The State of Resting State Networks

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Abstract: Functional MRI (fMRI) is currently used for pre-surgical planning, but is often limited to information on the motor and language systems. Resting state fMRI can provide more information on multiple other networks to the neurosurgeon and neuroradiologist; however, currently, these networks are not well known among clinicians. The purpose of this manuscript is to provide an introduction to these networks for the clinician and to discuss how they could be used in the future for precise and individualized surgical planning. We provide a short introduction to resting state fMRI and discuss multiple currently accepted resting state networks with a review of the literature. We review the characteristics and function of multiple somatosensory, association, and other networks. We discuss the concept of critical nodes in the brain and how the neurosurgeon can use this information to individually customize patient care. Although further research is necessary, future application of pre-surgical planning will require consideration of networks other than just motor and language in order to minimize post-surgical morbidity and customize patient care.

Key Words: functional MRI (fMRI), resting state fMRI, resting state networks

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The scientific study of brain systems (systems neuroscience) has focused on the organization and localization of functionality within the brain. Many research efforts seek to understand how different regions of the brain work together to instantiate the many functions that the brain performs. Historically, information about functional localization was obtained from lesion-symptom mapping studies, extending from the early observations of the French physician Pierre Paul Broca.[1] Later, Sir Charles Sherrington used focal electric stimulation to map out the organization of the motor cortex in great apes. This work was followed by analogous mapping studies in humans performed by his student the neurosurgeon Wilder Penfield.[2] Noninvasive functional neuroimaging, beginning with positron emission tomography (PET)[3] and later functional magnetic resonance imaging (fMRI),[4,5] has greatly accelerated our understanding of brain function and organization. Both PET and fMRI measure local increase of blood flow and oxygen availability in tissue. fMRI detects changes in the blood oxygen level dependent (BOLD) signal, as local neural activity manifests as a relative decrease in concentration of deoxy-hemoglobin in the blood.

The paradigm most often used in studying the brain with fMRI is that of imposing a cognitive, sensory, or motor task and subsequently observing the change in BOLD signal during the task performance relative to rest or control periods. For the purpose of this review, we will refer to these studies as task-based fMRI (T-fMRI). Numerous tasks have been studied and reported in the literature, providing us a wide understanding of the many different systems that function across the brain. One important observation from these studies is that brain metabolism is only minimally altered by the performance of mentally demanding tasks.[6] The implication of this observation is that the intrinsic activity of the brain at rest uses a substantial amount of energy, and thus must be of great importance for the normal function of the brain. There are several techniques used to study intrinsic or resting state brain activity. However, in this manuscript, we will focus on fMRI, and we will refer to this activity as resting state fMRI (RS-fMRI).

BOLD fMRI is possible because deoxy-hemoglobin is paramagnetic. Consequently, the local concentration of deoxy-hemoglobin causes signal loss on T2∗-weighted imaging.[7] Locally increased neural activity leads to both increased blood flow and increased oxygen utilization. However, blood flow changes are greater than the changes in oxygen extraction.[7] The net result is that increased neural activity leads to locally decreased concentration of deoxy-hemoglobin, which reduces signal loss on T2∗-weighted images, thereby increasing the BOLD fMRI signal. The electrophysiological correlates of BOLD signals have been determined to be broadband local field potentials, primarily in the gamma (30 to 100 Hz) frequency range, which, in turn, reflect local neural excitability.[8] These mechanisms apply to both positive and negative modulations of the BOLD signal and underlie both T-fMRI and RS-fMRI.

Resting State Networks (RSNs)

Biswal et al[9] are credited with the first observation that resting state activity is synchronous (correlated) between the left and right motor cortex, as well as most other brain regions involved in movement, and this synchronous activity was subsequently found to be present across multiple brain systems in addition to the motor system.[10,11] Areas of the brain that demonstrate synchronous activity have been called functional systems, intrinsic connectivity networks, and, as we refer to them here, resting state networks (RSNs). The topography of RSNs closely corresponds to responses elicited by a wide variety of sensory, motor, and cognitive tasks.[12,13] Intrinsic activity persists in a modified form during sleep[14] and under certain types of sedation.[15,16] Several RSNs have been identified in all mammalian species investigated to date.[17,18] This phylogenetic conservation implies that coherent intrinsic activity must be physiologically important despite its high metabolic cost.[19]

There is evidence supporting the idea that RSNs are hierarchically organized.[20,21] When one attempts to find RSNs by use of hierarchical clustering, there is a dichotomous distinction between the most prominent network, the default mode network (DMN)

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(detailed below), and most other networks.[22] Progressively finer distinctions between RSNs can be made at successively lower levels of the hierarchy. A feature of RS-fMRI data is that some unsupervised classification strategies may find any number of ''RSNs,'' depending on how many networks are requested[23]; however, many of these ''RSNs'' do not correspond to responses observed during T-fMRI. Another interesting feature is that RSN membership is sometimes not all-or-none. In other words, some parts of the brain may belong to multiple RSNs, albeit unequally,[24] although this point frequently is suppressed in winner-take-all representations of RSNs, for example, as in.[25] Further, it appears that the primary function of intrinsic activity is not on-line processing.[26–28]

There is evidence for the role of RS-fMRI correlations in the maintenance of the stability of the brain's functional organization which was provided by Laumann et al.[28] In this study, the authors tried to find evidence of dynamic changes in BOLD correlations that could reflect moment to moment changes in cognitive content of the brain. The authors concluded that changes in BOLD correlations over time are largely explained by a combination of sampling variability, head motion, and fluctuations in arousal during scanning. The authors concluded that a single correlation structure adequately describes the resting state structure of the brain as measured with BOLD fMRI. Similarly, Gratton et al[29] revealed that individual differences in correlation structure are much larger than state-induced (eg, performing a cognitive task) changes in the correlations.

The importance of RSNs to the mapping of brain function lies in the fact that their topography corresponds to activation maps elicited in task based fMRI paradigms.[12,13] These networks include the surgically defined ''eloquent'' areas of the somatosensory, language, and visual networks (VIS), which can provide valuable information for Neurosurgeons in the preoperative setting. Over the last decade, in addition to using T-fMRI, we have been using resting state methods to provide additional pre-surgical planning information to the Neurosurgeons at our hospital with very positive results (Note: *the use of RS-fMRI is currently not approved by the FDA*). Other RSNs that are easily identified and are currently of research interest include more recently identified control and attention networks (Fig. 1). These networks are not currently used for pre-surgical planning and many Neurosurgeons and Neuroradiologists are not familiar with their location and function. That said, there have been numerous studies in the neurosurgical literature of regions typically considered outside of ''eloquent cortex'' that have clinically relevant results.[30–33] We believe that as the sophistication of surgical navigation techniques increases, there will be more awareness for the need to preserve these vital networks. In the remainder of this manuscript, we will briefly cover our analysis techniques and discuss an up to date set of RSNs, including important network hubs, which are areas that connect or interact with multiple networks.

METHODS

Processing strategies depend on the fact that spontaneous neural activity is correlated (coherent) within widely distributed regions of the brain. Many processing strategies yield highly reproducible results at the group level.[10,34] The most commonly used analysis methods are spatial independent component analysis[35] or seed-based correlation mapping.[36] In this review, we will focus on previously published seed-based data-driven methods. For the RSNs presented in Fig. 1, seed-based correlations were computed and then techniques adapted from the field of network science were used to identify RSNs. The principal difficulty with any resting state analysis is the exclusion of non-neural artifact, which typically is accomplished using regression techniques.[37]

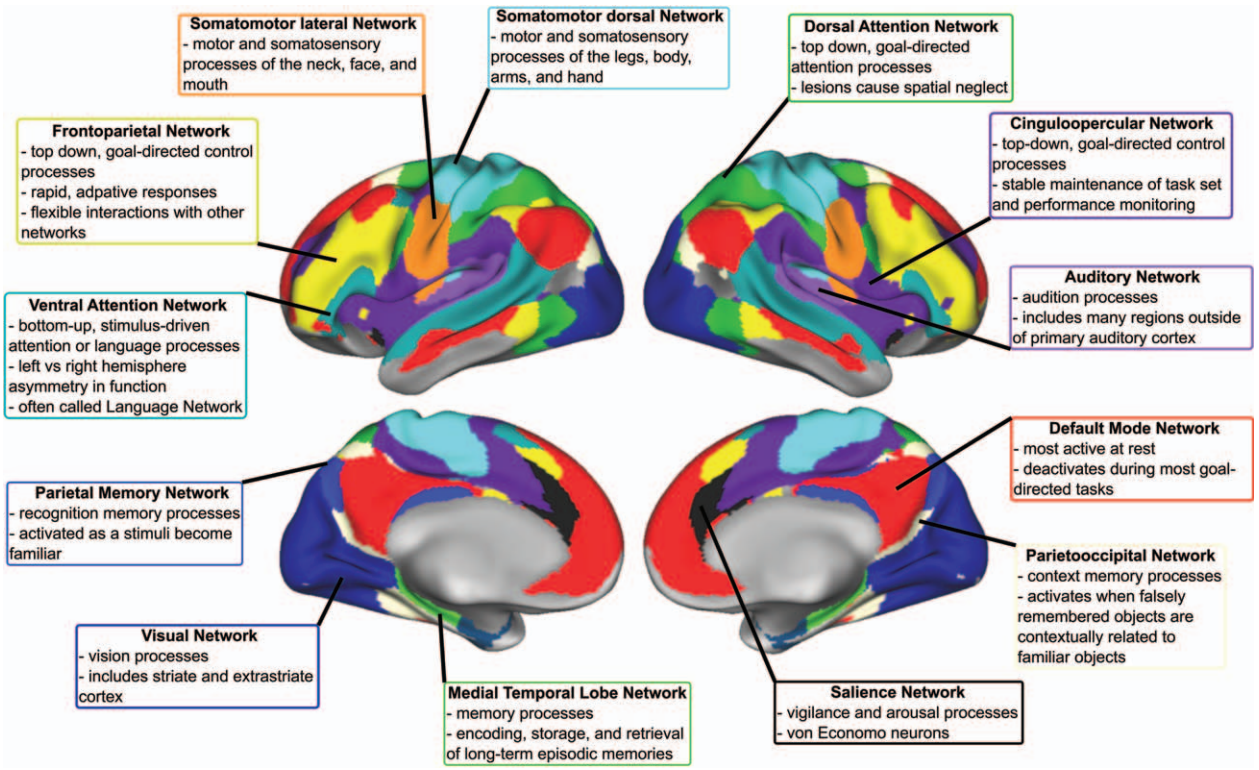

FIGURE 1. Color-coded surface-based presentation of the resting state networks discussed in the manuscript.

Pre-processing procedures used in our laboratory[12,38,39] include compensation for slice-dependent time shifts, elimination of systematic odd-even slice intensity differences due to interleaved acquisition, and rigid body correction for head movement within and across runs. The fMRI data are intensity scaled (1 multiplicative factor applied to all voxels of all frames within each run) to obtain a mode value of 1000. This scaling facilitates assessment of voxel-wise variance for purposes of quality assessment but does not affect computed correlations. Atlas transformation is achieved by composition of affine transforms connecting the fMRI volumes with the T1- and T2-weighed structural images. Head movement correction is included in a single resampling to generate a volumetric time-series in 3 mm cubic atlas space.

Additional preprocessing in preparation for seed based correlation mapping includes the following: (1) spatial smoothing (Gaussian blur extending approximately over twice the original voxel size), (2) voxelwise removal of linear trends over each run, (3) temporal band-pass filtering (to retain frequencies in 0.008 to 0.09 Hz), and (4) reduction of spurious variance by regression of nuisance waveforms derived from head motion correction and extraction of the time series from regions of noninterest in white matter and CSF. In our laboratory, step (4) includes regression of the global signal, that is, the mean whole-brain signal. A consequence of global signal regression is that all subsequently computed correlations are effectively partial correlations of first-order controlling for widely shared variance.[12]

Global signal regression (GSR) before correlation mapping is a highly effective means of reducing widely shared variance and thereby improving the spatial specificity of computed maps.[12,40,41] Some part of the global signal undoubtedly is of neural origin.[42] However, much (typically, most) of the global signal represents non-neural artifact attributable to physical effects of head motion[43–46] and variations in the partial pressure of arterial carbon dioxide.[47] Absent GSR, all parts of the brain appear to be strongly positively correlated.[48–51] GSR causes all subsequently computed correlation maps to be approximately zero-centered; in other words, positive and negative values are approximately balanced over the whole brain.[12] Thus, GSR unambiguously does negatively bias all computed correlations, although iso-correlation contours, that is, map topographies, remain unchanged. This negative bias has caused some to criticize GSR on the grounds that it induces artifactual anti-correlations.[52,53] More recent objections to GSR focus on the possibility that it can distort quantitative functional connectivity differences across diagnostic groups.[54] However, this objection to GSR is irrelevant in the context of using RS-fMRI for purposes of RSN mapping in individuals. Furthermore, as GSR remains the most effective strategy for the elimination of motion-related systematic biases in correlations, we chose to implement it here.[13,55] The use of GSR introduces (or reveals, depending upon one's perspective) distant-dependent artifacts into the correlations, which is ameliorated via censoring of high motion frames. Here, this was achieved by censoring all frames with a Framewise Displacement value $\geq$0.2 mm.[56]

Seed-based correlation mapping is one of the most widely adopted techniques for studying cofluctuations in intrinsic neuronal activity, or functional connectivity.[34,57] The high adoption rate of the seed-based approach is partly attributable to simplicity of implementation, and to the ease with which the results can be interpreted. Pearson product-moment correlation is the most widely used measure of functional connectivity.[9,57,58] Some seed-based analyses require prior knowledge of the locations of regions of interest (ROI) and these can be obtained from previously determined atlas coordinates or from task-based fMRI data. For instance, a simple motor paradigm may be used to generate data involving the motor network. The activation data are then analyzed, and the voxel (or set of voxels) with the strongest activation is used as a "seed" region to then study the resting state data. Once the coordinates of the seed region have been identified, the resting state time courses from the rest of the brain are compared with this region, and a correlation map is generated. Figure 2 shows an example of a connectivity matrix

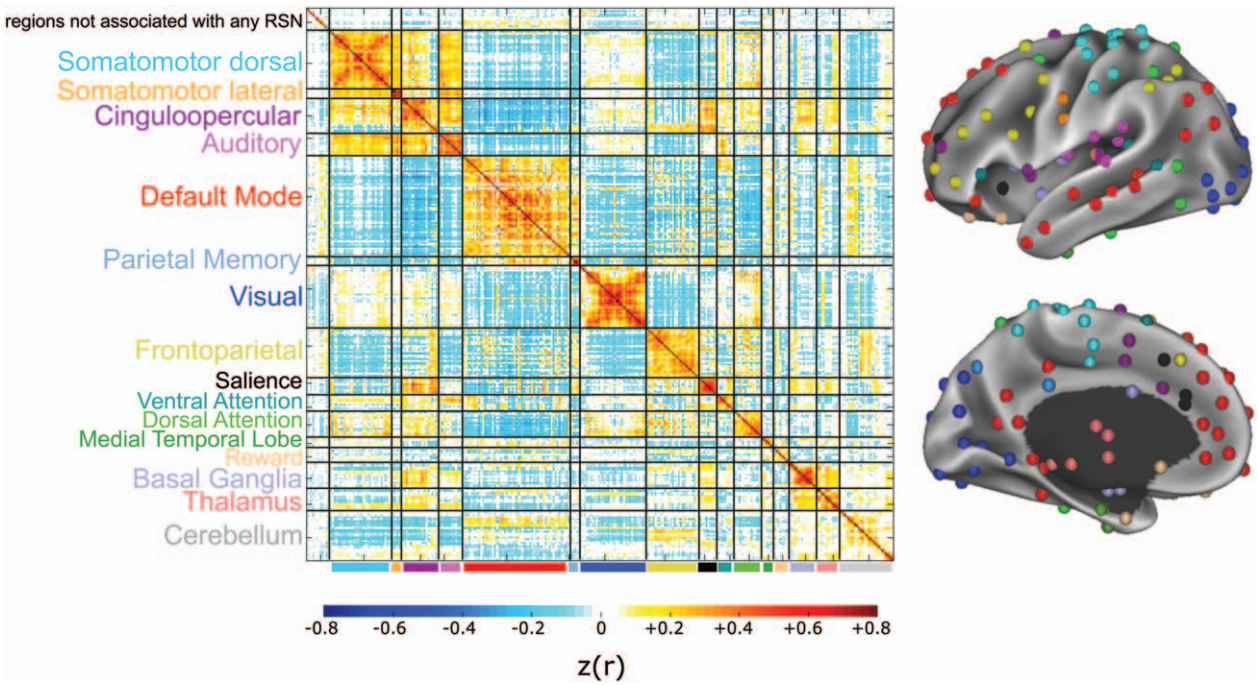

FIGURE 2. On the left is a typical connectivity matrix between a standard set of 300 regions of interest representing the resting state networks presented in Fig. 1. On the right is a color-coded surface representation of the location of the regions of interest.

between a standard set of 300 ROIs[59] representing the RSNs in Fig. 1. Note the block diagonal structure of this matrix, which is a consequence of strongly correlated regions within each RSN.

RESULTS

Sensorimotor Networks

Somatomotor Network (SMN)

The motor and somatosensory homunculus is familiar to all students of neuroscience dating from the pioneering work of Sherrington, and later, Penfield. The cytoarchitectural organization of these areas was also recognized as unique by Brodmann over 100 years ago (as Brodmann areas 1 to 4). The location of Areas M1 and S1 (primary motor and somatosensory cortex) is very consistent across subjects in the pre- and postcentral sulcus and of primary concern to the neurosurgeon in order to avoid causing paralysis or motor weakness in patients. The SMN also includes the supplementary motor area, an area that can cause temporary motor symptoms when disrupted. The SMN was the first RSN to be identified by Biswal et al.[9]

Visual Network (VIS)

The VIS identified by RS-fMRI includes both striate cortex (V1, Brodmann area 17) and many extra-striate areas in the occipital lobe. Sometimes, further divisions within the VIS are identified that reflect a foveal versus peripheral distinction.[60] Like the SMN, these areas are highly conserved anatomically across subjects and are of great concern to the neurosurgeon seeking to minimize visual field deficits. The VIS occupies a large fraction of the posterior cortical surface, especially in mammals.

Auditory Network (AUD)

The auditory network (AUD) consists of primary auditory cortex (A1) and some peripheral auditory regions located mostly in the insula and superior temporal gyrus.[61] The AUD is often included as part of language areas of interest to the neurosurgeon during pre-surgical planning.

Association Networks

Most RSNs in association cortex are more recently identified, more variable across individuals, and map onto higher-level cognitive functions; however, these regions of the brain are rarely considered ''eloquent'' cortex. Perhaps it is worth reconsidering this distinction, as many of the networks discussed below are involved in essential aspects of human life, such as executing task control, forming memories, and attending to the world. But, as we discuss below, it may be the case that particular regions (hubs) are the most important to preserve during neurosurgery.

Default Mode Network (DMN)

The regions that compose the DMN were discovered by a meta-analysis of 9 diverse PET ''activation'' studies.[62] This meta-analysis revealed consistently *decreased* cerebral blood flow (''deactivation'') in a specific set of regions during performance of a broad range of cognitive tasks. On the basis of this result, it may be inferred that the DMN is most active when subjects are not engaged in any particular goal-directed task, hence, the designation, ''default.''[63] Subsequently, it was shown that the full topography of the DMN may be recovered by correlation mapping of resting state fMRI data using a seed region in the posterior cingulate/precuneus cortex (PCC).[64] In this respect, the DMN is no different than any other functional system. What is noteworthy is that the very existence of an entire functional system, now known as the ''DMN,'' was not suspected until it was revealed by functional neuroimaging. This point is all the more remarkable because the DMN accounts for a large fraction of the brain's anatomy, as it is the largest RSN. Multiple high-level functions have been attributed to the DMN (episodic memory, prospection, social cognition); however, accumulating evidence indicates that chimpanzees,[65] monkeys,[15,17] and even rodents[18,66] have a DMN.

Dorsal Attention Network (DAN)

The Dorsal Attention Network (DAN) is composed of the gyri adjacent to the intraparietal sulcus, cortex near the MT+ complex, and both the frontal and secondary eye-fields (2 regions directly anterior to M1 that are on the superior and inferior sides of the middle frontal gyrus). The DAN is the most prominent network of the so-called ''task positive'' regions of the brain (ie, regions that tend to activate during goal-directed tasks).[22] Its negative correlation with the DMN is the most consistently seen negative correlation across the brain. There is evidence to suggest the DAN is responsible for top-down, goal-directed attention processes. A real-world example of this type of process is driving in an unfamiliar neighborhood and actively looking for an address or street sign. An example from radiology is actively looking for a metastatic focus on an MRI after being given the patient history. A classic task that activates the DAN in a T-fMRI study is the Posner task.[67] A striking example of left-right asymmetry to the brain is seen with injury to elements of the right DAN that can lead to persistent symptoms of spatial neglect.[68]

Interactions between the DAN and the VAN (described next) are of great importance for brain function and are reviewed in the literature.[38,69]

Ventral Attention (VAN) and Language Network (LAN)

Another prominent attention network is the VAN,[70] which is thought to be responsible for bottom-up, stimulus-driven attention processes. Regions that constitute the VAN are detailed below. A real-world example of the VAN in action is the quick reaction of hitting the brakes when another car swerves in front of you. Another example would be the automatic, unconscious ducking that occurs when a thrown ball is heading towards one's head. An interesting feature of the VAN is its large overlap with the common language areas. Left hemisphere VAN regions include parts of the superior temporal sulcus and both Broca's and Wernicke's Areas.

The VAN is an exception to the general correspondence seen between areas activated in T-fMRI and RSNs, mostly due to the left-right asymmetry between language and stimulus-driven attention processes. Some of the areas strongly activated by language tasks overlap with left-lateralized VAN regions. This overlap, particularly with Broca's and Wernicke's Areas, has led some investigators to call the VAN the Language Network (LAN).[25] However, the VAN does not include any somatomotor cortex that represents the face (vocalization), any visual cortex, including the visual word form area (reading), or any auditory cortex (listening) regions, all of which are necessary for language function. Furthermore, the VAN includes multiple areas that are usually not considered language areas, including the remainder of the frontal operculum that is not Broca's Area, a large portion of the temporal lobe, dorsomedial prefrontal cortex, a region near the intraparietal sulcus (IPS)/middle frontal gyrus, and corresponding regions in the right hemisphere.

Frontoparietal Network (FPN)

The FPN, sometimes called the Frontoparietal Control Network, is a set of brain areas in dorsolateral prefrontal cortex, the inferior parietal lobule, the middle of the middle temporal gyrus, and a dorsomedial prefrontal region anterior and superior to anterior cingulate cortex. The FPN is thought to be responsible for top-down,

goal-directed control processes. These processes have been referred to as executive or cognitive control. In particular, the FPN is activated when fast, adaptive control is required during a task. Furthermore, the FPN is thought to act as an intermediary between other RSNs, coordinating their interactions in a flexible manner.[71,72]

A real-world example of an FPN function would be when a driver suddenly realizes that they are drifting out of their lane and makes a sudden correction. An interesting aspect of the FPN is that it has the largest overlap with regions of high individual variability in both the cortex[73,74] and cerebellum.[75]

Cinguloopercular Network (CON) and Salience Network (SAL)

Another network involved in task control is the Cinguloopercular Network (CON), which is composed of the opercula, anterior cingulate cortex, the anterior insula, regions anterior to the supplementary motor area, and a few other frontal and medial parietal regions. The difference between the CON and the FPN is that the CON is thought to be involved in sustained aspects of control, such as stable maintenance of task set and performance monitoring. Specific experimental designs are required to dissociate the CON and FPN in T-FMRI, yet RS-FMRI separates them quite readily. Furthermore, a recent lesion study provided a double dissociation between these two control networks.[76] An example of using the CON would be during a complex card game in which the player has to maintain the rules and goals of the game. The CON is sometimes called the Salience Network (SAL), as the first papers describing this network came out around the same time but with different names for the same brain regions.[72,77,78]

However, there is a separate RSN called the SAL, which adds to the confusion between the CON and SAL.[25] Moreover, the SAL is sometimes combined with the CON in studies, which further compounds the confusion. The SAL (the RSN separate from the CON) is composed of inferior anterior insula and the most anterior aspect of anterior cingulate cortex. These are the regions of the brain in which von Economo (spindle) neurons have been discovered.[79] The SAL is thought to be involved in maintaining vigilance and arousal as well as responding to salient stimuli, two extremely important functions for the radiologist.

Parietal Memory Network (PMN)

The Parietal Memory or Parietomedial Network (PMN) is composed of the superior portion of the parieto-occipital fissure and the portion of posterior cingulate cortex that is adjacent to the splenium and posterior body of the corpus callosum. It sometimes includes a portion of the intraparietal sulcus as well. The PMN is thought to be involved in recognition memory functions, as it becomes activated as stimuli become familiar (without explicit instructions to make memory judgments). For a review of its functions, see Gilmore et al.[80]

Medial Temporal Lobe Network (MTL)

The Medial Temporal Lobe Network (MTL) includes the hippocampus, para-hippocampal regions, and entorhinal cortex. Experiments with the famous patient HM demonstrated that the hippocampus is necessary for long-term encoding, storage, and retrieval of episodic memories.[81] Studies of HM and another famous patient KC showed that many nondeclarative memory functions (eg, procedural memory, eye-blink conditioning, and priming effects) do not involve the hippocampus. Sometimes entorhinal cortex is identified as a separate RSN. In addition to regions of the hippocampus, place and grid cells, which encode a spatial map of the visual world, are found in entorhinal cortex.

Parietooccipital Network (PON)

The Parietooccipital Network (PON) is composed of parahippocampal cortex, retrosplenial cortex, the superior portion of the precuneus, and the most posterior part of the angular gyrus. The PON is sometimes called the Context Memory Network because it is involved in visual context memory, as described by Bar et al.[82]

Other Regions Outside of the Cerebral Cortex

The majority of the striatum, thalamus, and cerebellum align with the aforementioned RSNs.[75,83,84] Yet, several well-described subcortical regions of the brain have been found to form their own RSN with orbitofrontal and ventromedial prefrontal cortex. They are the nucleus accumbens and amygdala. This RSN is plausible because these regions are anatomically connected[85] and are thought to be important for emotion, reward, and other valence processing.[86,87] Unfortunately, the areas that form this RSN are in the inferior parts of the brain that are poorly visualized with fMRI due to nearby portions of the skull creating susceptibility artifact. Some studies have called this RSN the Limbic Network.[13,84]

Hubs of the Brain

There is evidence to suggest that there are brain areas that are hubs of the brain's network architecture, similar to major airports or train stations.[88] These areas connect (if considering structural networks) or interact (if considering functional networks) with many other regions of the brain, forming pathways or links between several brain systems. Some studies have revealed that damage to these regions produces severe behavioral deficits, including widespread cognitive dysfunction.[89,90] The location of these hubs could be variable across individuals, but would be especially important to localize for the Neurosurgeon before surgery in order to prevent and reduce morbidity. There is no consensus in the literature on the exact location of these hubs, with some areas derived from neuroscientific considerations in normal subjects,[89,91] some derived from neurological patient registries,[90] and others from small case studies in neurosurgery.[30–33]

DISCUSSION

In this article, we provide an introduction to RSNs and network hubs. We survey a set of RSNs that has emerged from the literature in recent years. It is important to realize that this is an area of active research, and thus, this collection of RSNs may further evolve over time as we learn more about the brain.

We anticipate that as our understanding of RSNs increases and individualized patient care (precision medicine) becomes more common, the use of RSNs in pre-surgical planning will increase, with resulting further decrease in postsurgical morbidity. These developments will necessitate that Neurosurgeons and Neuroradiologists have a greater understanding of RSN topography and the location of critical hubs between these networks.

In addition to improved localization of function, it will be necessary to improve our understanding of the different ability of functional areas to recover after surgical intervention. For example, the sensorimotor networks, which are highly stable across individuals, do not exhibit good functional recovery from insult. We hypothesize that RSNs that demonstrate greater functional variability across individuals will also demonstrate more plasticity during recovery, with functionality that is more resistant to damage from surgical resection.

We anticipate this evolution in insight will lead to an expanded understanding of what is considered ''eloquent'' from a neurosurgical perspective. As this notion grows to encompass more areas of the brain, the surgical paradigm may evolve from one of surgical

avoidance of an eloquent region to a more nuanced and tailored decision-making process given each patients unique cognitive and social needs. As an example, there may be very different priorities between what cognitive operations are prioritized between a businessman (complex executive functions) and a professional dancer (visuo-spatial attention). With an ever-expanded notion of eloquence the question may change from ''can we preserve function – yes or no,'' to one that is more tailored, namely, ''can we preserve the functions that are essential to your lifestyle.'' These insights will further enhance a Neurosurgeon's ability to plan an optimal surgical strategy.

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