Resting-State Functional MR Imaging: A New Window to the Brain[1]

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Learning Objectives:

After reading the article and taking the test, the reader will be able to:

- Explain the basic methodology of resting-state (RS) functional MR imaging
- Name major resting-state networks (RSNs) commonly identified at RS functional MR imaging
- Describe the evolution of RSNs during the lifespan, including maturation of RSNs during development and decrease during aging
- Discuss involvement of RSNs in alterations of consciousness, psychiatric diseases, and dementia
- Describe strengths and limitations of currents concepts of RS functional MR imaging and consequently current trends and improvements

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Resting-state (RS) functional magnetic resonance (MR) imaging constitutes a novel paradigm that examines spontaneous brain function by using blood oxygen level–dependent contrast in the absence of a task. Spatially distributed networks of temporal synchronization can be detected that can characterize RS networks (RSNs). With a short acquisition time of less than 10 minutes, RS functional MR imaging can be applied in special populations such as children and patients with dementia. Some RSNs are already present in utero, while others mature in childhood. Around 10 major RSNs are consistently found in adults, but their exact spatial extent and strength of coherence are affected by physiologic parameters and drugs. Though the acquisition and analysis methods are still evolving, new disease insights are emerging in a variety of neurologic and psychiatric disorders. The default mode network is affected in Alzheimer disease and various other diseases of cognitive impairment. Alterations in RSNs have been identified in many diseases, in the absence of evident structural modifications, indicating a high sensitivity of the method. Moreover, there is evidence of correlation between RSN alterations and disease progression and severity. However, different diseases often affect the same RSN, illustrating the limited specificity of the findings. This suggests that neurologic and psychiatric diseases are characterized by altered interactions between RSNs and therefore the whole brain should be examined as an integral network (with subnetworks), for example, using graph analysis. A challenge for clinical applications of RS functional MR imaging is the potentially confounding effect of aging, concomitant vascular diseases, or medication on the neurovascular coupling and consequently the functional MR imaging response. Current investigation combines RS functional MR imaging and other methods such as electroencephalography or magnetoencephalography to better understand the vascular and neuronal contributions to alterations in functional connectivity.

Brain function can be studied in vivo by using a variety of noninvasive methods. Electroencephalography (EEG) and magnetoencephalography (MEG) measure electrical activity directly linked to the function of groups of neurons and have excellent temporal resolution. Functional magnetic resonance (MR) imaging based on blood oxygenation level–dependent (BOLD) contrast (1–3) has much better spatial resolution, but measures a downstream effect modulated by neurovascular coupling (ie, a local vascular effect in response to a neuronal activation) with a typical delay of 4–6 seconds. The physiologic basis of the functional MR imaging response has been investigated by direct comparison of functional MR imaging and intracortical recordings in the monkey, showing that functional MR imaging signal corresponds best to local field potentials (4,5).

Initially, functional MR imaging was developed to measure changes in BOLD contrast between two conditions (eg, task and no task, the no-task condition often referred to as "rest"). Many signal averages are needed to create stable measures for each condition, due to fluctuations occurring due to MR imager and physiologic noise. Such fluctuations also contain meaningful information related to spontaneous brain activity (6), much like the waves occurring in EEG and MEG where such temporal signals have a spatially dependent pattern, referred to as functional connectivity networks.

One of the first functional MR imaging networks described is the so-called default mode network (DMN) (7). In many task functional MR studies, reversed contrasts (ie, focusing on decreased activity during task performance) revealed consistent deactivation of regions in the precuneus, parietal cortex, and orbitofrontal regions (6). Since this network seems most active in the absence of a task, the name DMN was coined (7) in analogy to the "system-idle" function on Windows computers.

The DMN can also be identified from so-called resting-state (RS) (or "no-task") functional MR studies. Instead of imposing an external task, the RS BOLD fluctuations can be analyzed by using data-driven types of analysis techniques, such as independent component analysis, that decompose the RS functional MR data sets into spatial patterns with temporal correspondence (8). This has led to the description of 10–20 RS networks (RSNs), including the DMN, that are remarkably consistent across subjects and time (9). Common RSNs are illustrated in Figure 1 and described in Table 1.

One of the main advantages of RS over task-based functional MR imaging is the lack of restrictions to a single domain (presumably probed specifically by a task) with a limited number of stimulus intensities (which may be too simple or too complex for a given subject). Also, RS functional MR imaging can be applied to populations incapable of performing task-based functional MR imaging such as children, subjects with dementia, and patients with reduced consciousness (coma or sedation). More fundamentally, task-based functional MR imaging examines just one domain and its related network, while RS functional MR imaging probes all networks and their inter-relationships simultaneously.

RS functional MR imaging is gaining substantial attraction in the neuroscience community and several clinical applications are starting to emerge, some of which will be discussed in the review. RS functional MR imaging is opening a new window to the brain with unprecedented possibilities. This is well illustrated by the rapidly increasing numbers of publications and dedicated new journals, as well as in funding opportunities such as the Human Connectome Project.

Essentials

- Resting-state (RS) functional MR imaging overcomes limitations of task-based MR imaging by probing multiple neuronal networks simultaneously during a 5–10-minute acquisition and reveals brain physiology.
- RS functional MR imaging can be used to identify alterations in functional connectivity in many neurologic and psychiatric diseases, even in neonates and in patients with coma or dementia.
- Data analysis techniques are still evolving from simple region of interest–based correlation analyses to data-driven methods, graph theory, and pattern recognition.
- Neurologic and psychiatric diseases are often characterized by complex alterations in the pattern of multiple functional networks, not only by single networks such as the default mode network.
- Better understanding of physiologic and pharmacologic effects and confounds are needed before clinical application can be established.

Data Acquisition and Analysis Techniques

Data acquisition for RS functional MR imaging is very similar to task-based functional MR imaging. T2*-weighted imaging is applied for sensitivity to the BOLD signal, most often using multisection echo-planar imaging, acquiring data section by section, with reasonable spatial resolution (typically 3–4 mm isotropic) and a typical temporal resolution of 2–3 seconds to image the whole brain. Typical total acquisition time is 5–10 minutes, yielding 100–300 whole-brain volumes. Experiments suggest that acquisition times as short as

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Abbreviations:
AD = Alzheimer disease
ADHD = attention deficit hyperactivity disorder
ASD = autism spectrum disorders
BOLD = blood oxygenation level dependent
DMN = default mode network
EEG = electroencephalography
MEG = magnetoencephalography
RS = resting state
RSN = RS network

Conflicts of interest are listed at the end of this article.

Figure 1

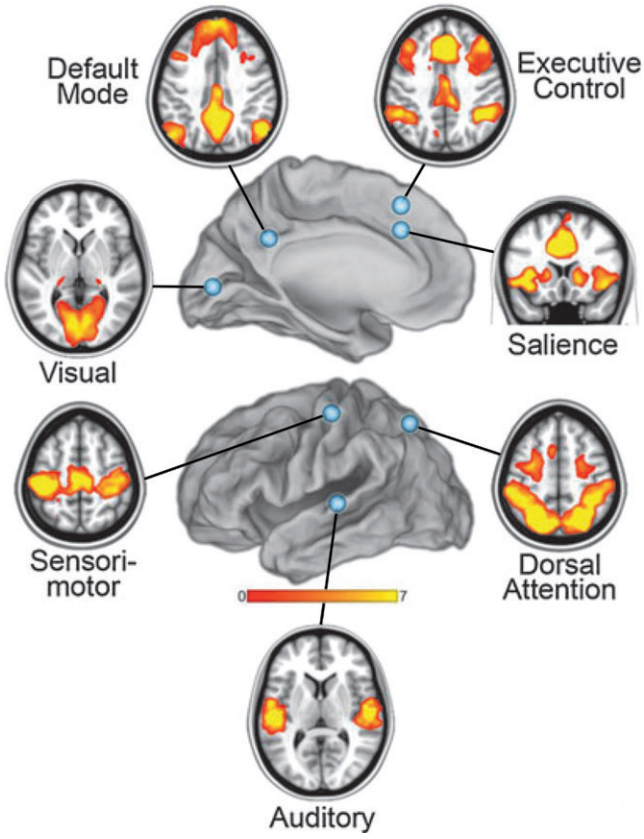


Figure 1: Typical RS functional connectivity networks in healthy control subjects. Mean RS functional MR imaging networks shown in axial view and three-dimensional reconstructions. Colors represent percentage BOLD signal change, overlaid on the average anatomic images in standard space. More detailed information on the function of these networks is given in Table 1. (Reprinted, with permission, from reference 188.)

5 minutes are long enough to get stable measures of functional connectivity (10,11), although others showed that reliability greatly improves when increasing the acquisition time to 13 minutes (12). In specific cases, longer acquisition times may be required to allow a more in-depth analysis.

More recently, "multiband accelerated" echo-planar imaging has been developed (13). With this technique, multiple sections are acquired simultaneously rather than section by section, allowing whole-brain functional MR imaging coverage in less than 1 second (down to 0.5 second) at a spatial resolution as low as 2 mm isotropic (Table 2). Although only a few studies have been reported (14–16), this faster imaging allows more accurate sampling of physiologic confounds and potentially increases the sensitivity to detect RS functional MR imaging networks in the brain.

Increasing field strength is theoretically beneficial for RS functional MR imaging, since signal-to-noise and contrast-to-noise ratios increase with field strength (17,18). Although scanning at 1.5 T can work well, most RS functional MR imaging studies are performed on 3-T imagers. With the installation of (ultra) high-field-strength imagers of 7 T or more, technical developments are ongoing to allow whole-brain RS functional MR imaging at high field, attempting to benefit from increased signal-to-noise and contrast-to-noise ratios and therefore improved spatial specificity of functional connectivity measures.

Table 1

Commonly Detected RSNs

RSN	Description
DMN	Precuneus and posterior cingulate, bilateral inferior–lateral–parietal and ventromedial frontal cortex. Involved in introspection and active episodic memory; becomes deactivated during specific goal-directed behavior
Visual processing network	Striate cortex, occipital pole, and lateral visual areas. Mostly primary visual cortex, but extending to higher-order visual processing
Sensorimotor network	Primary sensorimotor cortex, supplementary motor area and secondary somatosensory cortex. Detection and processing of sensory input and preparation and execution of motor functions
Executive control	Mesiofrontal areas, including anterior cingulate and para-cingulate cortex. Involved in executive control and working memory function
Salience network	Dorsal anterior cingulate cortex and bilateral insulae. The network responds to behaviorally salient events
Dorsal attention	Superior parietal and superior frontal areas, including intraparietal sulcus and frontal eye-fields. Involved in voluntary (top-down) orienting and selective attention
Auditory network	Superior temporal gyrus, including Heschl gyrus, including primary auditory and associated areas

Table 2

Typical Parameters of T2*-weighted Imaging for RS Functional MR Imaging

Parameter	Multisection Echo-Planar Imaging	Multiband accelerated Echo-Planar Imaging
Echo time (msec)	30–40	30–40
Repetition time (msec)	2000–3000	500–1500
Flip angle (degree)	80–90	50–70
Voxel size (mm)	3–4	2–3

Note.—Multisection echo-planar imaging is most often used for RS functional MR imaging. More recently, multiband accelerated echo-planar imaging has become available, allowing whole brain coverage below 1 second.

Figure 2

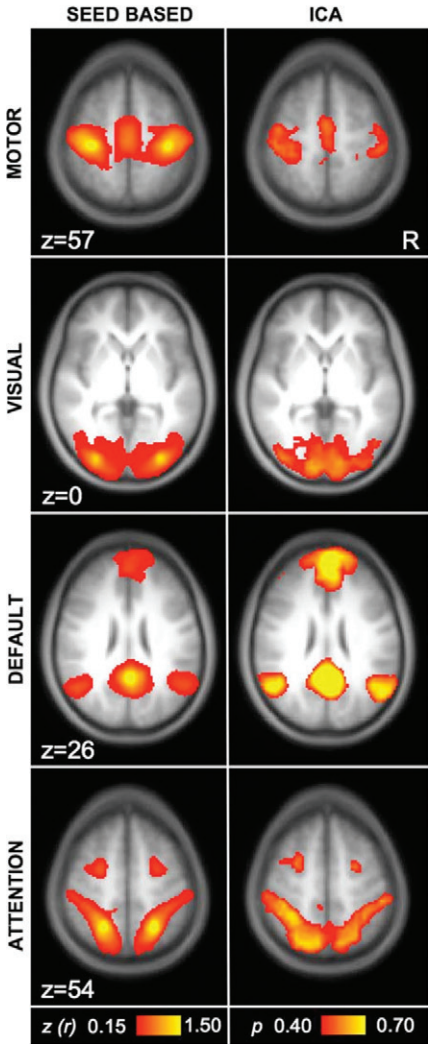


Figure 2: Comparison of seed-based and independent component analysis–based RSNs. Similar functional connectivity results are obtained by seed-based and independent component analysis *(ICA)* techniques. Left: Images obtained using seed-based RS functional MR imaging for regions within motor, visual, default, and attention networks. Right: Images obtained from the same data using independent component analysis as implemented by FSL (FMRIB software library) software. Note that the two approaches, for the networks analyzed, yield convergent results. (Reprinted, with permission, from reference 10.)

Given the technical challenges at 7 T, the more readily available 3-T systems will likely remain the dominating field strength in the coming years.

With some exceptions, the instruction to subjects during RS functional MR acquisition is either to keep eyes open or closed (with indications that eyes closed gives weaker temporal BOLD connections throughout the brain [10]), not to fall asleep, and not to think of anything in particular. Some investigators instruct subjects to focus on a fixation point. Since the precise instruction can affect functional connectivity (ie, eyes open versus eyes closed) (10,19), it is important to have instructions consistent across subjects within a study. Little is known about the confounding effects of coffee, nicotine, and food intake on RS functional connectivity.

Physiologic confounds have received much attention in RS functional MR imaging analyses (20–22), in contrast to task-based functional MR imaging. Important confounding factors are physiologic signals associated with heartbeat, respiration, and motion. Connectivity between brain regions can be suggested on RS functional MR images if different brain regions share variance caused by these physiologic signals. Correction methods have been developed to avoid these "noise" connections (10,21,23,24) (see below).

The aims of analyzing RS functional MR data are to generate statistical maps of significant temporal BOLD connections between brain regions (functional connectivity) and study differences in patients or changes after an intervention. In standard analyses one assumes that over the time period of acquisition (ie, 5–10 minutes), the functional connections are not changing. Preprocessing techniques are similar to those routinely applied in task-based functional MR imaging analyses, including motion correction, temporal and spatial filtering, and image registration to standard space. An important difference with task-based functional MR imaging is that data cannot be analyzed by using a model of expected task-related brain activation and require alternative methods for analysis.

Various techniques exist to determine functional brain connectivity maps; here we discuss two popular methods (Fig 2):

Seed-based correlation analysis (10,24) requires an a priori definition of one or more region(s) of interest. The spontaneous RS functional MR imaging signal of the seed region is used as input function to determine for each voxel whether or not it is connected with the seed using correlation or general linear model techniques. Physiologic confounds can be removed in the preprocessing phase if such signals have been registered during imaging. Alternatively or additionally, sources of noise (white matter and cerebrospinal fluid signals) can be included in the statistical model to account for temporal variance associated with these regions.

Independent component analysis (8,24–26) is a technique to separate a complex dataset into additive sub-datasets. When applied to RS functional MR imaging data, independent component analysis decomposes the RS functional MR imaging data into so-called spatial components. Each component consists of a collection of brain regions with an internally consistent temporal signal (ie, regions within a component are functionally connected). Independent

component analysis identifies RSNs, but also identifies components of non–gray matter signals, physiologic artifacts, and noise (8), implying that user-induced corrections for these signals may not be necessary. Whereas seed-based correlation analysis is a univariate technique (analyzing the correlation of the seed region with each other voxel separately, disregarding the relationships between multiple data points), independent component analysis is a multivariate technique, taking into account relationships between multiple data points.

These and other techniques show test-retest reproducibility of RS functional MR imaging to be low (27) to moderate to high (10,19,28–30) to outstanding (31). Differences in data acquisition, data analysis, and physiologic variations—for example, depending on the time of day or prior consumption of caffeine—may explain these reproducibility differences. Those factors indicate the need for strict standardization of RS functional MR imaging with respect to clinical applications.

Welcome to the Matrix

The majority of RS functional MR imaging studies analyze connectivity between specific brain regions or networks and the rest of the brain. Analysis techniques include seed-based correlation and independent component analysis (see above). One drawback is that interconnectedness between such networks and between the full ranges of brain regions may be neglected. Graph theory describes the whole brain as a single interrelated network. Stimulated by work in the field of EEG and MEG, advances in RS functional MR imaging analyses have made graphs applicable to study brain networks, a rapidly developing field (32–34).

Graph analyses first require the definition of so-called nodes (functionally homogeneous brain regions). Nodes can be anatomically defined in standardized anatomic space, which may not appropriately reflect individual functional and structural variability, and disturb network estimation methods (33). Alternative definitions of nodes are the use of individual voxels, although this can be computationally problematic. Using complete RSNs as nodes may also be problematic, since these are complex networks themselves rather than homogeneous nodes (33). Functional parcellation techniques defining functionally homogeneous regions in each individual based on their RS functional MR imaging data are promising for this purpose (35) but have not been applied yet.

Next, connections between the nodes are determined. Approaches include (partial) correlations, causality measures, and coherence measures (for a more extensive overview [33]). For example, using simple correlations, matrices can be presented, showing all node-to-node connections, which are often binarized to facilitate feature extraction (Fig 3).

Using the resulting network estimation of connected and unconnected nodes, measures to examine the properties and topology of the brain as a complex network can be determined (32,36). Typical measures are: *(a)* Centrality: how prominent are nodes in a network? *(b)* Node degree: number of connections of a node; *(c)* Degree distribution: the distribution of the number of node connections; *(d)* Characteristic path length: average length of all node-to-node connections; *(e)* Modularity: the formation of subnetworks of nodes. Reviews on this topic provide an extensive description of measures to characterize network topology (32,34).

These network measures show that the brain's overall organization appears efficient, having a modular and so-called small-world structure (37–39). The latter represents an optimal organization of local specialization and global integration at reduced wiring costs. Patient studies using graph theory with RS

Figure 3

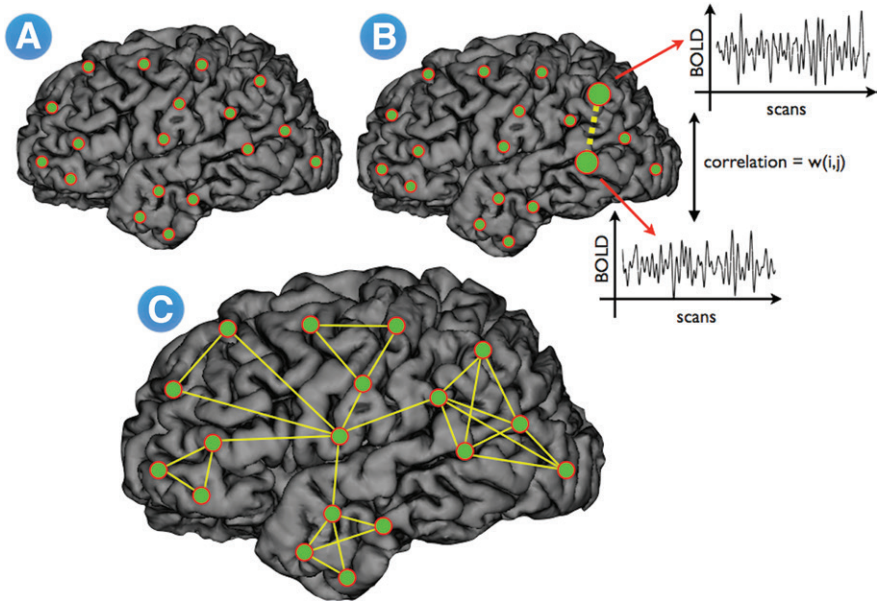
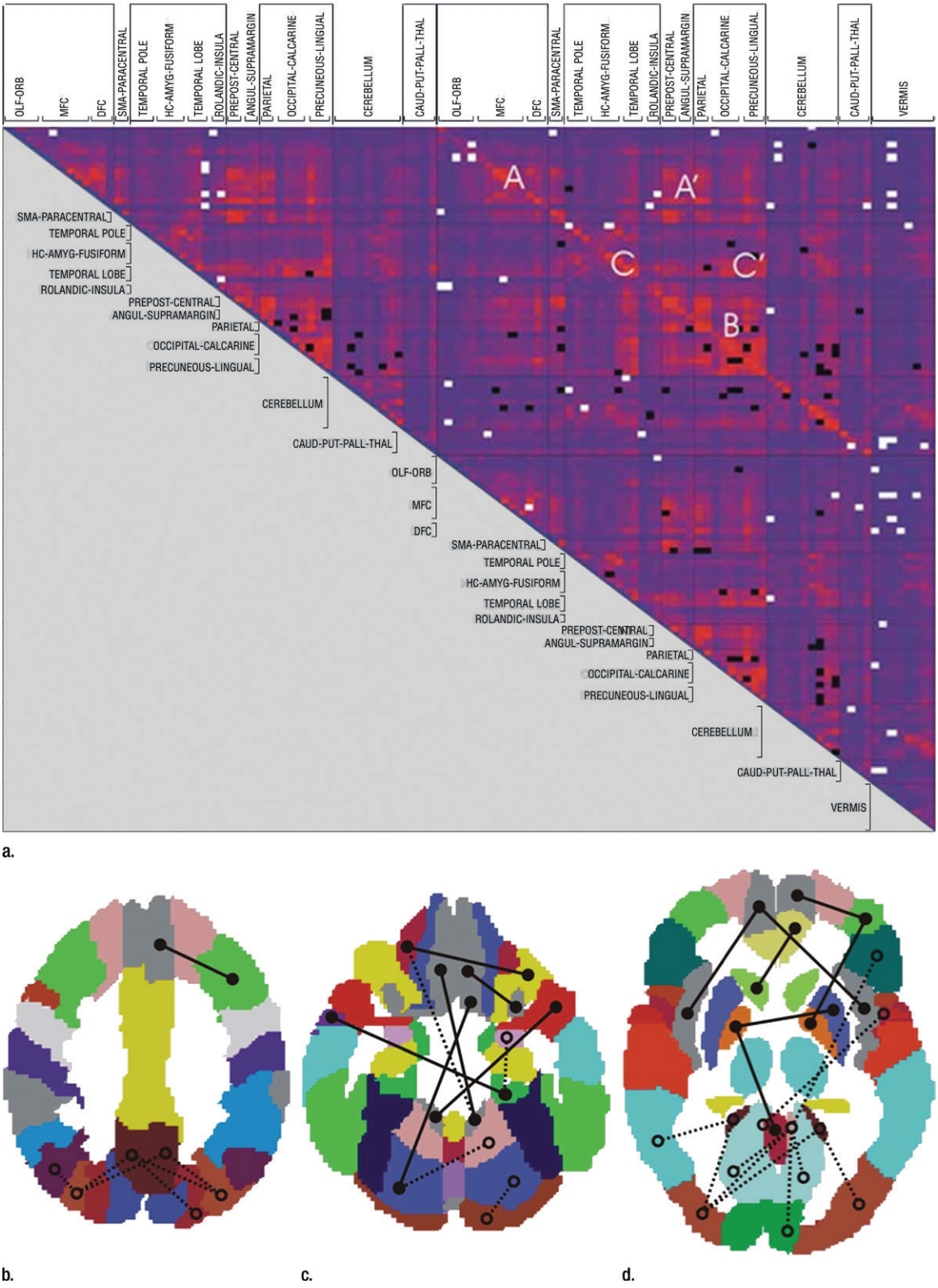


Figure 3: Modeling the functional brain network. The functional brain network can be represented as a graph, consisting of nodes and connections between regions that are functionally linked. First, the collection of nodes is defined. These can be brain regions, defined by a preselected template *(A)*. Second, the existence of functional connections between nodes in the network needs to be defined (eg, level of correlation between the nodes). Within a graph approach, level of functional connectivity between each possible pair of nodes in the network is computed (ie, between all possible regions or voxel pairs), resulting in a connectivity matrix *(B)*. Finally, the existence of a connection between two points can be defined as whether their level of functional connectivity exceeds a certain predefined threshold. This results in modeling the brain as a functional network with connections between regions that are functionally linked *(C)*. (Reprinted, with permission, from reference 34.)

Figure 4


OLF-ORB
MFC
DFC
SMA-PARACENTRAL
TEMPORAL POLE
HC-AMYG-FUSIFORM
TEMPORAL LOBE
ROLANDIC-INSULA
PREPOST-CENTRAL
ANGUL-SUPRAMARGIN
PARIETAL
OCCIPITAL-CALCARINE
PRECUNEOUS-LINGUAL
CEREBELLUM
CAUD-PUT-PALL-THAL
VERMIS
A
A′
C
C′
B
a.
b.
c.
d.

functional MR imaging are emerging. Findings include changes in global and local networks in Alzheimer disease (AD) (Fig 4) (40,41) and abnormal network characteristics in schizophrenia (42). Despite differences in source and temporal resolution, the spatial structures of RSNs defined by MEG are similar to those with RS functional MR imaging (43), and global characteristics of network organization are comparable between the two techniques (eg, 44–46).

The relation between functional (RS functional MR imaging) and anatomic (diffusion tensor imaging) connectivity is of interest to further understand normal brain connections and potential alterations in these relations in neurologic and psychiatric diseases. Graph analysis offers a method to study this interrelation. Network parameters appear comparable between anatomic and functional networks, and structural connections are highly predictive of functional connections (32,38,47). Further, RS functional MR imaging connectivity is "constrained by, but not fully dictated by" anatomic connectivity (48). However, the exact relationship in controls, and the potential change of this relation in disease, is currently unknown.

Brain Development and Normal Aging

The majority of RSNs show an evolution during the lifespan, most dramatically during gestation and infancy, but carrying on into old age. The majority of RSNs are highly mirror symmetric, implicating interhemispheric transcallosal connections of homologous areas. While the number of callosal axons increases massively during gestation and the postnatal period, a substantial portion of axons are in fact transient and eliminated competitively during the early postnatal period (49). By contrast, the number of neurons, which are the dominant source of the BOLD response, remains almost constant (50), but obviously their connections (in networks) develop well into adulthood by the process of arborization and dendritic maturation. As a consequence of neuroanatomic evolution, RSNs evolve during the lifespan.

Basic RSNs are firmly established at term age (51). Even in preterm infants, emerging RSNs can be detected during the period of rapid neuronal growth in the last trimester of gestation (52). The significant longitudinal changes in RSNs in the preterm period parallel the rapid neuroanatomic changes in the last trimester (53). This implies that RSNs are formed before the acquisition of cognitive competencies in later childhood, and that at least some form of consciousness must be present in utero.

Networks in preterm infants have strong interhemispheric and limited intrahemispheric connectivity (54). This pattern differs from the neural networks described in adults, which are characterized by both interhemispheric and intrahemispheric connectivity (53). Precursors of the DMN are present in normal term infants but not in preterm infants even at term-equivalent age (53). Moreover, thalamocortical connections, critical for neurodevelopment, demonstrate substantial differences between term and premature infants at term. In preterm infants, the degree of alteration of RSNs depends on the severity of periventricular white matter damage (55).

Maturation of networks proceeds well into infancy. The DMN, for example, seems to consist of individual subunits in 5–8-year-old children, most likely reflecting immaturity (56), and at the age of 7–9 years, the DMN subregions are only sparsely connected (57). In addition to these cortical–cortical interactions, cortical–subcortical interactions such as thalamocortical connectivity also mature from childhood to adolescence and adulthood (58). Whole-brain functional connectivity continues to evolve from children (11–13 years) to young adults (19–25 years) with a complex change in the size of functionally connected regions and the strength of their connections (59). Overall, the development of RSNs from 7 to 30 years of age follows a nonlinear asymptotic growth (Fig 5) curve

Figure 5

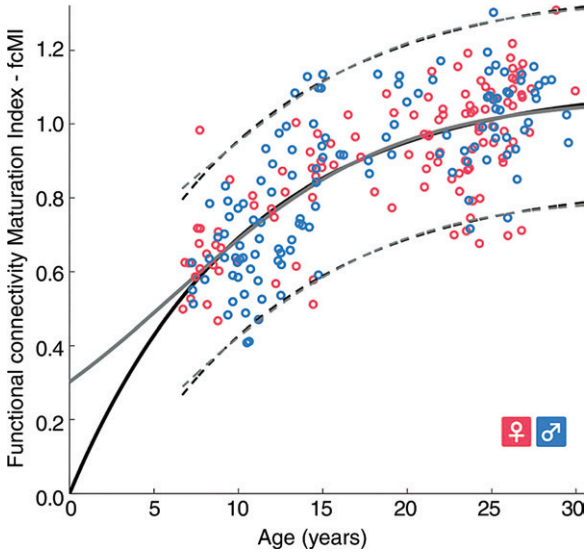


Figure 5: RSN changes during the lifespan in children. Functional connectivity brain maturation index (y-axis), a measure of functional connectivity across the entire brain, versus age of 7–30 years (x-axis) of 238 RS functional MR studies. (Reprinted, with permission, from reference 60.)

Figure 4: Altered whole brain connectivity in AD revealed by graph analysis. **(a)** Matrix of significant differences of functional connectivity between patients with AD and controls (two-tailed *t* test, $P < .05$ uncorrected). White and black dots represent brain area pairs with increased and decreased synchronization in AD, respectively. **(b–d)** A subset of connectional differences corresponding to the matrix (**a**) are plotted at three superior-to-inferior levels through a brain template. Solid lines = enhanced functional connectivity in AD; dashed lines = reduced functional connectivity. Note the pattern of generalized posterior (parietal and occipital) functional connectivity reductions and increased frontal functional connectivity. (Reprinted, with permission, from reference 41.)

Figure 6

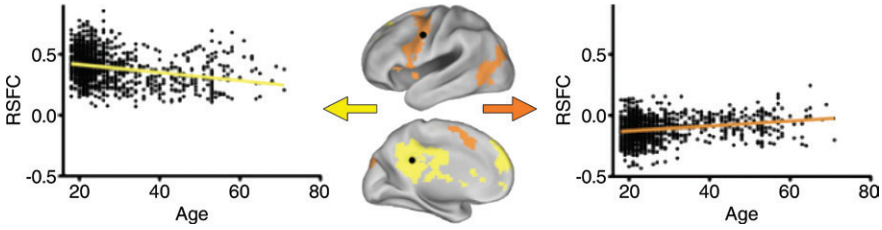


Figure 6: RSN changes during the lifespan in adults. Illustrative areas exhibiting age-related variation in RS functional MR imaging properties. Significant group-level variance in RS functional connectivity (*RSFC* on y-axis) is explained by age. Age-related functional connectivity measures are presented in scatterplots. Orange regions are areas increasing connectivity with older age, whereas yellow regions show increasing connectivity with younger age. (Reprinted, with permission, from reference 65.)

Figure 7

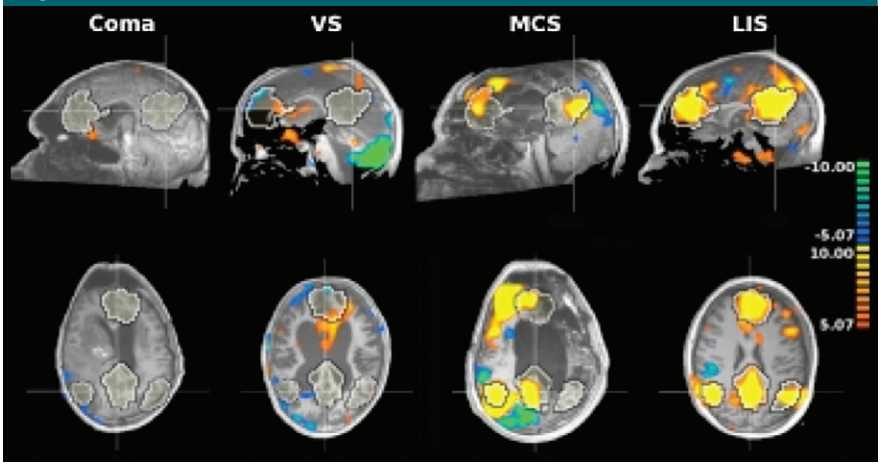


Figure 7: RSN changes in traumatic coma. The DMN in patients with coma, vegetative state *(VS)*, minimally conscious state *(MCS)*, and locked-in syndrome *(LIS)*. The DMN was extracted with independent component analysis. The black and white contour represents a template of the DMN extracted from 11 awake healthy subjects with independent component analysis. Yellow and orange colors represent the areas which activities positively correlate with the time course of the DMN. (Reprinted, with permission, from reference 66.)

and may even be used to predict brain maturity based on RS functional MR imaging data (60).

Changes in RSNs are also found with aging, with the best-established finding being a decrease in the DMN (61,62). In contrast to age-related reductions in the DMN (63) and corresponding decrease in functional density (ie, functional connectivity analyzed with a more recent methodology) (64), functional connectivity increases across a range of networks in frontal and parietal regions (63) with parallel increase in functional density in somatosensory and subcortical networks (64). Overall, increasing age is associated with decreasing connectivity in posterior parietal midline structures including essential parts of the DMN yet increasing medial and lateral prefrontal connectivity (65) (Fig 6).

Consciousness, Pain, and Anesthesia

Coma and Reduced Consciousness

Given their robustness, RSNs in part seem to reflect hard-wired structures and are thus (partly) independent of consciousness, though one would assume that at least a certain level of consciousness is required to maintain RSNs. The level of consciousness can be altered by anesthesia. Increasing levels of anesthesia progressively reduces DMN activity from awake, to mild sedation, and finally to loss of consciousness (66,67) (Fig 5). Propofol-induced loss of consciousness affects higher-level networks, including the DMN, more than lower-level visual or auditory networks (68).

In brain injury–related states of reduced consciousness and coma, the DMN activity gradually diminishes from minimally conscious state to vegetative state to coma to brain death (66,69,70). In the locked-in state (Fig 7), the DMN is not significantly different from that in healthy control subjects consistent with preserved cognitive functions (66). The combination of findings from drug-induced coma and brain injury–related coma suggests that intact consciousness is necessary for the presence of higher-level RSNs. One potential confound in the context of brain injury is a disease-related alteration of the neurovascular response. This could potentially modify the neurovascular origin of the functional MR imaging signal, as discussed in more detail below.

Sleep and Sleep Disorders

Sleep is a less profound yet much more common and physiologic alteration of consciousness. The transition from wakeful rest to light sleep is associated with a general increase in the BOLD signal variance and increased correlations within the dorsal attention network (71). Subtle shifts in network architecture are consistent with reduced external attentiveness and increased internal and self-referential processing (72). Increasing sleep depth in non–rapid eye movement sleep stages is paralleled by decreased contributions of the posterior cingulate cortex/retrosplenial cortex, parahippocampal gyrus, and medial prefrontal cortex to the DMN (73) (Fig 8). Alterations in RSNs occur already at stage 1 sleep and parallel neuroelectric alterations in EEG (74). DMN connectivity progressively decreases from light to deep sleep and partially recovers during

rapid eye movement sleep, which is associated with a higher level of arousal (75). This alteration of the DMN during sleep stages seems to parallel those during decreasing levels of consciousness in coma as discussed above.

Pain and Migraine

Migraine without aura, as a frequent model of pain, results in increased intrinsic connectivity between DMN and right central executive network and the right anterior insula during attacks (76) as well as increased functional connectivity between left and bilateral middle temporal lobe, orbitofrontal cortex, and left dorsolateral prefrontal cortex (77) yet reduced functional connectivity within right frontoparietal networks, middle frontal gyrus, and the dorsal anterior cingulate cortex (78). These modifications increase with increasing duration of the disease (76,77) and negatively correlate with the pain intensity of migraine attacks (78). Collectively, these studies suggest that repetitive pain reshapes functional connectivity networks with notably increased intrinsic connectivity, as a function of disease duration and severity. This functional and presumably pathologic reorganization of brain networks may explain the functional impairments in migraine patients. Fluctuations in functional connectivity may modify the personal and subjective perception of pain (79). Functional connectivity functional MR imaging studies may demonstrate not only the direct impact of pain but also, for example, alterations in dorsal anterior cingulate cortex/dorsomedial prefrontal cortex and anterior insula related to anxiety and emotional regulation in shoulder apprehension, that is, the mental anticipation of potentially painful movements (80). Similar to brain injuries discussed above, the known alterations in blood flow and vascular reactivity in migraine may be a systematic confound for the functional MR imaging signal due to the underlying neurovascular coupling.

Drugs and Addiction

The main advantages of RS functional MR imaging (measuring dynamic interactions between all brain regions rather than predefined regions of task-induced activation, independent of task performance) are also important considerations for human drug and addiction research. Pharmacologic RS functional MR imaging examines short- and long-term effects of drugs on functional connectivity. Often, drug-induced changes in behavior, subjective experiences, and metabolite concentrations in the blood are also determined. RS functional MR imaging is also used to study addiction-associated changes in functional connectivity, either with or without the application of a pharmacologic challenge.

In recent years, pharmacologic RS functional MR imaging was successfully applied in humans. Caffeine induced widespread reductions of connectivity and increased temporal variability of BOLD correlations (81–83). Administration of alcohol, morphine, ketamine, and tetrahydrocannabinol showed distinct "fingerprints" of increases and decreases in functional connectivity (84–86). Nicotine intake also modulated dynamic interactions between various networks, including the DMN (87,88). Addiction studies showed RS functional MR imaging connectivity reductions in bilateral prefrontal regions in cocaine users (89) (Fig 9) and in the orbitofrontal regions, thalamus, and cuneus in heroin users (90). Abnormal connectivity of the ventral and dorsal striatum in cocaine addiction was reduced after methylphenidate administration (91).

Figure 8

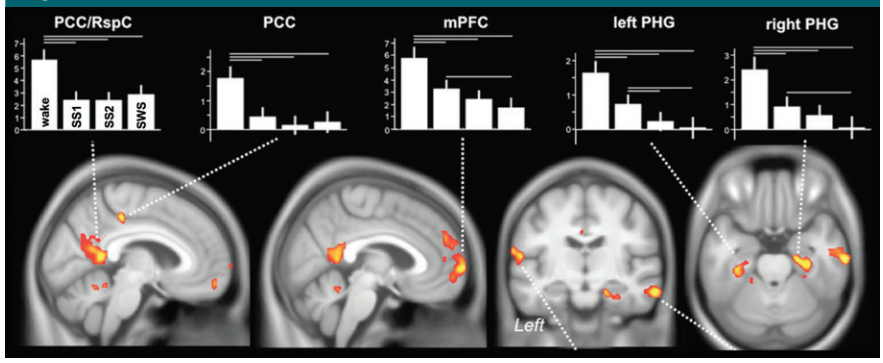


Figure 8: Sleep-stage–dependent changes within the DMN. Clusters represent areas with significant main effect of sleep stage on focal DMN strength ($P < .05$). Graph bars represent contrast estimates for each factor level (ie, wake, sleep stage 1 *[SS1]*, sleep stage 2 *[SS2]*, and slow wave sleep *[SWS]*) as extracted from the peak voxels. *mPFC* = medial prefrontal cortex, *PCC* = posterior cingulate cortex, *PHG* = parahippocampal gyrus, *RspC* = retrosplenial cortex. (Reprinted, with permission, from reference 73.)

Figure 9

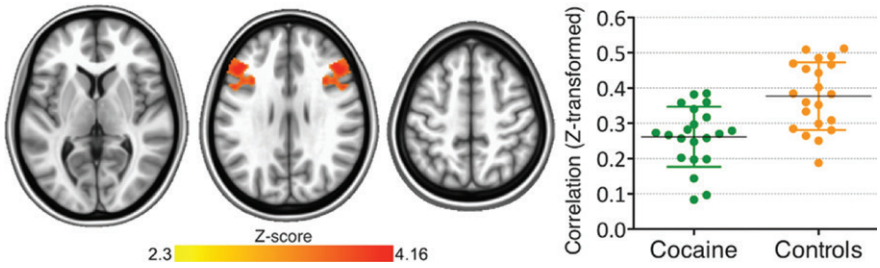


Figure 9: RSN changes in cocaine users. Left: Area for which the control group exhibited significantly stronger voxel-mirrored homotopic connectivity than the cocaine-dependent group ($Z > 2.3$, cluster-level $P < .05$, corrected). Right: Mean voxel-mirrored homotopic connectivity values across the area exhibiting significant group differences. (Reprinted, with permission, from reference 89.)

In alcoholics, RS functional MR imaging connectivity during early alcohol abstinence may even predict future relapse (92).

Pharmacologic RS functional MR imaging has also been used to target specific neurotransmitter systems. Dopaminergic effects include alterations in connections within and between basal ganglia, lateral, and medial frontal regions, DMN, ventral striatum, and midbrain (91,93–96). Prolonged administration of a serotonergic agent reduced connections between the dorsal nexus and the hippocampus (97). Although this suggests specific RS functional MR imaging effects of drugs that target different neurotransmitter systems, results need to be confirmed and effects directly compared.

A caveat is that pharmacologic interventions can affect physiology, which may cause artifactual changes in RS functional MR imaging connectivity (eg, by affecting heart rate and respiration). Therefore it is essential to monitor physiologic signals and to correct for physiologic confounds in the analyses (see data analysis section). However, although corrections are important, they do not necessarily affect the observed RS functional MR imaging connectivity changes, as the location of confound effects can be different from regions where drug effects occur. This has been shown for morphine-induced changes in heart rate and respiration, where the observed drug effects in RS functional MR imaging connectivity are robust against any physiologic correction method (Fig 10) (23).

Since pharmacologic RS functional MR imaging can be applied in preclinical animal studies, in healthy volunteers, and in patients, it might be a suitable translational technique for drug development studies. Of special interest for drug development applications are the studies of placebo-controlled repeated imaging. These studies offer the opportunity to relate drug-induced changes in RS functional MR imaging connectivity with drug-induced changes in behavior, subjective experiences, and metabolite concentrations (84–86).

Currently, it is not known how reproducible drug effects with RS functional MR imaging are, as the number of replication studies is limited. If the technique proves to give reproducible results, it may be used to aid drug

Figure 10

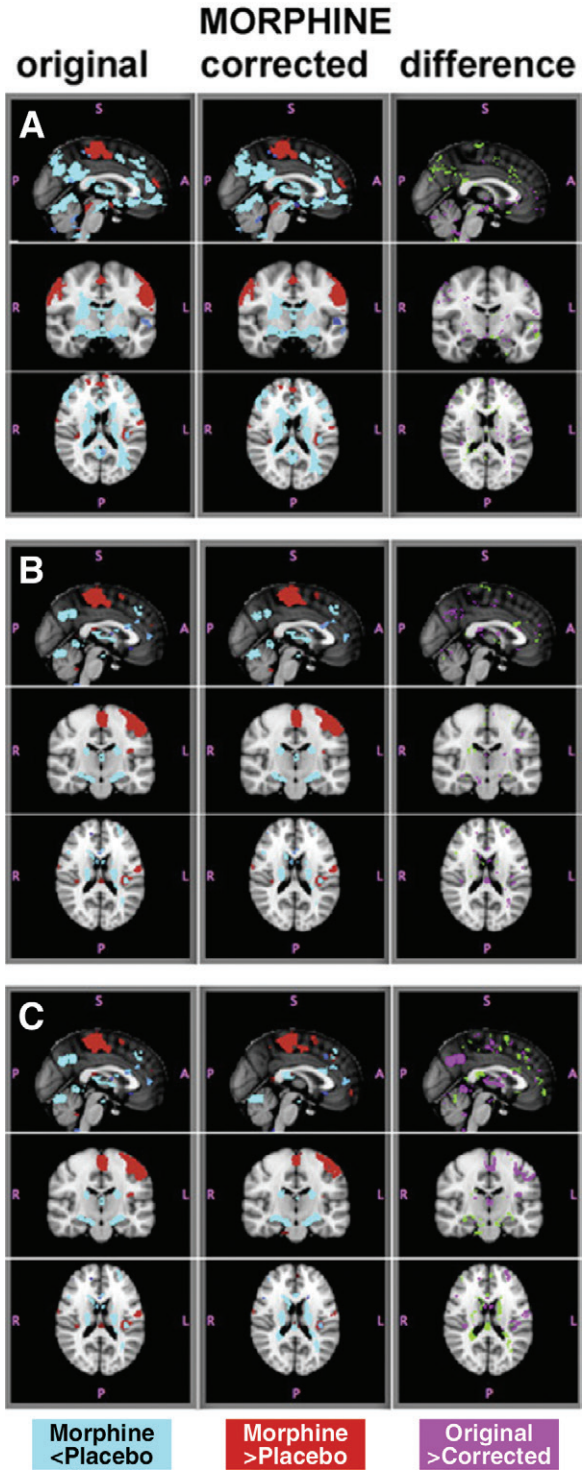


Figure 10: Effects of physiologic correction on morphine-induced functional connectivity changes. The first two columns show decreases (light blue, morphine < placebo) and increases (red, morphine > placebo) of functional connectivity after morphine administration compared with placebo. The first column shows the effect of morphine on functional connectivity without any correction. The second column shows morphine effects on functional connectivity with correction. The third column shows the subtraction of binarized cluster effects of the first two columns (corrected $P < .05$; purple, original > corrected; green, original < corrected). Three different methods of physiologic signal correction are compared: *A*, Effect of including respiration as a covariate; *B*, effect of "retrospective image correction" RETROICOR (189); and *C*, effect of "respiration variation and heart rate correction". (Reprinted, with permission, from reference 23.)

development, potentially offering important information of whether a drug influences central nervous system function, in which concentration, and its mechanism of action.

Dementia and Neurodegenerative Diseases

In neurodegenerative disorders like AD and other dementias there is a need for biomarkers that bridge the gap between early molecular alterations like amyloid deposition (which occurs in the preclinical stage) and neurodegeneration, a later manifestation (which may be too late a feature, especially in drug trials) (98). Functional markers like fluorodeoxyglucose positron emission tomography (PET), arterial spin-labeling, and BOLD functional MR imaging are potential candidates to bridge that gap.

While task-based functional MR imaging studies have shown alterations in specific domains (eg, episodic memory function in AD) (99,100), this method is limited because of the need to restrict analysis to a single domain with a single stimulus-intensity. Also, cognitive decline may itself interfere with task adherence and performance, issues that are less prominent when applying RS functional MR imaging. Functional connectivity is emerging as a promising approach to reveal early abnormalities in the brains of subjects with dementia (101). The most frequently studied network in dementia is the DMN (Fig 11), which engages the posterior cingulate cortex, the parietal cortex, and medial temporal lobe—areas known to be affected in AD and other dementias.

The majority of RS functional MR imaging studies found reduced DMN connectivity in patients with AD but also in the earlier phase of mild cognitive impairment (102–104). DMN abnormalities are found even in unaffected carriers of familial AD (105) and subjects with cognitive complaints (106), and increased DMN activity in healthy subjects with the APOE4-genotype (a risk factor for AD), possibly as a compensatory phenomenon

Figure 11

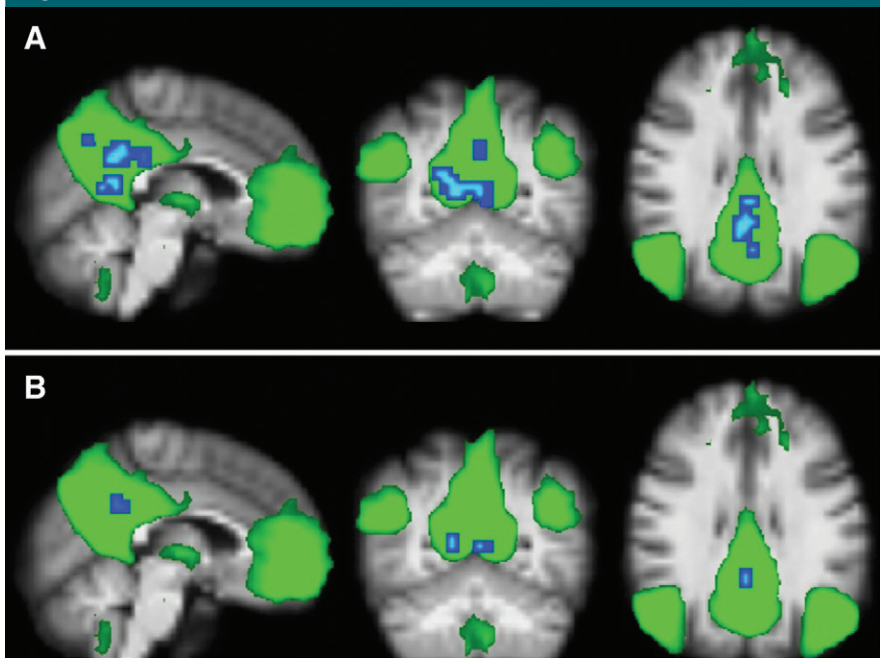


Figure 11: Reduced functional connectivity in the DMN in AD. Clusters of decreased functional connectivity (blue voxels) in patients with AD compared with control subjects ($P < .05$ familywise error corrected) within the group DMN (green voxels), *A*, corrected for age, sex, and origin of data set, *B*, with additional correction for normalized gray matter volume. (Reprinted, with permission, from reference 104.)

to conceal early subclinical damage (107). By contrast, DMN connectivity with certain regions may be increased in subjects with Lewy-body dementia (108). However, reduced DMN connectivity has also been reported in a variety of other diseases (eg, Parkinson disease, multiple sclerosis), and is by no means specific for AD.

In subjects with frontotemporal dementia, other networks are affected. In the behavioral variant of frontotemporal dementia, the most marked abnormalities are found in the so-called salience network (109,110) (engaged in attention focusing on most pertinent sensory data). Especially in the behavioral variant, there is reduced connectivity of the anterior cingulate and striate cortex. Even in asymptomatic gene carriers for frontotemporal dementia, functional connectivity is already affected in the anterior midcingulate cortex (111) and DMN (110). Interestingly, the salience network may display increased connectivity in patients with early AD; some speculate this is an attempt to compensate for the failing DMN connectivity, but there is no evidence this is functionally beneficial (41,112). The combined analysis of DMN and salience network connectivity appears an attractive approach to distinguish AD from frontotemporal dementia (113).

Interestingly, the type of network disruption in dementia seems to parallel the topography and perhaps spread of disease (114). While AD affects mostly DMN, behavioral and language subtypes of frontotemporal dementia may affect different networks primarily. It thus seems that there is a selective vulnerability of individual networks for a certain type of (molecular) disease, perhaps driven by a unique cytoarchitectonic make-up and transneuronal spread within such networks (Fig 12).

Using graph analysis, major hubs in the brain seem to be affected by AD and its preceding stages (115). Reduced functional connectivity can be found already in healthy elderly controls in

Figure 12

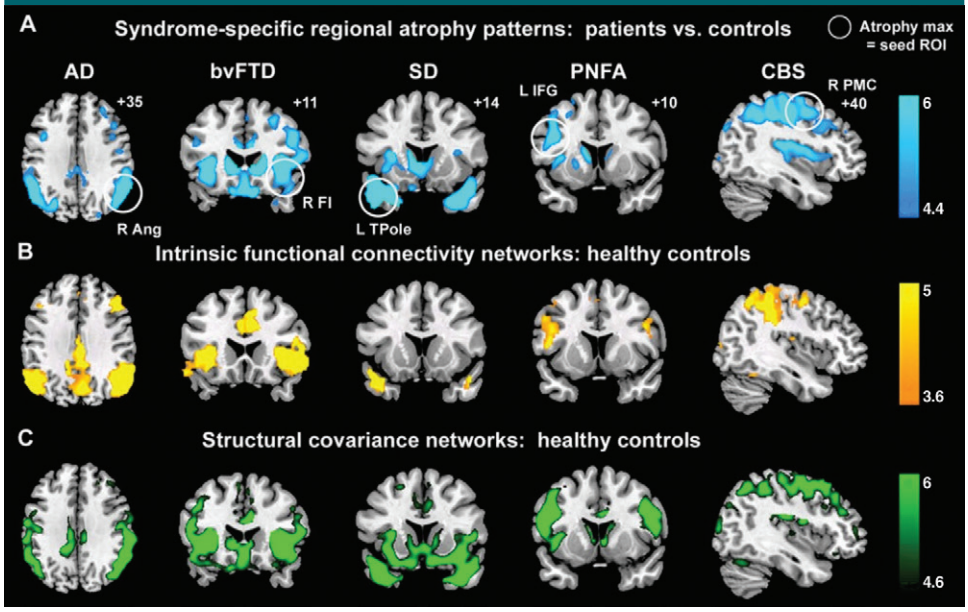


Figure 12: Convergence of syndromic atrophy, healthy networks, and healthy structural covariance patterns. *A*, Five distinct clinical syndromes showed dissociable atrophy patterns, whose cortical maxima (circled) provided seed regions for functional connectivity and structural correlation analyses. *B*, RS functional MR imaging experiments identified five distinct networks anchored by the five syndromic atrophy seeds. *C*, Healthy subjects further showed gray matter volume covariance patterns that recapitulated results shown in *A* and *B*. For visualization purposes, results are shown at $P < .00001$ uncorrected (*A* and *C*) and $P < .001$ corrected height and extent thresholds *(B)*. In *A–C*, results are displayed on representative sections of the MNI template brain. On coronal and axial images, the left side of the image corresponds to the left side of the brain. *bvFTD* = behavioral variant of frontotemporal dementia, *SD* = semantic dementia, *PNFA* = progressive nonfluent aphasia, *CBS* = corticobasal syndrome. *ANG* = angular gyrus, *FI* = frontoinsula, *IFG* = inferior frontal gyrus, pars opercularis, *PMC* = premotor cortex, *TPole* = temporal pole. (Reprinted, with permission, from reference 114.)

relation to amyloid beta deposition as seen with PET, that is, at an early preclinical stage of the neurodegeneration in individuals at risk for cognitive decline (116). A decreased numbers of hubs and reduced connectivity within the DMN have been found not only in AD, but even in healthy volunteers with silent amyloid deposition on PET images (103,117,118).

Less is known about other degenerative diseases. In subjects with Parkinson disease, there may be altered connectivity of basal ganglia with brain stem and motor areas (119,120) but also in the DMN (121). In subjects with prodromal Huntington disease, reduced connectivity is found of the caudate with cortical areas, including premotor regions (122). Even premanifest gene carriers for Huntington disease show reduced connectivity, although to a lesser extent than manifest Huntington patients (123). Also in amyotrophic lateral sclerosis, functional connectivity between motor areas is altered (124).

Developmental Disorders and Psychiatry

RS functional MR imaging is very attractive for neuroimaging research in psychiatry, with a rapidly increasing number of publications in the field, with abnormal findings identified in many conditions.

Depression is associated with variable modifications in RSNs, including increased or decreased connectivity across multiple areas, including the anterior cingulate and posterior cingulate cortex/precuneus, amygdala, and the DMN (125–130) (Fig 13).

Bipolar disorder shows decreased corticolimbic connectivity in particular of the medial prefrontal cortex and the anterior cingulate cortex with limbic-striatal structures (131,132).

Schizophrenia also has been reported to show variable increase or decrease in DMN, as well as variable relationships between DMN and other RSNs (133–140). Results of first-degree relatives of persons with schizophrenia are again variable and include increased connectivity within the DMN and a strong trend toward decreased connectivity in meso/paralimbic-sensory-motor RSNs (140,141). In conjunction with the variable results of depression as discussed above, this shows that RS functional MR imaging results are often times variable in the domain of psychiatry, probably related to patient selection, duration, and severity of the disease, as well as exact data analysis methods.

Bipolar disorder has shown decreased corticolimbic connectivity, in

particular of the medial prefrontal cortex and the anterior cingulate cortex with limbic-striatal structures (131,132).

Attention deficit hyperactivity disorder (ADHD) again has been reported to show variable alterations of RSNs, the most consistent finding being reduced connectivity within the DMN and increased connectivity in the salience network (142–149).

Autism spectrum disorders (ASD) are associated with decreased connectivity within the DMN (150–153) but also hyper-connectivity of the posterior cingulate and retrosplenial cortices and hypo-connectivity between precuneus with visual cortex and basal ganglia (154). Moreover, ASD children have ectopic striatal connectivity as well as increased functional connectivity between striatum and heteromodal associative and limbic cortex (155). By pooling multiple international datasets, the first large-scale studies in this domain in 360 male subjects with ASD and 403 male age-matched control subjects found both some regions with hypo-connectivity in particular in corticocortical and interhemispheric connections while other regions exhibited hyper-connectivity. This indicates a complex pattern of pathologic functional connectivity in ASD (156) (Fig 14).

Posttraumatic stress disorder is associated with decreased DMN connectivity (157) and alterations of connectivity of regions involved in emotional processing such as the amygdala (158). This neuroimaging evidence for functional alteration in posttraumatic stress disorder may contribute to the appreciation and understanding of this disease.

Anxiety disorders include several subtypes, each with related RS functional MR imaging findings. Panic disorder is associated with abnormal functional connectivity in the limbic network, in particular increased connectivity between the right amygdala and the bilateral precuneus (159). Social anxiety disorder features, among others, increased negative right amygdala connectivity with the left middle temporal gyrus, left supramarginal gyrus, and left lateral occipital cortex, yet unchanged DMN connectivity (160), as well as reduced functional connectivity between amygdala and orbitofrontal cortex (161). Childhood emotional maltreatment has associated alterations in the limbic and salience networks (162).

In summary, the DMN is implicated in the majority of RS functional MR imaging studies and diseases in psychiatry. This implies a high sensitivity, yet a low specificity. Many psychiatric diseases are characterized by a complex alteration of a pattern of RSNs, not by isolated alterations of a single RSN such as the DMN. Evidence for this is provided in studies showing that schizophrenia and psychotic bipolar patients have overlapping alterations in multiple RSNs, as well as unique patterns (meso/paralimbic-sensory-motor in schizophrenia and meso/paralimbic-frontotemporal/paralimbic in bipolar disorder [141]). In the same vein, ADHD and ASD have overlapping RSN alterations, yet ADHD-specific alterations in right striatum/pallidum and ASD-specific alterations in bilateral temporolimbic (163). Psychiatric diseases such as schizophrenia are thus characterized by complex alterations of brain connectivity notably among

Figure 13

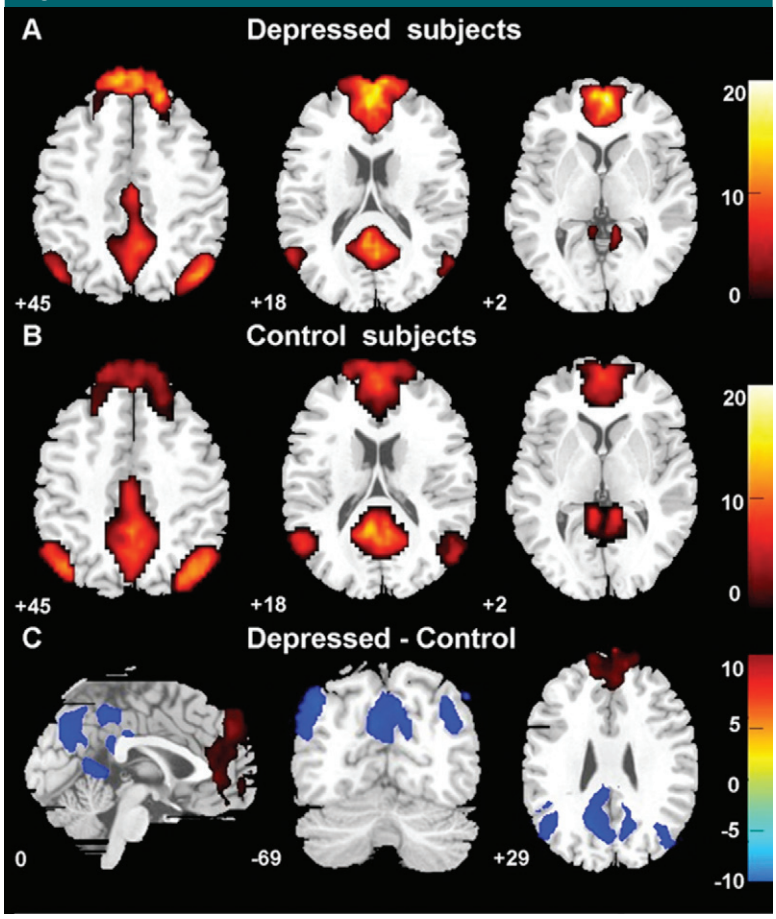


Figure 13: DMN alterations in depression. Axial images show the group DMN extracted by independent component analyses in, *A*, 32 depressed subjects and in, *B*, 33 healthy control subjects ($P < .05$). *C*, The major depressive disorder patients showed significantly increased functional connectivity in the medial prefrontal cortex and ventral anterior cingulate cortex (labeled red) but significantly decreased functional connectivity in the posterior cingulate cortex/precuneus and angular gyrus (labeled blue) relative to the healthy control subjects ($P < .05$). The *t* score bars are shown at right. (Reprinted, with permission, from reference 129.)

Figure 14

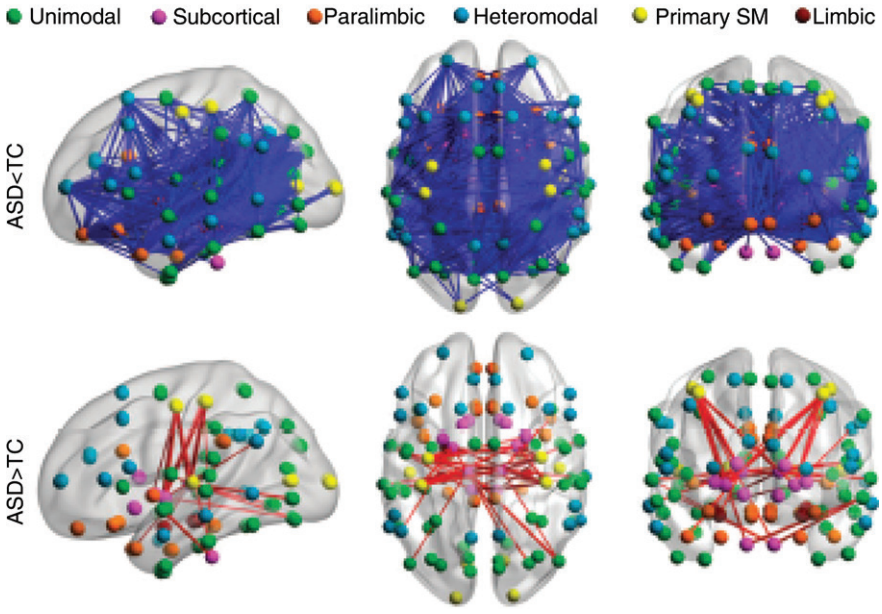


Figure 14: Functional connectivity changes in ASD. Whole-brain intrinsic functional connectivity analyses in ASD versus typical control subjects *(TC)* for intrinsic functional connectivity between each of the 112 parcellation units (56 per hemisphere) included in the structural Harvard–Oxford Atlas. Parcellations are represented with their center of mass overlaid as spheres on glass brains. The top panel shows the intrinsic functional connections (blue lines) that were significantly weaker in ASD versus typical control subjects. The bottom panel shows the intrinsic functional connections that were significantly stronger in ASD relative to typical control subjects (red lines). Each Harvard–Oxford Atlas unit is colored based on its membership in the six functional divisions (yellow = primary sensorimotor *[SM]*; green = unimodal association; blue = heteromodal association; orange = paralimbic; red = limbic; pink = subcortical). (Reprinted, with permission, from reference 156.)

central hub regions of the brain and consecutive altered functional brain dynamics (42) and not by alterations of single RSNs.

A limitation resides in the observation that even within a given disease—for example, schizophrenia—different studies report variable degree of decreased or increased correlations within the DMN (133–140). This observation in turn suggests that patterns of RSN alterations may vary along the course of the disease and depending on the severity of disease—for example, in schizophrenia (136) or depression (127). The comprehensive understanding of alterations of patterns in RSNs in psychiatric diseases requires large datasets at different stages of each disease, which are on the horizon thanks to the possibilities of data sharing and cloud computing. One example is the autism brain imaging data exchange, or ABIDE, database for RS functional MR imaging studies in ASD (156).

White Matter Disease

White matter contains the myelinated axons that connect the neurons and are an essential scaffold that support and underpin the neurons responsible for functional connectivity. White matter integrity and structure can be readily quantified by using diffusion tensor imaging. Its organization is relevant to understand functional connectivity. However, assuming that loss of white matter integrity in white matter diseases is associated with functional connectivity changes in a simple predictive manner is an oversimplification.

Multiple sclerosis, once considered a pure white matter disease, features clear neurodegenerative components, though (gray matter) atrophy may be clinically covert in the early phases. Important insights have been gained through analysis of RSNs, revealing altered functional connectivity from disease onset. In multiple sclerosis, mostly reductions in RS functional MR imaging connectivity have been reported: in the visual system in the peristriate visual cortex (164), and overall decreases and network efficiency related to cognition (165).

In patients with a clinically isolated syndrome, suggestive of multiple sclerosis, mostly increased functional connectivity is found compared with healthy controls (Fig 15a) and patients with more advanced disease (166). This includes various networks including the DMN, where in late phases of multiple sclerosis, there is reduced functional connectivity (167). Most likely, initial neuroaxonal damage is compensated for by enhanced brain activity (Fig 15b), while such compensatory mechanisms fail when damage accrues (168). Recovery (visual) or training (cognition) may reverse such diminished connectivity: In the visual system, recovery from optic neuritis may show stronger functional connectivity in the extrastriate cortex (164). Following cognitive training, patients with multiple sclerosis showed increased functional connectivity in relevant regions, including the anterior cingulate (169).

Diffuse white matter damage also occurs in small vessel disease, diabetes, human immunodeficiency virus (HIV) infection, and intoxications. In line with MEG findings (170), RS functional MR imaging studies in type 1 diabetes without microangiopathy, found increased functional connectivity in the visual and motor areas (Fig 16), while in those with microangiopathy (retinal or renal) there may be decreased connectivity in networks involving attention, working memory, auditory and language processing, and motor and visual processes (171). Patients with type 2 diabetes show reduced functional connectivity in the DMN, despite similar brain volume and cognition (172). In diabetic patients with pain, widespread reductions in connectivity may occur in

Figure 15

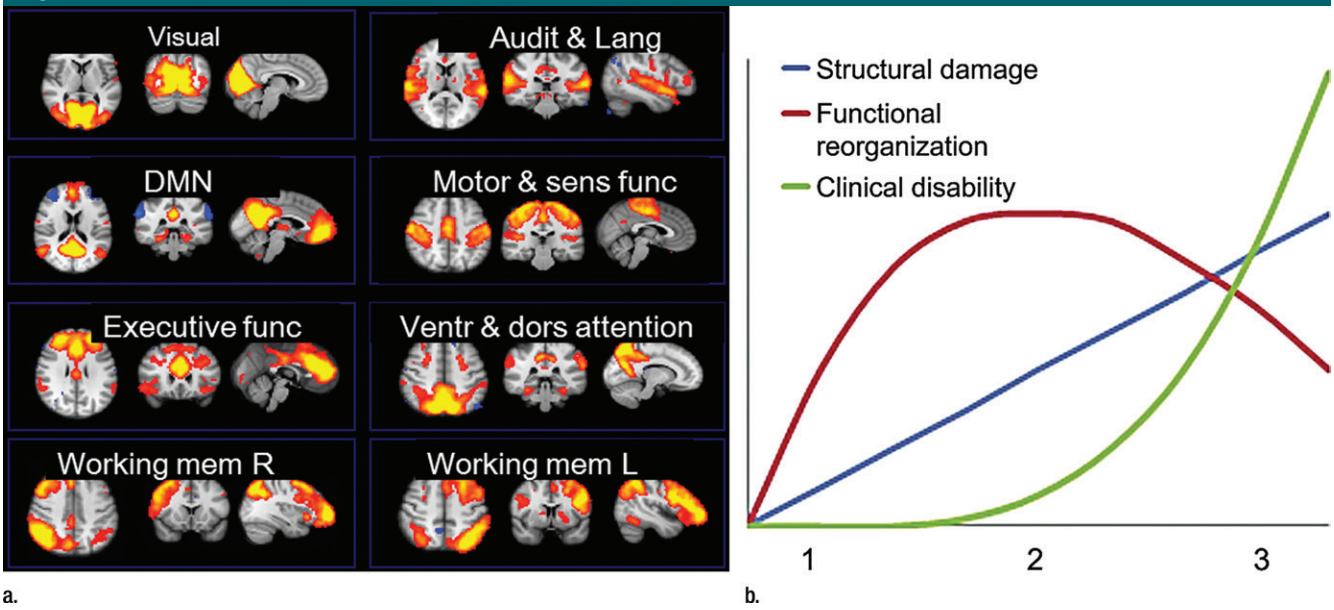


Figure 15: Early compensatory RS functional MR imaging activity in multiple sclerosis. **(a)** In six of eight networks identified using independent component analysis, increased synchronization was found in patients with a clinically isolated syndrome compared with healthy control subjects or patients with more advanced relapsing-remitting disease. (Reprinted, with permission, from reference 168.) **(b)** It is hypothesized that subclinical damage in early disease is compensated for by increased functional activity and that clinical impairment only becomes obvious when compensatory mechanisms are exhausted. (Reprinted, with permission, from reference 166.)

parieto-fronto-cingulate networks controlling attention to external stimuli, involved in self-monitoring, pain processing, and salience detection (173). In subjects with HIV, decreased functional connectivity has been reported in the DMN and salience networks, consistent with accelerated brain aging (174). Also in hepatic encephalopathy, reduced functional (and structural) connectivity within the DMN has been reported (175).

Limitations and Outlook

Within the past decade, RS functional MR imaging has taken off as a major tool to study functional connectivity in vivo with improved spatial resolution compared with MEG and EEG. It complements other MR techniques, notably task-based functional MR imaging and diffusion tensor imaging, to examine the brain's functions and connectivity at rest. RS functional MR imaging proves to be a very rich source of brain connectivity data, which can be obtained within 10 minutes of imaging and offers an unprecedented new window into the brain. Abnormal functional connectivity has been reported in a wide variety of neurologic and psychiatric conditions. The networks affected can be disease specific, though often similar networks are affected, for example, the DMN, illustrating limited specificity of the findings. Also, the interaction between the various RSNs is incompletely understood. For example, in a model of tinnitus (176), the voluntary downregulation of the primary auditory target region by means of real-time functional MR imaging neurofeedback led not only to a downregulation of the auditory network, yet also to modification in the functional interactions between multiple RSNs including auditory and visual and attention networks related to the cognitive processing demands and visual feedback. These findings indicate that neurologic and psychiatric diseases may be characterized by altered interactions between different RSNs, not simply by altered single RSNs, and moreover, that disease progress and treatments may further modify these interactions between different RSNs. Such interactions between multiple RSNs across the whole brain as an integral network (with subnetworks) can also be examined specifically, for example, using graph analysis (177).

Clearly, RS functional MR imaging holds great promise as a method to examine brain function, even in children and subjects with cognitive decline or even coma. One potential confound, in particular in clinical applications, is that typically there is no control that participants do not fall asleep. Additionally, the methods of analysis and data modeling are still evolving and may explain why findings are not consistent across studies, or why even within studies, there is considerable overlap between patients and controls. To a certain extent this may reflect true physiologic variability that is currently not well understood. For example, most analysis techniques assume that RSNs remain constant, while in fact they may alter spontaneously (178), by exogenous stimulation

Figure 16

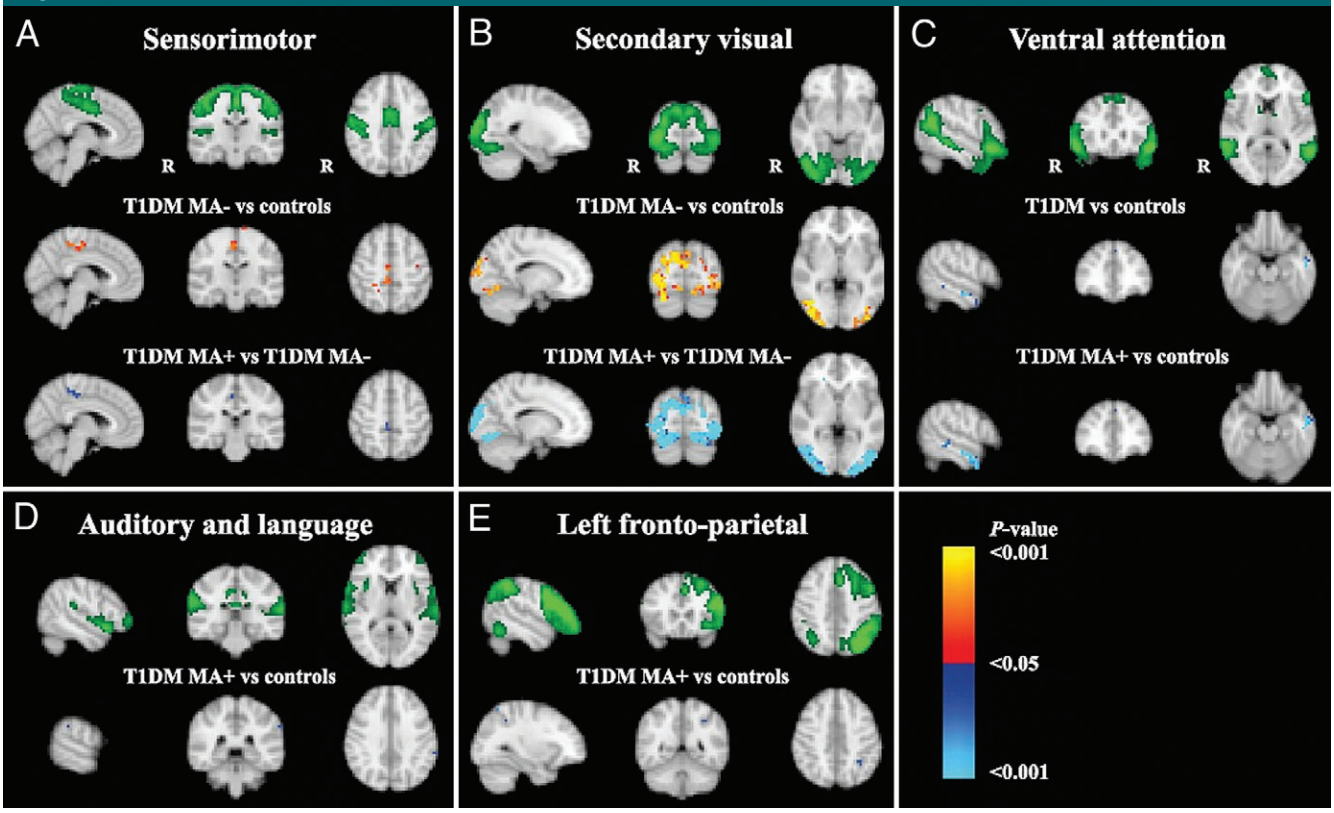


Figure 16: Altered functional connectivity in type 1 diabetes. Presented are the RS functional MR imaging networks shown in radiologic convention that show significant differences in type 1 diabetes *(T1DM)*. For each network, upper row shows voxels exceeding $z = 3.9$ ($P < .0001$) in green. The lower rows represent significantly differences found by the dual-regression method in subjects with microangiopathy *(MA+)* or those without *(MA-)*. The more yellow or light blue, the lower the *P* value. (Reprinted, with permission, from reference 171.)

(179), by learning (180,181), or voluntarily (176). These potentially confounding factors must be better understood and controlled for before RS functional MR imaging can be used in patient care. Emerging methodologic advances in pattern recognition (182) suggest it might be possible to detect disease in individual patients based on RS functional MR imaging, for example in the domain of multiple sclerosis (183) or ADHD (148) or to predict brain maturation (60).

Furthermore, it is unclear how to interpret altered RSNs as a function of disease, recovery, and treatment. This also reflects a fundamental lack of knowledge of how various diseases might affect neurovascular coupling. RS functional MR imaging is based on the indirect neurovascular BOLD response, which might be confounded by diseases (dementia, coma, stroke), aging, and medication (184–186). Recent investigations therefore combine RS functional MR imaging and electrophysiological methods (EEG or MEG) to disentangle neurovascular versus neuroelectric effects of RSNs (74,187).

Data analysis techniques for RS functional MR imaging have substantially evolved from a rather simple correlation analysis of the BOLD raw signals in regions of interest to complex independent component analyses and whole-brain graph analyses. In contrast, the underlying effect of all these analysis techniques, notably the neurovascular coupling, remains poorly investigated in particular in young children, aging, diseases, and medication. Only recently, studies have started emerging that use, for example, CO_2 challenges to calibrate the BOLD response or combine RS functional MR imaging with EEG or MEG to correlate neurovascular and neuroelectic effects of RSNs, and to exclude potential alterations due to impaired vascular responses (eg, atherosclerosis, medication).

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