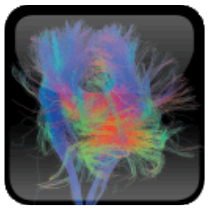

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Functional specialization and network connectivity in brain function

Chapter:
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Do mental processes depend from ‘localized’ brain regions or are they ‘global’ resulting from the integrated functioning of the brain as a whole? Brain lesion studies and neuroimaging methods have given evidence of both interpretations, allowing contemporary neuroscience to reach the conclusion that localized regions of the brain do carry out specific cognitive functions but they do so through multiple and complex interactions with many other brain regions forming large-scale networks.

Focal nature of cognitive functions

Evidence for functional specialization from lesion cases

Historically, the notion that different cognitive abilities are related to the function of specific brain regions took a relatively long time to become

widely accepted by the scientific community (see chapter 1). Such a concept was long resisted by ‘holistic’ perspectives of the brain which viewed each part as contributing to all functions. It was only with the anatomo-clinical works of Broca and Wernicke on language disorders in the 1860s and 1870s that that the concept of functional specialization was put on a sure footing.[1] Prior to this, the first intuition that mental functions were based in the brain had been advanced by Franz Joseph Gall in his controversial doctrine of phrenology.[2]

In 1861, Broca described a patient who lost the ability to speak following a stroke. Although able to understand language and repeat single words, and free of significant limb weakness, this individual could not articulate sentences or express himself in writing. Post-mortem examination revealed a lesion in the left posterior lateral region of the frontal lobe, subsequently termed Broca’s area.[3] Broca described other similar cases, and by inferring the correlation between post-mortem anatomical lesions and language disorders (anatomo-clinical correlation method), he concluded that language is localized in the left hemisphere.

About a decade later, Carl Wernicke described another case of language disturbances following a stroke. This patient could speak fluently but in a meaningless way and could not understand spoken or written language. After his death, the damaged area was found to be in the posterior left temporal lobe at the junction with the parietal lobe, subsequently termed Wernicke’s area. On the basis of his and Broca’s findings, Wernicke proposed a model of language as a multi-component process, in which each component would have a specific, distinct anatomical localization.[4] He distinguished a centre for motor–verbal functions, localized in the left frontal regions, responsible for language articulation and production, from a centre for auditory–verbal functions, localized in the left temporal region, responsible for language perception. Lesions to the former would cause a non-fluent aphasia with intact comprehension (Broca’s aphasia), while lesions to the latter would cause a fluent aphasia with impaired comprehension (Wernicke’s aphasia).

In the same decades, studies by Fritsch and Hitzig in dogs further reinforced the notion that different functions are localized in different cortical regions by demonstrating that the stimulation of anterior regions of the cerebral cortex causes contralateral movements, and that their disruption causes contralateral paralysis.[5] Functional specialization was further supported by animal studies identifying oculor-motor centres in the frontal lobes,[6] auditory centres in the temporal lobes,[7] and visual centres in the occipital lobes (see also chapter 1).[8]

Many other cognitive functions were localized by investigating patients who had suffered from focal brain lesions. One of the most famous cases was reported by Harlow in 1848 who described Phineas Gage who, after having sustained a frontal lobe injury, presented profoundly altered social and interpersonal skills, to the point that people who knew him beforehand described him as 'no longer being Gage'. This first suggested that frontal brain regions are involved in social behaviour.[9]

Another landmark case was described by Scoville and Milner in 1957. Following bilateral temporal lobe resection in the attempt to treat his epilepsy, a patient named Henry Molaison (famously known as HM) became severely amnesic. He had permanently lost the ability to acquire new information (anterograde amnesia) and recall memories of the years immediately prior to surgery (retrograde amnesia), despite having normal reasoning skills, language, and short-term/working memory.[10] HM provided the first evidence that the hippocampus and surrounding medial temporal structures are essential for the consolidation of information in long-term memory.[11]

Following these single case studies, the study of lesions in humans evolved and expanded. Large groups of patients were assessed to establish correspondences between the brain and symptoms in a more quantitative, robust way, permitting statistical inference at the level of population.[12,13] Standardized scales to measure cognitive abilities were developed and used to compare patients' performance to healthy controls.[14]

The lesion method is based on the assumption that if a certain brain region is necessary for a certain function, then a lesion to that area should lead to a deficit in that function, whereas this should not occur when the brain region is undamaged (simple dissociation). Further expansion of the lesion method came with the concept of *double dissociation*, considered to be the strongest evidence for functional specialization and segregation. It requires the comparison between two patients (or groups of patients) different in terms of lesion localization: if one patient is significantly more impaired in function A, while the other is significantly more impaired in function B, then it is concluded that the two functions are independently associated with the two damaged areas.

Using the double dissociation technique, several investigators including Ennio De Renzi in stroke-lesioned patients,[14,15] Freda Newcombe in soldiers who had sustained focal and stable brain wounds during the Second World War,[16] Brenda Milner in surgical patients who had had lobectomies,[17] Gazzaniga in patients who had undergone callosotomy,[18] all demonstrated differential deficits following left and right hemisphere

lesions and specialization of the right hemisphere for visual–perceptual and spatial tasks and left hemisphere for speech and skilled movements. Newcombe, for example, provided the first evidence of dissociated visual–perceptual and spatial deficits following, respectively, temporal-posterior lesions and dorsal-parietal lesions of the right hemisphere,[19] supporting the concept of a dorsal and ventral visual stream.

Through the study of lesion cases, the concept of functional specialization became a dominant theme in neuroscience. It is mainly thanks to this approach that today we are able to localize deficits such as aphasia, unilateral neglect, and impaired executive function at the bedside.

Evidence for functional specialization from structural imaging

The need to study large groups of patients together with the advent of computer tomography (CT) and magnetic resonance imaging (MRI) encouraged development of methods that allow comparison of lesions across different patients,[20] including transposition of brains into common, stereotactic spaces.[21] One common method consisted of identifying regions of lesion overlap. The extent and location of damage in a group of patients could be visualized in a colour-coded ‘lesion density map’, in which the region damaged in the highest number of patients would be surrounded by regions damaged by a progressively decreasing numbers of patients.[22,23]

Two approaches have been used to relate symptoms to lesions. One groups patients by location of their brain lesions and then examines differences in symptoms. For example, a study by Grafman and colleagues on veterans who suffered penetrating head injuries in Vietnam showed that soldiers with lesions in the ventromedial regions of the frontal lobes were more aggressive and violent than those with lesions in other brain areas.[24] The second approach groups patients by symptoms and then examines lesion location. For example, Damasio and colleagues classified patients with focal brain lesions according to whether they had selective deficits in naming famous persons, animals, or tools. By using lesion density maps, they showed that each of these category-specific deficits was associated with overlapping of lesions in different temporal lobe regions, arguing for a role of higher-order association areas outside of classic language areas in word retrieval.[25]

MRI offers a higher spatial resolution than CT and allows for more comprehensive characterization of lesions by ‘dividing’ the brain into three-dimensional units of volume (voxels). In one of the first studies that used a *voxel-based* approach, Adolphs and colleagues demonstrated involvement of somatosensory cortices as well as the amygdala in

emotion recognition, by comparing the voxel-based lesion density map of patients with impaired emotion recognition with that of unimpaired cases. The resulting *difference map* revealed that voxels within the somatosensory cortex were significantly associated with impairment.[26]

Building on statistical approaches used in functional imaging (see next section), recently developed techniques such as *voxel-based lesion symptom mapping* (VLSM)[27,28] allow for improved symptom mapping by computing statistical tests iteratively for each and every voxel. The technique relies on comparison of continuous or discrete behavioural variables on patients grouped according to whether they have damage in that given voxel and then correcting for multiple comparisons. This is an example of a 'mass-univariate' approach because each voxel is assumed to be independent of another. Importantly, VLSM does not require patients to be grouped a priori according to lesion location or performance cut-offs, but produces statistical values for each given voxel indicating whether damage to that voxel has a significant effect on the cognitive variable of interest.[29,30,31,32,33]

Although fundamental to study symptom–lesion associations, voxel-based symptoms mapping methods are limited by their assumption that each voxel can be damaged independently of other voxels. It has been recently argued that this assumption is not biologically valid, as lesions in the human brain tend to follow patterns depending, for example, on vascular supply in the case of stroke. It is possible that 'collaterally damaged' voxels may be always associated with voxels that are instead critical for a certain deficit and therefore may systematically confound lesion–symptom associations, suggesting that multivariate rather than mass-univariate approaches may be better suited to identify true anatomical correlates of deficits/symptoms.[34]

Structural MRI data can also be analysed with procedures that provide subject-specific estimated maps of grey matter volume or thickness,[35,36,37,38] which are more suitable for studying subtle structural changes and, differently from VLMS, do not rely on 'radiologically visible' and discrete lesions. Among them, *voxel-based morphometry* (VBM) involves segmentation of the grey matter, spatial transposition of all the subjects' images to the same stereotactic space, and 'modulation' to obtain voxel-specific values of grey matter density (or volume). These values can then be used in regression analyses to compare groups of individuals or perform correlations with continuous variables of behavioural/cognitive performance. This is achieved with voxel-based statistical analysis aimed at identifying, for example, distribution of voxels of significant volumetric differences between two groups, or voxels whose grey matter density significantly correlates with performance.

VBM has been particularly useful in identifying brain–symptom associations in neurodegenerative diseases, in which pathological processes causing grey matter loss or atrophy are widespread and involve different brain regions to a variable degree. They are therefore are better represented by continuous variables rather than binary measurements, which are more suited to define discrete lesions. In patients with dementia or other neurodegenerative diseases, VBM has been reliably used to identify patterns of grey matter atrophy. For example, several VBM studies[39,40,41] have found that patients with Alzheimer's disease (AD) have focal atrophy in the medial temporal lobes, posterior cingulate/precuneus, and other association areas in a pattern that mirrors the spread of neurofibrillary tangles,[42] while the behavioural variant of frontotemporal dementia (FTD) is associated with atrophy in the frontal lobes.[43,44] Semantic dementia is associated with asymmetrical anterior temporal lobe atrophy. By contrast, progressive nonfluent aphasia is associated with left perisylvian atrophy.[45] In addition, VBM has also been extensively used to make inferences on the association of focal atrophy with specific cognitive deficits.[46,47,48,49] As an example, a VBM correlational analysis in patients with frontotemporal dementia reported that severity of apathy correlated with atrophy in the right dorsolateral prefrontal cortex, whereas severity of disinhibition correlated with atrophy in mesolimbic structures.[50]

Several other MRI-based tools have been used to study volumes of a priori defined regions of interest (ROIs) or rates of atrophy over time in neurodegenerative diseases. In AD, ROI-based measures of hippocampal volumes are significantly reduced compared to age-matched controls,[51,52,53,54] and the rate of change measured from serial MRIs obtained six months or one year apart significantly increased.[55,56,57,58]

By the use of correlational analyses, VBM and ROI-based methods allow for indirect inferences about the localization of specific symptoms in patients with dementia. However, differently from lesion–symptom mapping techniques, they do not prove the *necessity* of a brain region for a specific cognitive function.

Evidence for functional specialization from functional imaging in healthy subjects

Functional imaging has revolutionized the field of brain function mapping over the last 20 years. Activation-based positron emission tomography (PET) and task-based functional MRI (task fMRI) detect changes in metabolism or blood flow while subjects are engaged in sensorimotor or cognitive tasks and can be used to produce activation maps revealing which parts of the brain are engaged. These functional techniques have

allowed extension of the concept of functional localization from the study of brain-injured patients to the study of healthy people.

PET activation studies measure focal variations in cerebral blood flow. A radiotracer is injected in the bloodstream while the subject is engaged in different tasks (usually an experimental condition and a control condition), with the assumption that blood flow will increase in brain regions where there is increased neural activity.[59] Task-based fMRI relies on the Blood Oxygen Level Dependent (BOLD) contrast, which is dependent on local changes in cerebral blood flow, cerebral blood volume, deoxyhaemoglobin concentration, local haematocrit, and changes in oxygen consumption. When a brain area is more active, it consumes more oxygen, causing an increase of blood flow and a change in the BOLD signal.[60,61] PET activation studies and task-based fMRI do not directly measure neural activity, but instead measure changes in parameters (metabolism and BOLD) correlated with neural activity that occur with a delay, limiting the temporal resolution of these techniques.

PET activation studies and task-based fMRI studies do not provide absolute measurements of physiological parameters but measure changes that occur in response to a task relative to another task, used as a control condition. By subtracting signal changes occurring during the control task from those occurring during the experimental task, it is possible to identify areas of increased activation associated with the task of interest, assuming that areas active in both control and experimental conditions have been cancelled out. To establish localization and strength of the association between the experimental condition and the measured brain changes, the functional images that have been acquired over time during different conditions and across different subjects need to be realigned and mapped into standard stereotactic, voxel-based spaces. Then, methods allowing statistical inference need to be used.

The most commonly used method to identify functionally specialized brain responses is statistical parametric mapping (SPM), which allows use of standard statistical tests on each voxel and assembles the resulting statistical parameters into images.[62] These are then used to compare different conditions and to identify regionally specific changes of signal attributable to the experimental task (Fig. **2.1**).[63] Importantly, if a significant associations is found, this does not mean that the identified area is *necessary* for the specific function or cognitive process, nor that it is *specific* for it, because it may also be involved in other functions or tasks.

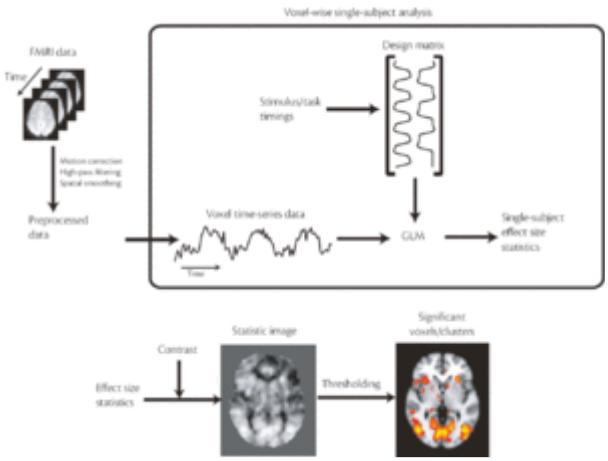

Fig. 2.1
Schematic representation of single-session analysis of fMRI data. fMRI data are acquired while stimuli are presented to the subject, who performs a task in the scanner. Data are then pre-processed (including motion correction, temporal filtering, and spatial smoothing) and entered into a regression model (general linear model, GLM) that expresses the observed BOLD response in terms of a linear combination of explanatory variables (in the design matrix) derived from stimulus/task timings and the haemodynamic response function (HRF), together with an error term. Voxel-specific effect-size statistics describe how well the modelled responses to the stimulus/task (explanatory variables) explain the continuous data. Thresholding is performed in a way that accounts for multiple comparison correction.

Courtesy of the Analysis Group of the Centre for Functional MRI of the Brain (FMRIB) from the FSL (FMRIB Software Library) course.

Since the advent of functional imaging techniques in the late 1980s and early 1990s, a huge number of studies have reported focal activations in response to specific tasks across a range of cognitive domains,[64] providing striking evidence for the concept of functional specialization. A review of these studies is outside the focus of the present chapter but a few early studies are worth considering as examples.

In a PET activation experiment, Zeki and colleagues showed that occipital area V4 is specific for colour vision, by comparing activations obtained during presentation of multicolour abstract images with those obtained during presentation of the same images in black and white, and that V5 or area MT is specific for motion perception, by comparing activations obtained during presentation of moving relative to stationary black and white patterns (see also chapter 6 for further examples).[65]

One important limitation of the subtraction method used in the early functional activation studies is that it depends on the assumption of 'pure insertion', that is, that a component process can be added into a task without affecting other processes. To modulate possible interactions between different cognitive components in neuroimaging experiments and disentangle the effect that one component has on the other, more sophisticated experimental techniques such as *factorial design* were implemented.[66] For language, a factorial design was used, as an example, to compare object naming with colour naming. It allowed identification of modality-independent naming areas in prefrontal and posterior temporal regions, and areas involved in object recognition in bilateral anterior temporal regions.[67]

The results of several functional imaging studies have challenged the traditional view of a one-to-one correspondence between brain regions and cognitive processes. On the one hand, single cognitive processes frequently elicit activation of several brain regions or distributed patterns of activations.[64,68] On the other hand, activations of single brain regions are frequently elicited by a wide range of cognitive tasks, even when these have been carefully modulated with factorial experimental designs.[68,69] Thus, although extensively supported by lesion cases and functional imaging studies, the concept of functional specialization alone may not be sufficient to explain brain functioning and organization in human.

Network organization of cognitive functions

Towards the concept of distributed functional networks

Wernicke had first suggested that complex cognitive functions such as language result from distributed systems of linked focal brain regions. He proposed a model of language as a multi-component process, in which each component has a specific anatomical localization but is connected to the other components, reconciling evidence for functional specialization that he and others had provided with the notion that cognitive functions depend on integrated functioning across brain regions.[4] He even hypothesized the existence of a *conduction aphasia* that would be associated with a lesion of the pathways connecting the left hemisphere frontal and temporal lobe centres, characterized by preserved fluency and comprehension but impaired repetition and paraphasic speech (the use of incorrect words or phonemes while speaking).

In addition to conduction aphasia, other 'disconnection syndromes' resulting from damage of white matter tracts between cortical areas were described. As an example, alexia without agraphia, in which patients are

able to write and speak but cannot read, was first described by Dejerine 1891 and associated with lesions to the white matter in proximity of the angular gyrus that interrupt the connections between the visual cortex and language areas. In 1965, the anatomical bases of disconnection syndromes were reviewed by Geschwind[70,71] who provided a theoretical framework that paved the road for modern concepts of distributed brain networks.[72] Around the same time, Alexander Luria, one of the founders of neuropsychology, proposed a model of human mental processes based on complex functional systems or 'functional units' that involved groups of brain areas working in a coordinated, hierarchical, and organized way.[73]

Related to this ideas is the notion that a lesion can cause functional damage 'remote' from the anatomical site of the lesion. This concept was extensively studied by Monakow who coined the term *diaschisis*—loss of function due to transient, indirect damage to remote parts of the brain not anatomically close to the site of the primary injury but functionally connected to it.[74] His work fostered the view of the brain as a complex, dynamic system in which function could be lost transiently. Evidence for diaschisis comes from functional imaging studies that show hypometabolism in regions remote from the cortical lesion,[75] demonstrating directly the existence of remote functional effects.[76]

These ideas led to the refutation of functional localization as the sole and sufficient explanation of brain function. Brain–symptom correlations started to be searched not only in specific, single brain regions but also in larger-scale networks connecting different regions across the brain. With the additional benefit of knowledge about anatomical structural connections from tracing methods in the autopsied brain, Mesulam proposed a model of brain function based on distinct, multifocal large-scale functional systems.[77] In his scheme, there is a spatial attention network anchored in the posterior parietal and dorsolateral frontal regions, a language network involving Wernicke's and Broca's areas, a memory network linking the hippocampus and inferior parietal cortex, a face/object recognition network anchored in temporal cortices, and a working-memory/executive-function network connecting prefrontal and inferior parietal cortices.[78]

Subsequently, McIntosh demonstrated the existence of networks by measuring the covariance of activity between regions in PET activation studies, thus identifying patterns of co-variation or *functional connectivity.*[79] For example, he studied people who had learned that an auditory stimulus signalled a visual event and found activation in left occipital visual areas when auditory stimuli were presented alone. He

then showed that this occipital activation correlated with activation in the prefrontal cortex and that it accounted for most of the change in occipital activity.[80]

It is now widely accepted that the brain functions through large-scale networks including multiple specialized cortical areas reciprocally connected with parallel, bidirectional, and multisynaptic pathways. Thus deficits can be caused either by damage to specialized cortical areas, by damage to their connecting pathways, or both.[72,81,82]

Neuroimaging methods to study brain connectivity

Several methodological advances have allowed study of brain connectivity and large-scale brain networks from different perspectives. *Functional connectivity* refers to the functional relationship between brain regions inferred by searching for correlations in the fMRI signal between two or more brain regions (functional covariance). The structural bases of this relationship are ultimately assumed to exist through mono- or multisynaptic pathways.[83,84]

Correlations in the fMRI signal (BOLD signal) can be studied among regional changes occurring in response to cognitive tasks but also among regional changes that occur in the absence of tasks, while participants are simply at rest (resting fMRI). In fact, it has been shown that the BOLD signal not only changes as a consequence of cognitive or 'task-related' demand, but also shows low frequency spontaneous fluctuations (0.01–0.1 Hz) that are temporally correlated and organized within specific spatial patterns in the brain.[85,86] The networks of brain regions whose spontaneous activity rises and falls coherently have been termed *resting state networks*.

To study functional correlation, a 'seed' voxel or anatomical ROI is 'seeded' to generate a correlation map showing all other regions in which signal changes significantly correlate with those within the seed region (seed-based correlation analysis). This approach is *hypothesis-driven* and requires a priori selection of the ROI or 'seed'. Alternatively, a more exploratory, *data-driven* approach can be used to create a matrix of correlations across each voxel/region with all other voxels/regions in the brain. Correlation matrices can be decomposed into spatial modes using, for instance, principal component analysis (PCA) or independent component analysis (ICA) to identify large-scale networks or maps of spatially independent and temporally correlated functional signals.[87,88,89]

Among the several resting state networks identified with ICA-based approaches, the *default mode network* (DMN, Fig. **2.2A**)—which includes

posterior cingulate cortex and precuneus, the medial prefrontal cortex, and lateral parietal regions—is considered to be specifically engaged during task-independent introspection or self-referential thought. The DMN was fist identified in task-related fMRI by studying task-induced *deactivations* (i.e. decreases in BOLD signal during experimental conditions compared to baseline or resting conditions).[90] It can also be identified with 'seed-based' methods examining correlations from regions such as the posterior cingulate.[91,92]

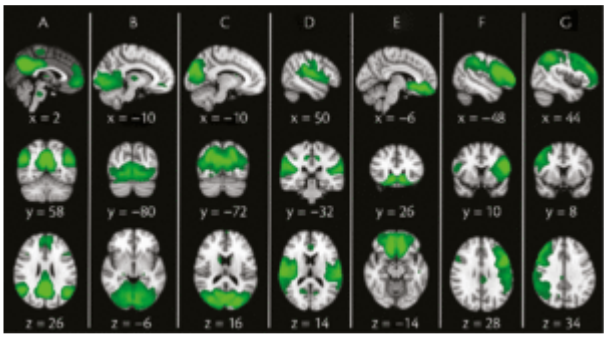

Fig. 2.2
Resting state networks (RSNs). Spatial maps of resting state networks (RSNs) obtained using independent component analysis (ICA). The three most informative orthogonal slices for each RSN are shown. A) DMN; B) ventromedial visual RSN; C) dorsolateral visual RSN; D) auditory RSN; E) orbitofrontal RSN; F) left frontoparietal RSN; G) right frontoparietal RSN. Coordinates are in MNI.

In addition to the DMN, other commonly identified networks are the 'executive control' networks linking dorsofrontal and parietal regions, the 'salience' network linking anterior cingulate to insular and limbic regions, and networks related to primary visual, auditory, and sensorimotor regions (Fig. **2.2**).[86,88,89,93,94] Resting state networks (RSN) have been shown to be consistent across subjects[95] and to match activations found in task-based fMRI studies, suggesting that they reflect functionally significant brain networks.[96,97,98]

Effective connectivity represents another way to study functional correlations and network function. Different from functional connectivity, this method incorporates additional information such as anatomical

constraints and considers interactions of several brain regions simultaneously. It is aimed at explicitly quantifying the influence that one region has on another and establish whether their connections are causal and have a specific directionality (from region A to area B rather than B to A).[100] Effective connectivity approaches include *dynamic causal modelling* (DCM) that allows testing of specific models of how different parts of a functional network are dynamically linked and coupled. DCM is less 'model-free' and more hypothesis-driven (and more computationally sophisticated) than functional connectivity. It tests dynamic interactions and is therefore task-dependent and condition-specific, and has been mainly applied to task-based fMRI studies, although it has been recently extended to modelling of resting-state data and comparing multiple different models.[101,102]

The principles used to investigate functional and effective connectivity from fMRI data can also be applied to data obtained with neurophysiological techniques such as electro-encephalography (EEG) and magnetoencephalography (MEG), allowing mapping of networks at high temporal resolution as well as studying frequency band-specific interactions.[103,104]

Structural connectivity refers to the white matter connections between brain regions. These can be visualized with tracing methods in animals or *ex vivo* methods in autopsied human brains, or inferred *in vivo* with structural imaging techniques such as diffusion tensor imaging (DTI). DTI can be used to estimate the structural integrity of brain connections (i.e. axons and fibre tracts) by measuring diffusion of water molecules through tissues.[105] It provides measures of fractional anisotropy (FA), a particularly sensitive index of microstructural integrity of cerebral white matter, and of radial and axial diffusivity, which give indications of axonal damage and demyelination, respectively. Common methods to assess structural disruption are voxel-wise[106] or diffusion tensor imaging tractography (see chapter 8).[107] Structural connectivity can also be estimated by studying the correlation among regional structural measures such as local cortical thickness and volume across subjects (anatomical covariance), in a way similar to functional connectivity.[108,109] Structural covariance does not demand existence of a direct anatomical connection between the regions whose structural measures are correlated. As with functional covariance, the identified connections might not reflect axonal pathways and caution is required in interpreting the results. Nevertheless, networks identified using this approach have been found to reflect genetic influences as well as experience-related plasticity reliably.[110]

Brain networks derived from all the methods described above can be examined using *graph theory* in which connectivity elements (single brain regions or maps of resting state networks) are defined as *network nodes* and their mutual relationships as *network edges*. In this way, brain networks can be mathematically described as graphs which, in their simplest form, correspond to correlations matrices representing the strength of edges between pairs of nodes. At the highest level of abstraction, even the whole brain can be defined as a network and its properties described in terms of number of edges per node, resistance to damage, efficiency, hierarchy, and sub-networks, among other graph theory measures.[111,112] Although graph-theoretical approaches have several limitations, including the high dependence on how nodes are initially defined (with structural atlas-based or functional parcellations) and their high degree of abstraction, they have the potential of becoming more meaningful and interpretable in the near future.[113]

Large-networks abnormalities in neurodegenerative diseases

Connectivity methods have now been applied to neurological diseases. This has been particularly promising in the context of neurodegenerative diseases, which are associated with gradual and specific patterns of progression of pathology across the brain. Indeed, it has been increasingly suggested that different pathologies target specific large-scale networks.[114,115]

Since its identification, the DMN has been shown to be particularly relevant for AD, since it includes regions know to be vulnerable to atrophy, amyloid deposition, and reduced metabolism in patients with AD.[116] DMN functional connectivity is reduced in patients with AD compared to healthy controls.[117] Similarly, ROI-based studies using the hippocampus or the posterior cingulate as ‘seeds’ show decreased functional connectivity with regions of the DMN such as the medial prefrontal cortex, but increased functional connectivity with frontal and frontoparietal regions.[118,119,120,121]

More recent studies that used ICA-based methods confirm that patients with AD have significant decreased functional integrity and connectivity in regions of the DMN.[122,123,124,125] Among them, the few studies that also explored other resting state networks[99] found that that functional connectivity within frontal and frontoparietal networks is increased in patients with AD relative to controls, thus having the opposite connectivity effect than the DMN.[99,123,124,126] Importantly, these most recent studies examined changes in functional connectivity occurring over and above the structural changes that occur in neurodegenerative

diseases by including VBM measures of atrophy as a covariate of no interest.

A number of resting-state fMRI studies have explored functional connectivity in other neurodegenerative diseases. For example, in patients with behavioural variant of frontotemporal dementia, functional connectivity was decreased in the salience network and increased in the DMN, a pattern opposite to the one found in patients with AD.[127] In patients with Parkinson's disease, functional connectivity is reduced in a network involving basal ganglia, and normalizes upon administration of dopaminergic medication.[128]

Do resting state networks identified with resting fMRI relate to actual brain functioning in response to cognitive demand? In healthy people, it has been increasingly shown that functional networks at rest reflect those utilized 'actively' during execution of tasks.[96,97,98] A recent study which combined resting and task-based fMRI also showed that this is true in patients, suggesting changes in functional connectivity secondary to neurodegenerative disease might directly reflect residual cognitive functioning in patients.[99] Effective connectivity has also been used in neurodegenerative diseases.[129]

In a seminal study combining anatomical covariance and functional connectivity,[130] Seeley and colleagues investigated patterns of atrophy of five different neurodegenerative syndromes (Alzheimer's disease, corticobasal degeneration, and the three variants of frontotemporal dementia) shown in blue in Figure **2.3**). Using the identified regions of greater atrophy in each disease as a 'seed', they then showed that in healthy people, seed-based covariance patterns of structural (Fig. **2.3**, green) and functional (Fig. **2.3**, yellow) measures mirrored syndrome-specific patterns of atrophy. This suggested that networks of functional and structural connectivity in the healthy brain are differentially vulnerable to specific neurodegenerative disease. More precisely, AD affects the DMN, the behavioural variant of frontotemporal dementia affects the salience network, semantic dementia targets the left temporal polar network, progressive non-fluent aphasia the left frontoparietal network, and corticobasal degeneration the sensory-motor network.

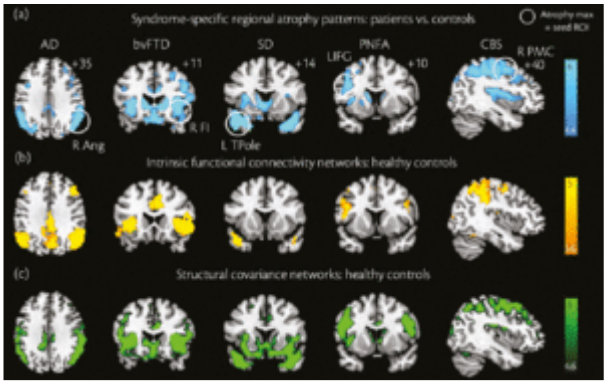

Fig. 2.3
Results of the study from Seeley, *et al*.[130] Syndrome-specific atrophy patterns (in blue), whose cortical maxima (circled) provided seed ROIs for functional (in yellow) and structural (in green) covariance analyses in a group of healthy controls.

In a subsequent study, the same authors further explored network properties of each region found to be atrophic in the five neurodegenerative diseases to identify regions whose normal functional connectivity profile best overlapped with disease-specific patterns of atrophy (which they termed ‘epicentres’). They then used graph-theoretical methods to explore possible models of disease spread and reported evidence for a model of trans-neuronal spread from highly vulnerable disease epicentres that, in healthy people, represent highly connected nodes or network hubs.[131]

Graph theory principles have also been applied to measures of cortical thickness covariance to explore network properties in patients with AD. Patients with AD have increased local connectivity of nodes (increased clustering) but decreased global efficiency (increased edges length between connected nodes), suggesting that AD is characterized by a deficit in long-range connectivity and associated with a reversion to less optimal connectivity and more localized connections.[132] AD patients also showed changes in the efficiency of specific nodes, with significant decreased efficiency in heteromodal temporal and parietal regions, and increased efficiency in frontal and occipital regions, in line with findings from functional connectivity.

One recent study specifically tested if network hubs, identified using DTI, in the normal brain are indeed vulnerable to specific brain disorders.[133] Analysis of data from published MRI studies suggests these hubs are atrophic across twenty-six different neurological and psychiatric conditions. More precisely, nine diseases including AD and schizophrenia have atrophy located in specific highly connected regions; that is, temporal lobe hubs were specifically associated with AD, whereas frontal and temporal cortical hubs were associated with schizophrenia. Similar results were obtained when highly connected hubs were derived from functional connectivity calculated from a meta-analysis of task-related functional imaging studies, rather than from DTI. The authors concluded that highly connected regions within networks identified with different connectivity modalities are more likely to be anatomically affected by brain disorders.

Future directions

The contraposition between the concepts of functional specialization and connectivity has been a major theme in the history of neuroscience. While evidence discussed in the first part of this chapter demonstrates the existence of functionally specialized areas, a growing body of knowledge discussed in the second part shows the importance of connections for brain functioning. Network approaches account for connectivity and nodal or regional specialization, offering the promise to reconcile these seemingly opposing perspectives.[134] Several worldwide initiatives have been recently set up with the aim of describing comprehensively all macroscopic functional and structural connections of the healthy brain, by mapping what has been termed ‘human connectomes’[135] (for a complete list of current research projects into macroscale connectomics, see reference 136). Some argue that this will help to attain a fundamental understanding of brain architecture and its relation with cognition and behaviour. Ultimately, it is hoped that it will be clinically useful to obtain individual-relevant reliable indices that can be used for identification of people at risk of specific diseases, prognostication, and measurement of treatment response.

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