often any chronic, focal deficits in patients with a previous stroke, head trauma, multiple sclerosis, or other neurological disease may appear worse if such systemic problems indirectly affect the brain and cause the acute confusional state.

**Dementia ("organic brain syndrome")**

Dementia is the general term for a diffuse impairment of cortical function that usually evolves less abruptly over a longer period of months to years, and impedes the daily function of a patient. Since this is a loss of previously acquired mental and intellectual ability, it differs from mental retardation or learning disorders where such capabilities were never attained. Memory loss is often the first deficit noted, but changes in judgment and intellect also occur. The intellectual decline of a college trained professional may take longer to manifest than that of an unskilled worker lacking any formal education. Aphasia, apraxia, and agnosia may be found on examination. Personality changes may include suspiciousness, mistrust, and paranoia, with behaviors varying from childishness to unprovoked anger or agitation. As dementia progresses, the patient gets disoriented to time and place, fails to recognize family and friends, and becomes unable to perform basic tasks of dressing, bathing, and eating.

The diagnosis of dementia relies heavily on the observations of family and friends since the patient may deny or be unaware of any cognitive trouble. A detailed history is imperative to find the cause of dementia, emphasizing the early discovery of a treatable or reversible etiology. Effective interventions could be made for patients abusing alcohol or drugs, taking medications incorrectly, or lacking vitamins from malnutrition. A history and physical findings of stepwise, focal neurological deficits make a vascular cause of dementia more likely. Elderly depressed patients may appear to be demented, so screening for depression is always worthwhile. On rare occasions, the presence of dementia in several, particularly younger, family members raises the possibility of a hereditary dementia.

The evaluation for dementia should include some standardized cognitive testing, such as the brief *Mini-Mental State Examination (MMSE)*, or a more detailed neuropsychological profile. This latter provides a baseline comparison for future testing, helps determine the type of dementia involved, and may reveal any elements of depression. A brain scan, preferably an MRI, serves to determine if chronic subdural hematomas, brain tumors or abscesses, multiple infarctions or hemorrhages, or normal pressure hydrocephalus causes dementia. Focal findings or asymmetries of the bedside neurological examination should prompt a more urgent brain MRI scan.

Unexplained fever and headache may be signs of a chronic meningitis causing dementia, where lumbar puncture may be necessary. HIV infection should be suspected in a younger patient with dementia. All patients with memory or cognitive impairment should have a complete blood count, chemistry profile, vitamin B₁₂ level and thyroid functions checked. An unremarkable diagnostic workup, including nonspecific generalized brain atrophy on an MRI scan, is typically found in patients with Alzheimer’s dementia, which historically has been a diagnosis of exclusion.
Cellular architecture

- **Pyramidal cells – most numerous**
  - Long apical dendrite and a basal dendrite
  - *Dendritic spines* - selectively modified by learning
  - Their axons leave cortex; excitatory (glutamate)

- **Non-pyramidal cells**
  - Various shapes or appearances
  - Their axons don’t leave the cortex; inhibitory (GABA)
  - “interneurons” of the cerebral cortex

- Neocortex has six layers

Connectivity within/between the cerebral cortex

- **Corpus callosum** – Interconnect the two hemispheres
  - *Genu* – frontal lobes
  - *Anterior body* – frontal lobe
  - *Posterior body* – parietal lobe
  - *Splenium* – occipital and temporal lobe

- **Anterior commissure** - Interconnects temporal lobe & components of the olfactory system

- **Association bundles or fasciculi**
  - Corticocortical connections in the same hemisphere
  - None are discrete point-to-point
  - Fibers travel in both directions, leaving and entering

- **Disconnection syndromes** – specific clinical syndromes that result when these connections are disrupted

Primary Cortical gyri and sulci
Neocortical areas

- **Primary** - “Direct link to the world” - Inputs from thalamic nuclei and outputs to brainstem and spinal cord. Contains precise, but distorted body map(s)
  - **Primary motor**: precentral gyrus (4)
  - **Primary somatosensory**: postcentral gyrus (3,1,2)
  - **Primary visual**: calcarine (17)
  - **Primary auditory**: transverse temporal gyrus (41)

- **Unimodal** - “More complex response functions”; Adjacent to primary cortical areas, same “function, but less precise” body map(s). Injury can cause an **agnosia**
  - **Premotor** (6): involves larger groups of muscles in an activity
  - **Supplementary motor** (6): assumption of postures or using muscles on both sides of the body
  - **Somatosensory** (5, 7)
  - **Visual** (18, 19, + others?)

- **Multimodal** - “High level intellectual functions”; These cortical association areas receive and send converging inputs and can respond to multiple stimuli or the response may vary depending under the particular circumstances. Injury can cause an **apraxia** (motor) or **neglect** (sensory)
  - **Parieto-occipital-temporal region** -
  - **Prefrontal area** - Executive functions of the brain – Planning, insight, foresight and basic aspects of personality
  - **Limbic area** - emotional and “drive” related behaviors
Language Localization (in almost everyone, left hemisphere) and syndromes resulting from injury

<table>
<thead>
<tr>
<th>Aphasic Syndrome</th>
<th>Lesion Site</th>
<th>Verbal Fluency</th>
<th>Verbal Repetition</th>
<th>Verbal Comp</th>
<th>Verbal Naming</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broca (motor)</td>
<td>1</td>
<td>non-fluent</td>
<td>poor</td>
<td>good</td>
<td>poor</td>
</tr>
<tr>
<td>Wernicke (sensory)</td>
<td>2</td>
<td>fluent</td>
<td>poor</td>
<td>good</td>
<td>poor</td>
</tr>
<tr>
<td>Conduction</td>
<td>3</td>
<td>fluent</td>
<td>poor</td>
<td>good</td>
<td>poor</td>
</tr>
<tr>
<td>Global</td>
<td>1, 2, 3</td>
<td>non-fluent</td>
<td>good</td>
<td>good</td>
<td>poor</td>
</tr>
<tr>
<td>Transcortical Motor</td>
<td>4</td>
<td>non-fluent</td>
<td>good</td>
<td>good</td>
<td>poor</td>
</tr>
<tr>
<td>Transcortical Sensory</td>
<td>5</td>
<td>fluent</td>
<td>good</td>
<td>good</td>
<td>poor</td>
</tr>
<tr>
<td>Anomic</td>
<td>6</td>
<td>fluent</td>
<td>good</td>
<td>good</td>
<td>poor</td>
</tr>
<tr>
<td>Mixed Transcortical</td>
<td>4, 5, 6</td>
<td>non-fluent</td>
<td>good</td>
<td>good</td>
<td>poor</td>
</tr>
</tbody>
</table>

"Regulation" of sleep-wake cycles

*Flip-Flop switches* - Two pathways that inhibit one-another so when one side gains control it turns the other off and stabilizes its own firing. This allows the production of two stable states and rapid transitions between each.

"Flip-Flop" switch #1

Neurons within the preoptic area and medullary reticular formation "turn-off" wakefulness.

The flip-flop analogy represents the rapid and complete transitions between wake and sleep states.

Suprachiasmatic nucleus

"Clock for circadian rhythms"

Approximately 10,000 neurons in the hypothalamus use retinal inputs to adjust to the day-night cycle.

"Flip-Flop" switch #2

Nuclei in the pons generate the REM sleep stage and different nuclei in the pons terminate REM sleep, they have a mutually inhibitory relationship. The REM-off neurons are further regulated by excitatory inputs from Orexin, locus ceruleus and dorsal raphe nuclei.

The flip-flop switch analogy represents the transitions between REM and non-REM sleep states.

Orexin secreting neurons (lateral hypothalamus) through their innervation of other brain & thalamic areas, play a key role in promoting wakefulness and arousal, locomotion and emotions.

In the syndrome of agnolalia, there is a loss of these neurons and resulting in excessive daytime sleepiness, disturbed REM sleep and episodes of skeletal muscle (not respiratory) paralysis (cataplexy).

Note: Essentials of the human brain. NASA.
The term **reticular formation** refers to the neuronal network within the brainstem, although it continues rostrally into the thalamus and hypothalamus and caudally into the propriospinal network of the spinal cord.

A “coordinating system” (like the Limbic system) with “connections” to sensory, somatic motor and visceral motor systems

Organization can be subdivided into two neuronal cell “columns” (medial to lateral) as well as on the basis of their specific neurotransmitter release

**Neuronal columns** (many nuclei and names, but these are some of the major ones):

- **“Medial tegmental field”** (large-celled nuclei)
  - Origin of the reticulospinal pathway
  - Role in coordinating posture, eye and head movements.
- **“Lateral tegmental field”** (smaller and fewer cells, shorter local projections)
  - Extends from the medulla to the pons
  - Coordinate autonomic and limbic functions (e.g. micturition, swallowing, mastication and vocalization)

The functions of the reticular formation include their ability to coordinate motor and sensory brainstem nuclei:

- **Pattern generator**
  - Eye movements; horizontal (PPRF) and vertical (riMLF)
  - Rhythmical chewing movements (pons)
  - Posture and locomotion (midbrain and pons)
  - Swallowing, vomiting, coughing and sneezing (medulla)
  - Micturition (pons)
- **Respiratory control** (medulla); expiratory, inspiratory, apneustic and pneumotaxic
- **Cardiovascular control** (medulla); vasomotor pressor/depressor, cardioacceleratory and inhibitory.
  - Afferents arise from baroreceptors (carotid sinus and aortic arch), chemoreceptors (carotid sinus, lateral reticular formation chemosensitive area in the medulla) and stretch receptors (lung and respiratory muscles)
  - Efferents arise from reticular formation neurons within the pons and medulla
- **Sensory modulation or “gate” control**
  - The term “gating” refers to “modulation” of synaptic transmission from one set of neurons to the next.

**Neuroanatomical “Roadmaps and sites” within the Reticular Formation**

**Afferents** mainly to the lateral portion of the RF (esp. the Gigantocellular, Caudal and PPRF)

- **Spinoreticular**
  - Collateral fibers of the spinothalamic tract, widespread bilateral distribution, but without somatotopy
- **Trigeminal, vestibular, auditory and visceral**
  - Project to the parvocellular zone (vestibular fibers also to the PPRF)
- **Cerebelloreticular**
  - Project to the paramedian reticular nuclei; primarily originate from the fastigial nucleus
- **Tectoreticular**
  - From the superior colliculus’ deeper layers
- **Corticoreticular**
  - Originate in motor and premotor cortex and targeted towards the cells of origin of the reticulospinal tracts (provides a mechanism of cortical feedback)
**Efferents** originate mainly from the Gigantocellular, Caudal and PPRF nuclei
- Projections to the spinal cord
  - Via the **Pontine** and **Medullary reticulospinal tracts**
  - Descend bilaterally, no somatotopy, terminate primarily in the intermediate gray of the spinal cord and can be excitatory or inhibitory
  - Effects axial muscles of posture and locomotion (may influence the central transmission of sensory pathways)
- Projections to the brainstem
  - Via the **Reticulobulbar tract** (many brainstem reticular formation fibers travel within the **central tegmental tract**)
  - Has indirect connections to cranial nerve motor and sensory nuclei, direct to dorsal column nuclei and to parasympathetic nuclei.

**Overview of the “Diffuse modulatory system”**

**Diffuse modulatory system** in part corresponds to the **Ascending Reticular Activating System (ARAS)** that represents a physiological concept.

The neurons of the diffuse modulatory system are located around the borders of the Reticular Formation and their long projections cover/reach wide areas of the brain (e.g. entire cerebral cortex, cerebellum). Neurons of the nuclei within this group play a role in modulating and influencing our level of arousal, sleep, learning, memory, cognition, locomotion and pain, by altering the cell properties (e.g. excitation) of those systems to which they project.

(The cerebral cortex also affects our level of alertness via its own projections to this diffuse modulatory system, as can real or imaginary mental imagery. Finally, the cerebral cortex can separately inhibit/enhance sensory input that allows the focus of our attention to shift as necessary or demanded by the situation.)

**Neurotransmitter release from components of the diffuse modulatory system:**

**Aminergic neuron locations:**
- Serotonergic – brainstem midline (most extensive and reaches “all” CNS gray matter)
- Dopaminergic – ventral tegmental nuclei (midbrain)
- Noradrenergic – most of these neurons are located in the locus ceruleus (pons)
  - (Epinephrine-secreting – relatively scarce, exist in the medulla)

**Cholinergic neuron locations:**
- Pedunculopontine nucleus

**Important anatomical and functional areas within the diffuse modulatory system include:**
- **Serotonergic and Noradrenergic Systems**
  - **General Description**
    - Wide distribution, large number of receptors and signal transduction elements leads to the complexity of their pattern of expression
    - Role in integrative behavioral and neuroendocrine functions, sleep-arousal mechanism, modulates the action of other neurotransmitters, pain suppression (via input to the periaqueductal gray)
  - **Aminergic neuron locations**
    - **Raphe Nuclei** – origin of serotonergic projections to widespread areas of cerebral cortex, cerebellum, brainstem and spinal cord. Afferents to these neurons arise from the cerebral cortex, hippocampus, hypothalamus and periaqueductal gray
    - **Locus Ceruleus** – origin of noradrenergic (noradrenaline, norepinephrine) projections to all areas of the central nervous system (via the central tegmental tract, median forebrain bundle, dorsal longitudinal fasciculus and superior cerebellar peduncle). Afferents to these neurons arise from different reticular nuclei, periaqueductal gray, hypothalamus, amygdala and prefrontal cortex
**Cerebral Cortex – “Neocortical networks”**

### “Neocortical Network” – Language

**Role:** Language requires a distributed cortical network around the sylvian fissure. The left hemisphere is dominant for language in almost all right handed and 2/3rds of left-handed individuals.

**Anatomical Network:** Broca area (left frontal operculum and left inferior frontal gyrus) is involved in “expressive” language that includes grammar and processing of phonemes for speech articulation. Wernicke area (posterior temporal gyrus, supramarginal gyrus and angular gyrus) contains the mental representation and temporal order of phonemes (speech sounds) that form words. The left middle temporal gyrus and anterior temporal cortex are involved in word comprehension.

**Clinical deficits or syndromes:**
- **Broca aphasia** – Is a nonfluent aphasia with impaired expression of language
- **Wernicke aphasia** – Is a fluent aphasia with impaired comprehension of language
- **Conduction aphasia** – Interruption of the arcuate fasciculus that connects Broca and Wernicke area impair word repetition.

### “Neocortical Network” – Perceptual - Motor

**Role:** Visual perception of extrapersonal space, perceptual-motor coupling for motor control

**Anatomical Network:** Temporo-parietal-occipital junction (integrates visual, somatosensory and auditory information to generate a map of extrapersonal space) and Premotor cortex (receives commands and then provides or generates the motor programs that are appropriate to accomplish the motor task; eye, arm and hand movements and speech articulation). The premotor cortex and supplementary motor cortex are the areas that are responsible for motor learning and generating the proper set of motor sequences for visual guided or motivated/goal directed behavior in the absence of visual clues. Their information is then forwarded to the primary motor cortex that encodes the motor acts. The inferior frontal gyrus and frontal operculum are the cortical areas that are responsible for generating the motor commands (descend though the corticobulbar tract) to cranial nerve nuclei and pattern generators that control the lips, tongue and jaw muscles to support functions such as swallowing (bilateral cortical representation) and speech production (lateralized to the left hemisphere).

**Clinical deficits or syndromes:**
- Dysfunction in this network can lead to apraxia (inability to perform learned, skilled, purposeful movements in the absence of a problem with attention, weakness/sensory loss or impaired understanding; usually a result of a left hemisphere lesion.
- **Limb apraxia** – here an individual either doesn’t know what to do (e.g. hang a picture on a wall) or how to do something (e.g. use a hammer).
**Role**: Executive functions (Decision making, action planning, response to feedback to modify behavior, behavioral flexibility, inhibition of inappropriate behavior) and social behavior (recognition of emotions of others, insight and empathy).

**Anatomical Network**: Primarily made up of the prefrontal cortex that is an integral component of other networks (emotion and social, attention and memory). The dorsolateral prefrontal cortex is highly interconnected with other prefrontal areas, cortical association areas and paralimbic areas. The medial prefrontal and orbitofrontal are interconnected with the cingulate gyrus, anterior insula, hippocampus and amygdala.

**Clinical deficits or syndromes**:
- **Lateral prefrontal syndrome (Dysexecutive syndrome)** – Deficit of attention, working memory, planning and response selection and apathy.
- **Ventromedial prefrontal syndrome (“acquired sociopathy”)** – Impaired insight, lack of empathy, inability to observe social skills, risk taking behavior, poor social decision making.

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**Role**: Acquisition of fear responses, emotional processing of information for decision making, social recognition and behavior

**Anatomical Network**: Amygdala serves as the hub (serial processing of information) and interacts with the orbitofrontal and medial frontal cortex and the anterior and mid portions of the cingulate gyrus

**Clinical deficits or syndromes**:
- Bilateral dysfunction results in impaired recognition of facial expression and emotions and reflected in social behavior
- Dysfunction contributes to the cognitive/behavioral manifestations of neurodegenerative disorders
- Dysfunction mediates some of the emotional and autonomic manifestations of seizures that originate within the temporal lobe
- **Klüver-Bucy Syndrome** – Severe bilateral injuries (degeneration) of the amygdala results in difficulty in recognizing objects, excessive visual attentiveness, loss of normal fear/anger responses, marked/indiscriminate hypersexuality, changes in eating behavior
**“Neocortical Network” – Directed Attention**

**Role:** Attention can be considered the ability to selectively enhance the detection of certain stimuli at the expense of others.

**Anatomical Network:** The brainstem neuromodulator system, especially the diffuse projections from the locus coeruleus to the cerebral cortex help with generalized arousal. Helping to maintain attention incorporates the anterior insular cortex and anterior and midcingulate cortex ("salience” network or helping to assign a positive or negative meaning to the stimuli). Orientation to the stimuli involves the lateral parietal and frontal cortex and consists of a dorsal and a ventral network. The dorsal network is bilateral and comprises goal-directed attention (top-down), while the ventral is predominantly in the right hemisphere and is stimulus driven or attention is driven by the intensity or novelty of the stimulus (bottom-up).

**Clinical deficits or syndromes:**
- **Neglect** – contralateral to the site of injury (usually seen with right inferior parietal lobe injuries) so, the individual may neglect stimuli, objects, etc. on their left side and attend more to those on their right side.
- **Extinction** – with less prominent dysfunction in the right inferior parietal lobe the individual may demonstrate an inability to detect stimuli on the left side, when applied simultaneously applied to the left and right side of their body but can detect stimuli when only applied to one side at a time.

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**“Neocortical Network” – Object and Face Recognition**

**Role:** Recognition of the tactile, visual or auditory features of an object that allows perception of that object as a whole.

**Anatomical Network:** The primary visual, auditory and somatosensory cortex all contribute to the multimodal cortex located within the temporal lobe where all these modalities are integrated (ventral visual stream).

**Clinical deficits or syndromes:**
- **Agnosia** - Inability to recognize (and name) an object by using somatosensory, visual or auditory clues, but can still perceive it. Patents may still be able to recognize the object by using a sensory modality that is not affected.
- **Auditory agnosia** – Inability to describe a sound that is heard (usually a bilateral lesion that involves the unimodal auditory sensory association cortex).
- **Protopagnosia** – Inability to identify faces (usually seen in lesions of the anterior-mid portions of the fusiform gyrus).
- **Tactile agnosia (astereognosis)** – Unable to identify an object by palpating it (usually seen with lesions in the primary sensory cortex or unimodal somatosensory cortex of the parietal lobe).
- **Visual object agnosia** – Inability to recognize, name an object or describe its use, but may recognize it if allowed to palpate it (usually seen in lesion of the posterior inferior occipitotemporal cortex; fusiform gyrus).
**Role:** Learn, store and retrieve information about autobiographical (events, places and time) and semantic knowledge (factual knowledge that is learned; historical events, categories, features of things). The medial temporal lobe initiates the steps in learning facts and names and more permanent storage occurs in the lateral temporal lobe.

**Anatomical Network:** Medial temporal lobe [includes the hippocampal formation, entorhinal cortex (gateway for neocortical inputs into the hippocampal formation), perirhinal cortex and parahippocampal cortex].

**Clinical deficits or syndromes:**
- **Amnesia** – loss of autobiographical and semantic memory; usually in the setting of bilateral temporal cortex damage.
Terms and their definition/description (*these are the ones you need to know)

*Primary cortical area*: Neurons within the primary sensory cortex respond to specific features of their sensory stimuli and are those that receive input from thalamic sensory relay neurons. They form a topographical map that is distorted so that highly discriminating parts of the nervous system or body have disproportionately larger representations. Primary sensory areas include: Somatosensory area (Postcentral gyrus; Brodmann areas 3, 1, 2), Primary visual area (Cortex adjacent to the calcarine sulcus; Brodmann area 17) and Primary auditory area (Transverse temporal gyri; Brodmann area 41 and 42). The Primary motor cortex gives rise to most of the corticospinal tract (Precentral gyrus; Brodmann area 4). In one sense all these areas directly relate to the outside world.

*Unimodal cortical area*: These cortical areas “surround” each primary cortical area and are related to that sensory modality but elaborates on it. Sensory areas include: Somatosensory area (Superior parietal lobule; Brodmann areas 5), Visual area (Cortex adjacent to Primary; Brodmann area 18 and 19) and Auditory area (Superior temporal gyrus; Brodmann area 22). The Motor cortex includes the posterior aspects of the superior, middle and inferior frontal gyri (Brodmann area 6).

*Multimodal cortical area*: Integrates input related to several sensory modalities and often referred to as the association cortex. This comprises cortical areas in the posterior parietal area (encodes object location and movement to guide visual attention and programming of movements), lateral temporal cortex (integrates visual, somatosensory and auditory features of an object for object recognition) and have reciprocal connections with the prefrontal cortex (provides executive control of attention, goal-oriented behaviors and through connections with the cingulate gyrus and amygdala, participate with emotional control).

*Cortical Plasticity* – Ability of the cerebral cortex to undergo anatomical and functional changes in response to the circumstances

*Domain* – an abstract concept that implies that specific regions of the brain, based on inputs and intrinsic organization, subserve specific functions, roles or produce a specific output (currently this concept is under revision)

**“Neocortical Network”:** The cerebral cortex contains a mosaic of cortical areas that differ in function, architecture, connectivity, and/or topographic organization. A combination of local connectivity (within-area) and long-distance (between-area) connectivity enables each area to perform a unique set of computations. Some areas also have characteristic within their organization that reflects specialized representations of distinct types of information. Cortical areas interact with one another to form functional networks that mediate behavior, and each area may be a part of multiple, partially overlapping networks.

*Connectomics:* Is an emerging field, where neuroimaging data are used to generate brain networks. Functional and structural brain networks can be constructed using rs-fMRI and diffusion tractography, respectively. The brain is divided into distinct regions based on structural or functional information. Each brain region represents a node that may be connected to other nodes in the brain network. In structural brain networks these connections represent anatomical white matter connections, whereas in functional brain networks, connections represent temporal correlations from functional MRI time series. The topological characteristics of brain networks are described using a mathematical approach known as graph theory. This quantifies relationships across the brain network. It includes measures of network segregation such as the clustering coefficient, which represents the fraction of a node’s neighbors that are connected to each other.

*Modularity:* Subdivision of a network such that a module is defined as a group of regions that are highly connected to each other with minimal connections outside the group.

*Node:* A brain region usually defined using a brain atlas.

**MRI - Diffusion tensor imaging (DTI):** DTI analyses the three-dimensional shape of the diffusion, also known as diffusion tensor and the diffusion tensor harvests valuable information about the microstructure of brain tissue. The diffusion tensor of white matter or gray matter tracts should be considered as a three-dimensional structure and resembles a three-dimensional ellipsoid in space with predominant diffusion of molecules along the main axis of the ellipsoid and restricted diffusion perpendicular to the ellipsoid (anisotropic diffusion). By combining the directional information and magnitude of anisotropic diffusion of the individual voxels, the course of white matter tracts can be reconstructed. This technique relies on the assumption that voxels with a similar orientation of their principal anisotropic diffusion direction are likely part of the same white matter tract. Powerful postprocessing mathematical algorithms allow white matter tracts to be studied and visualized in vivo. This technique is also known as tractography.

**MRI - Diffusion-weighted MRI (DWI):** The use of specific MRI sequences as well as software that generates images from the resulting data by using the diffusion of water molecules to generate contrast in MR images. It allows the mapping of the diffusion process of molecules, mainly water, in biological tissues, in vivo and non-invasively. (Molecular diffusion in tissues is not free, but reflects interactions with many obstacles, such as macromolecules, fibers, and membranes. Water molecule diffusion patterns can therefore reveal microscopic details about tissue architecture, either normal or in a diseased state). It can provide in vivo information about microstructural integrity both in grey and white matter tissue and is potentially more sensitive to early processes that represent degeneration of axons and myelin damage, which may occur early during a disease.

**MRI - Event-related functional MRI:** Can be a sensitive indicator of presymptomatic cognitive dysfunction as it may reveal changes in blood oxygen level-dependent signals, reflecting altered patterns of neuronal activity, before gross structural changes are seen.

**MRI - Resting state functional MRI (rs-fMRI):** Measures blood oxygen level-dependent signal fluctuations when participants are at rest.