Imaging structural co-variance between human brain regions

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Abstract

Brain structure varies between people in a markedly organized fashion. Communities of brain regions co-vary in their morphological properties. For example, cortical thickness in one region influences the thickness of structurally and functionally connected regions. Such networks of structural co-variance partially recapitulate the functional networks of healthy individuals and the foci of grey matter loss in neurodegenerative disease. This architecture is genetically heritable, is associated with behavioural and cognitive abilities and is changed systematically across the lifespan. The biological meaning of this structural co-variance remains controversial, but it appears to reflect developmental coordination or synchronized maturation between areas of the brain. This Review discusses the state of current research into brain structural co-variance, its underlying mechanisms and its potential value in the understanding of various neurological and psychiatric conditions.

There are marked inter-individual differences in the structure of cortical regions. For example, the between-subject variability in the volume of a specific gyrus is typically much greater than the between-subject variability in whole brain volume[1]. It has also been increasingly recognized that inter-individual differences in the structure of a brain region often covary with inter-individual differences in other brain regions — a phenomenon known as structural covariance. For example, individuals with greater cortical thickness of Broca's area of the inferior frontal cortex typically also have greater thickness of Wernicke's area of the superior temporal cortex[2]. In theory, inter-individual differences in regional

volume, thickness and surface area could be driven by factors that affect each person and each region independently. However, the phenomenon of structural co-variance shows that inter-individual differences in regional structure are in fact coordinated within communities of brain regions that fluctuate together in size across the population. Post-mortem studies of visual[3] and motor systems[4] were among the first to demonstrate these structural `correlations` between anatomical regions of the human brain, but the advent of computer-automated analysis of high-resolution structural MRI has enabled the *in vivo* study of correlation patterns across the whole brain in thousands of individuals (BOX 1).

In this article, we review the literature regarding structurally co-varying brain systems. We discuss details of the anatomical organization of these brain systems and show how this organization changes in normal development and healthy ageing. We highlight the role of genetic and environmental factors in structural co-variance, which have begun to be elucidated by twin studies and by studies of training-induced alterations in brain anatomy, and present evidence that various neurological and psychiatric conditions are associated with abnormal structural co-variance networks. Last, we assess the relationship between structural co-variance and other forms of brain connectivity, such as intrinsic activity and white matter networks, and discuss its future role in basic and clinical neuroscience.

The anatomy of structural co-variance

Organizational principles

Research and methodological developments over the past decade and a half have started to identify the organizational principles that govern the anatomy and `topology` of structural covariance networks (BOX 2). Brain areas that are highly correlated in size are often part of systems that are known to subserve particular behavioural or cognitive functions, highlighting the importance of known functional relationships between anatomical regions. For example, posterior and anterior language areas in the left hemisphere of the brain co-vary strongly in their cortical thickness[2]. The grey matter volume of the hippocampus co-varies mostly strongly with that of other regions known to be involved in the memory system, including the amygdala and parahippocampal, perirhinal, entorhinal and orbitofrontal cortices[5]. Motor, auditory, visual and other cognitive systems can also be discriminated on the basis of their patterns of anatomical co-variance[6].

Spatial proximity between brain regions is suggestive of the presence of white matter tracts between these regions[7–9], is indicative of coupling of their intrinsic activity[9–11] and generally implies higher-than-average structural co-variance between the regions. In general, there is an inverse relationship between the strength of structural co-variance and the physical distance between brain areas[12]. This parsimonious tendency to form stronger correlations over shorter anatomical distances may be linked to brain `segregation` and segregative network properties such as clustering and `modularity`[13].

However, there are also long-distance correlations between brain regions. Such exceptions may reveal the influence of brain `integration` and integrative topological properties on the formation of structural co-variance networks[11,14,15]. Although particularly strong correlations exist within cortical lobes and within subcortical structures, there are also strong

inter-lobar, thalamo–cortical and striato–cortical relationships[16–20]. Furthermore, strong, long-distance correlations exist between contralateral homologous regions[21]. The structural properties of a select minority of brain regions known as network hubs (in the association cortex) appear to disproportionately influence the structure of the rest of the brain, including spatially distant regions[12,22,23], whereas other areas (for example, the primary visual cortex) show correlations limited to their anatomical neighbourhood[12,21,22,24]. Networks derived from white matter tracts or synchronous neuronal activity between brain regions have a similar group of network hubs, which contribute to global efficiency by establishing paths of communication between all brain regions through a relatively small number of connections[25,26] (FIG. 1).

Does co-variance mean connectivity?

One of the key challenges in interpreting structural co-variance networks is the lack of clarity about what these patterns in imaging data represent at a cellular level. Owing to the scarcity of studies investigating the mechanisms of structural co-variance, questions remain as to its biological interpretation. To be specific, can we assume that structural covariance is influenced by synaptic connectivity between brain regions, and/or is structural co-variance influenced by genetic and developmental relationships between cell types and lamina?

A common interpretation of brain structural co-variance is that it indeed results from brain connectivity of some kind, such as the physical connectivity of white matter tracts or the functional connectivity of synchronous neuronal activation (BOX 3). Plausible mechanisms exist to support this notion. Synapses between neurons can have a mutually trophic and protective effect on subsequent neuronal development, possibly via glutamatergic NMDA pathways[27], with large numbers of such connections possibly leading to co-variance at the macroanatomic level[28]. Moreover, synchronous firing can induce synaptogenesis between neurons[29,30], suggesting the possibility of use-dependent coordinated growth. Studies that have begun to explicitly test these relationships[31,32] reveal that white matter connectivity and functional connectivity can explain a substantial portion but not all of the inter-regional structural covariance measured in human populations (FIG. 2).

Many regions that are directly connected through white matter tracts have been demonstrated to co-vary strongly in their morphology. For example, anterior and posterior language areas[2], contralateral homologues in many areas of the cortex[21] and the striatal–cortical–thalamic circuit[33] all show convergent white matter connections and structural co-variance. Structural co-variance networks and white matter networks also have similar network properties: both consistently show non-random, clustered, efficient and modular properties. However, similar network properties are found in diverse social, physical and biological systems, so sharing these topological features does not prove the equivalence of the underlying networks. The only whole-brain study comparing white matter (diffusion imaging) connections with cortical thickness co-variance between regions on a pair-by-pair basis suggests that there is a substantial but incomplete overlap, with 30–40% of inter-regional co-variance occurring between regions that are connected by white matter tracts[31] (FIG. 2b).

The pattern of inter-regional structural co-variance may be more akin to the pattern of functional connectivity than to that of physical white matter connections. This is not implausible, because although regions that are connected via white matter tracts are usually also functionally connected, strong functional connectivity can also arise in the absence of direct white matter connectivity[34,35]. Correlations between brain regions in intrinsic brain activity (which are measured using blood-oxygen-level-dependent (BOLD) functional MRI (fMRI) in a task-free setting) show striking overlap with population-based measurements of grey matter co-variance between those regions, at least for certain co-variance networks[23,36–38] (FIG. 2a). As the first studies have only just begun to quantify the relationship between structural co-variance and functional connectivity across the entire brain[32], the extent of this similarity currently remains provisional.

There are methodological hurdles in conclusively assessing the relationship between structural covariance and connectivity. Currently, the extraction of morphological features of interest from MRI scans remains imperfect (BOX 1). In addition, diffusion imaging methods have difficulty resolving crossing fibres, and many tracts are simply too small to be imaged at current scanning resolutions[39]. There are also unresolved methodological issues in measuring fMRI connectivity, as revealed by the recent concern over artefacts induced by in-scanner subject motion[40]. Technological improvements will allow increasingly accurate assessments of these relationships.

Coordinated neurodevelopment

The developmental significance of correlations between phenotypic traits, including the morphometry of anatomical structures, has been discussed in biological research outside neuroscience for many decades[41–43]: for example, regarding skeletal measurements of extinct pelycosaurian reptiles[44], floral dimensions in botanical species[45], human craniofacial anatomy[46–48] and many other experimental contexts[49]. High phenotypic co-variance is generally interpreted as evidence of developmental coordination or integration, which occurs within modules with components that are subject to similar developmental processes; by contrast, the developmental processes that influence distinct modules are relatively autonomous, resulting in low correlations at the population level[50–55].

Coordinated development may give rise to co-variance in various ways. Sharing a developmental precursor may result in co-variance between distinct parts of a mature organism[56]. Similarly, inductive signalling from one developing tissue to another or simultaneous exposure to signals from a third party may result in synchronized maturation and ultimately co-variation[54,55,57]. Shared genetic influences that are due to pleiotropy could underlie such coordinated development, as could correlational selection that is due to inter-related influences on adaptive fitness[58–60]. It has been demonstrated that anatomical co-variance is often linked to functional relationships: for example, covariance between bones that have the same muscular attachments[61] or are involved in the mechanics of the same behaviour[62–64]. Coordinated development may also reflect inherited ancestral relationships between phenotypic traits, even if these traits no longer have a functional relationship[53,65]. Finally, common environmental factors may influence coordinated

development and thus co-variance, with the relationship between genetic and environmental influences possibly varying on a case-by-case basis[45,49].

These cross-disciplinary precedents suggest that structural co-variation between brain regions may result from coordinated neurodevelopment, and this hypothesis is indeed consistent with preliminary imaging studies. A longitudinal study has demonstrated overlap between pairs of regions whose local cortical volumes were correlated and pairs of regions whose rates of cortical change were correlated over a 5-year period[66]. In a set of studies that tracked over 100 subjects across adolescence with three or more longitudinal scans, areas that were structurally co-variant were also correlated in terms of the rate of change in cortical thickness during development[32,67] (FIG. 2c). Both synchronized rates of change and cross-sectional structural co-variance appear to be maximal in the association cortex[67]. Although structural co-variance and fMRI functional connectivity (which was measured in a subset of the same subjects) showed a significant statistical relationship, brain-wide structural co-variance networks were more similar to networks of synchronized anatomical change[32].

It is therefore probable that synchronized change during development underlies inter-regional structural co-variance. These developmental relationships are in turn influenced by direct white matter connections and functional co-activation and probably also by other genetic and environmental factors (see below). The basic idea that structural co-variance represents the outcome of a mutually trophic benefit to the co-varying regions over the course of their development echoes work on the incentives for relationships between pairs of people that lead to the formation of complex social networks[68], suggesting that some of the principles of structural covariance network formation may be very general.

Genetics, cognition and behaviour

Genetics

Most of the variation in total brain size across human beings can be attributed to genetics[69–71]. Some striking examples are the single-gene disorders associated with specific alterations in brain structure and size[72,73], and many of these same genes have functions in cell division and cellular development under normal circumstances[74]. In healthy individuals, it is possible that brain anatomy and general intelligence are influenced by the same genetic factors[69,75]. Exploiting the fact that fraternal twins have about one-half of the genetic similarity of identical twins but have shared environmental influences, twin analysis of single brain regions can quantify the extent to which genetic factors underlie inter-individual anatomical differences. Such analyses have shown that the influence of genetic factors varies across the brain, with some gyri demonstrating proportionally greater heritability than others[76].

Although the genetic contributions to brain morphology could theoretically be driven by distinct genes operating on different brain areas, evidence suggests that genetic influences are themselves correlated. For example, there is preliminary evidence that structural co-variance between the amygdala and the anterior cingulate can vary depending on the presence of a polymorphism in the gene for a serotonin transporter[77]. Twin studies have

been used to identify correlation patterns between regions that are specifically due to shared genetic influences: strongly positive, genetically driven correlations appear to exist across much of the brain, with shared genetic influences accounting for a large portion of the co-variance measured in human populations[76,78,79].

However, these genetic correlations between brain regions are not all equal. Like brain networks derived from white matter connectivity or functional connectivity between brain regions, the network of genetically driven structural co-variance follows 'small-world' organizational principles[76]. Different genetic factors influence patterns of structural co-variance most strongly within different brain networks[79–82]; that is, there seem to be network-specific genetic influences. For example, regions that have strong genetic relationships with the anterior temporal cortex appear to be genetically unrelated to the primary visual cortex (and vice versa)[81]. Structural co-variance within the frontal–parietal network is particularly strongly determined by genetic factors[76,80,81]; frontal and temporal association areas, whose morphology is under relatively strong genetic control[83], also show among the highest genetically driven correlations with the rest of the cortex[78]. Correlations between homologous contralateral regions appear to have stronger genetic underpinnings, both in the subcortex[16] and cortex[78], than do ipsilateral correlations.

Cognition, behaviour and plasticity

There is an extensive literature relating the morphology of individual brain regions or systems, including cortical thickness, grey matter density, volume and surface area, to performance on neuropsychological tasks. For example, the size of the amygdala varies with performance in memory tasks[84], social phobia[85] and also the size of one's social network[86]. Morphological properties of diverse prefrontal regions are associated with performance in attentional and regulatory tasks[87–89], parietal and primary sensory regions have been linked to spatial and perceptual abilities[90,91] and intelligence has been associated with widespread variation in thickness across the cortical mantel[75,92,93]. Grey matter densities in the hippocampus and the caudate are correlated with different strategies used by subjects in a virtual navigation task, and these regions are negatively correlated with each other across the population[5]. Much if not all of the 'unexplained' variance in morphological properties across people is probably associated with behavioural and cognitive differences. Moreover, brain regions that co-vary with the same behavioural or cognitive variables could, in their accumulation, explain a substantial proportion of interregional co-variance patterns.

Indeed, behavioural and cognitive abilities are associated not only with regional morphometric properties but also with co-variance between regions. For example, people with a higher IQ have stronger correlations between the inferior frontal gyrus and thickness of other frontal and parietal brain areas than people with a lower IQ[2]. Musicians represent a particularly valuable 'natural experiment' of highly trained, skilled individuals who demonstrate alterations in their patterns of structural co-variance. For instance, trained pianists have reduced morphometric correlations between left and right sensorimotor areas compared with non-musicians, which may be related to bimanual coordination[94]. Musicians also have more localized (less diffuse) correlations between frontal and auditory cortical regions, possibly indicating an increased specificity of anatomical relationships[95], and

musicians with absolute pitch have particularly strong short-distance correlations between different cortical areas that are known to underlie language and auditory functions[96].

The relationships between structural co-variance and behavioural or cognitive abilities could in theory be purely genetically mediated, but learning and training have been shown to alter brain morphology even in controlled experiments. A well-known series of studies showed that expert taxi drivers have larger hippocampal volumes that are proportional to their job experience[97,98], even relative to bus drivers, who have more routinized spatial knowledge[99]. Musical training alters brain anatomy in an array of motor, language and auditory areas[100–102] after as little as ~1 year of musical training in early childhood[103]. Individuals who learn to read for the first time have alterations in grey matter density in language areas compared with illiterate control subjects[104,105], and learning to juggle over a period of months or even days is associated with thickening of movement-associated visual and posterior parietal cortex[106,107]. Clearly, experience and training can alter morphological properties of individual brain regions and probably also patterns of co-variance between regions, although the latter has not yet been directly shown.

Structural co-variance across the lifespan

Childhood and adolescence

Regional and global brain anatomy undergo profound alterations during childhood and adolescence. Total brain volume more than doubles from birth to the age of 2 years, at which point it is already 80–90% of adult size[108]. MRI data indicate decreases in total grey matter and increases in white matter through to the twentieth year of life, which are generally attributed to a combination of synaptic pruning and myelination (which, in the prefrontal cortex, is not completed until after the third decade of life)[109]. There is considerable regional heterogeneity in developmental change. From birth to young adulthood (18–24 years of age), the expansion of the lateral temporal, parietal and frontal cortices is almost double that of primary visual and medial temporal regions[110]. The developmental trajectories of thickness and surface area also vary across the cortical mantle, usually peaking before the age of 10 years and declining at varying rates during adolescence[111–114].

During this period of major regional changes in neuroanatomy, the adult pattern of inter-regional correlations emerges. This maturation of brain structural co-variance involves a mixture of linear and non-linear alterations with age. In a study that tracked the growth trajectories of various seed-based networks in four age groups across childhood and adolescence, the youngest children generally showed the sparsest structural co-variance patterns, and these were limited to neighbouring areas and their contralateral homologues. Two alternative trajectories subsequently emerged: some networks showed progressive linear expansion across the age range, whereas others peaked in expansion in a middle age group (11–15-year-olds) before contracting in later adolescence[6].

Such differences in maturational trajectories may reflect functional distinctions between brain systems. The co-variance networks that tended to expand linearly across childhood and adolescence included anatomical areas of the brain that are known to subserve attention,

cognition and language functions (which is consistent with previous evidence for tighter correlations between anterior and posterior language areas in young adults relative to a paediatric sample[2]); by contrast, primary sensory and motor areas tended to be included in networks that followed the alternative trajectory of early expansion and contraction[6] (FIG. 3a), suggesting that they develop earlier in terms of their structural co-variance with the rest of the brain, as compared with more protracted development in association and limbic areas[6,115].

Global network properties become established early in life, and the tension between segregation and integration is reflected in alterations across the lifespan. It is striking that even in neonates, weeks after birth, structural co-variance demonstrates the small-world hybrid of network efficiency and local clustering[116], suggesting that these properties may in fact develop *in utero*. Infants also already display modular patterns consisting of communities of brain regions with relatively strong within-community structural co-variance. Subsequently, modularity, local efficiency and global efficiency all increase during the first 2 years of life, after which these network properties appear to exist at or near young adult levels[116]. Maturation between the ages of 5 and 18 years appears to be largely non-linear in nature, with a substantial but transient shift towards greater integration and less local segregation in late childhood[115].

Healthy ageing

Ageing has long been associated with regional reductions in cortical grey matter, particularly in medial temporal and prefrontal areas of the brain. These anatomical changes have been linked to neurocognitive alterations, as shown by performance in memory and attention tasks[117–120]. Disruptions of white matter integrity measured with diffusion MRI suggest that the relationships between widespread brain regions may also be affected by ageing[121,122], plausibly affecting structural co-variance patterns measured across the population.

Indeed, grey matter reductions in healthy ageing occur in brain areas with high inter-regional correlations in morphology, including in memory, cognition and language networks. Experimental methods based on principal component analysis (BOX 2), which reduce information about inter-subject co-variance into specific age-related patterns, have found correlated patterns of atrophy within frontal–temporal networks and within subcortical networks[123–126]. Initial analyses revealed particular patterns of correlated atrophy ('components') that were subsequently also found in other samples[123,126]— an example of successful experimental replication of brain imaging findings. The functional significance of age-related changes in structural co-variance networks is supported by their links with neuropsychological performance, as the strength of these brain-wide co-variance patterns is correlated with individuals' scores on memory, attention and cognitive tests[123,127] (even in healthy young subjects[127]).

The alterations in structural co-variance networks in the second half of life reverse-mirror some of the trends of childhood and adolescence (FIG. 3). Reduced structural co-variance has been found in ageing (60–84 years of age) relative to younger (18–35 years of age) adults in those cognitive and language networks[128] within which co-variance tends to

strengthen with age during childhood and adolescence[6]. By contrast, co-variance in sensorimotor networks peaks early in childhood[6] but does not appear to differ between young and old adults[128]. In terms of global organization, the integrative properties of structural co-variance networks, as quantified by the global efficiency, strengthen from young to middle-aged adults, with parallel weakening of segregative properties[129]. In adults over the age of 60 years, however, these changes are partially reversed, so that the balance shifts to a more localized organization[129,130]. The modular covariance structure that is established early in life may also be altered in subjects over the age of 60 years[129,131], for example, with fewer network edges involving prefrontal regions that comprise an 'executive function' module in young adults[131].

Structural co-variance in brain disorders

Neurodegenerative disorders

The neuronal loss that is characteristic of neurodegenerative diseases is detectable by structural MRI in the form of decreased grey matter density and thinning of the cortical surface in affected brain regions: for example, the medial temporal lobes in Alzheimer's disease. These regional morphological changes show potential as early predictors of disease-onset and prognosis, but theories of degenerative disease increasingly focus on brain networks as opposed to individual regions. For example, atrophy in Alzheimer's disease may target regions of the default-mode network — a group of anatomical areas that are characterized by their relatively strong intrinsic activity when the brain is in a 'default' state[132] — because these regions may be vulnerable owing to their high metabolic load[133]. Alternatively, pathogenic molecules may spread (and induce atrophy) via synaptic connections analogously to prion disease[134,135]. In contrast to anatomical studies of specific brain areas, imaging the correlation structure between regions has the potential to reveal the pathology of Alzheimer's disease at the network level.

In fact, studies assessing such correlations have argued that neurodegenerative diseases target regions that, in healthy individuals, are particularly highly structurally correlated[36], and inter-regional correlation patterns in patient populations are also altered compared with interregional correlation patterns in healthy populations[136]. For example, patterns of grey matter loss in five types of dementia, including Alzheimer's disease, overlap with distinct networks of brain regions whose grey matter volumes strongly co-vary in the healthy population — networks that closely match patterns of intrinsic functional connectivity and are involved in the behavioural and cognitive functions affected by these diseases[36] (FIG. 4a). Even in the healthy ageing population, regional brain atrophy is linked to the deposition of the Alzheimer's disease-related protein amyloid-β, and the focus of this amyloid-related atrophy is part of a structural co-variance network that is associated with cognitive functioning[137]. Similar patterns of grey matter loss within networks of brain regions with high structural correlations can also be distinguished in cognitively normal young adults who are genetically at risk of developing Alzheimer's disease[138]. The fact that atrophy occurs within structural co-variance networks both highlights their functional significance in healthy individuals and supports network interpretations of neurodegenerative disease.

In addition to neurodegeneration in Alzheimer's disease coinciding with structural co-variance networks, patterns of structural co-variance themselves are altered by Alzheimer's disease in various ways. The Alzheimer's disease population shows decreased structural co-variance between certain regions compared with the healthy population — especially in long-distance and interhemispheric correlations — and increased correlations between some brain areas targeted by the disease[136,139,140] (FIG. 4b). It is probable that there is more than one cause for these alterations, and disease-related changes in structural co-variance can be difficult to interpret. Attenuated correlations between brain regions may be suggestive of disconnectivity or of localized degeneration, if this degeneration affects just one region of a co-variance network. By contrast, strengthened correlations may indicate overconnectivity or correlated grey matter loss in regions targeted by the same neurodegenerative process. Although neither increased nor decreased pairwise correlations would necessarily influence the global organizational properties of structural co-variance, these properties also appear to be altered in Alzheimer's disease in the form of heightened local clustering and inefficient paths between brain regions[136,139]. This suggests that, in patients with Alzheimer's disease, the whole-brain network is more segregated and less integrated compared with that in healthy individuals.

Schizophrenia

Neurobiological research on schizophrenia used to focus on single brain regions, such as parts of the dorsolateral prefrontal cortex, that were thought to somehow 'contain' the cognitive and emotional functions disrupted by the disease. The focus has since shifted to the interactions between specific brain areas and, more recently, to the possibility of a global pathology affecting connections across the brain. Indeed, schizophrenia has come to be regarded more and more as a disease of disconnectivity. Discoveries about patterns of structural co-variance in schizophrenia[17,22,141–160] complement studies that show disrupted white matter tracts[161,162] and functional connectivity[163–165] between brain regions in the disease.

Patients with schizophrenia show abnormalities in frontal–temporal and frontal–parietal correlations as well as in many other inter-regional correlations, as discussed below. Frontal–temporal correlations are of particular interest in schizophrenia because of the possibility that auditory hallucinations, which is one of the most common symptoms of the disease, could result from a disturbance in the relationship between auditory areas in the temporal cortex and higher cognitive areas in the dorsolateral prefrontal cortex. Indeed, there is evidence for a link between the strength of frontal–temporal co-variance and auditory hallucinations[142], and early case–control studies found positive frontal–temporal correlations in the regional morphology of patients with schizophrenia that were absent from controls[143–146]. Subsequent larger studies have generally confirmed alterations in frontal–temporal correlations in schizophrenia[147–151]. The increased correlations in patients may indicate coordinated grey matter loss during neurodevelopment; indeed, frontal and temporal brain areas also show cortical thinning in schizophrenia[113], possibly due to overpruning of synapses during adolescence[166,167].

If altered frontal–temporal correlations are related to auditory hallucinations, then impaired cognitive ability — one of the most devastating symptoms of schizophrenia — may have its roots in other abnormal anatomical associations. The strength of cortico–thalamic[141] and frontal–parietal correlations[152] is associated with performance by patients on recall and working memory tasks, respectively, suggesting a link to cognitive symptoms. In case–control studies, correlations between the volumes of inferior parietal lobe and prefrontal cortical regions were increased in people with schizophrenia[152–154] and in genetically at-risk non-psychotic individuals[155] compared with healthy controls. Thalamo–cortical correlations are also altered in patients with schizophrenia[17,141,156,157], predominantly in the form of attenuated correlations[17,141,157]. There are some inconsistencies between brain imaging studies of schizophrenia, which are perhaps due to heterogeneity in the patient population and the potential anatomical effects of different treatment regimens. Almost every region of the brain has been reported to be involved in altered patterns of structural co-variance in one or more case–control study of schizophrenia.

It is possible that specific alterations in inter-regional correlations reflect specific aspects of the constellation of symptoms of schizophrenia, but the widespread nature of these alterations may also indicate a kind of systemic alteration in the pattern of structural co-variance (FIG. 4c). Graph theoretical studies suggest that brain organizational principles may be disrupted in people with schizophrenia[22,157,158] and in genetically at-risk neonates[159]. Specifically, structural co-variance networks show increased clustering and longer paths between brain regions[157–159] in terms of both the physical distance between strongly correlated regions[22,158,159] and the topological network efficiency[157–159]. The increased physical distance between strongly correlated brain regions is also supported by relatively increased inter-lobar and weakened intra-lobar correlations in patients[150,151]. In addition, it is mirrored by recent findings about functional connectivity networks in schizophrenia, which showed a focused weakening of functional connectivity over short distances and a relatively greater prominence of long-distant connections[11]. The identity of the nodes that are central to the network also appears to be altered in schizophrenia, with a shift away from the frontal and/or multimodal cortex towards the primary sensory and/or paralimbic cortex in the patient population[22,157,158].

Other conditions

Although Alzheimer's disease and schizophrenia have been the focus of a large portion of the research on structural co-variance, other neurological and psychiatric diseases are no less amenable to these methodological approaches. Studies in a wider range of patient populations are necessary to determine whether any changes in structural correlations between brain areas are disease-specific, or whether disruptions to the normative structure of correlations tend to have similar consequences across diseases. This research is at a preliminary stage, but pathological structural co-variance has been demonstrated in epilepsy, autism and various other conditions.

The hypersynchronized electrical activity that underlies epileptic seizures could alter structural co-variance patterns or reflect connectivity-related vulnerabilities that are observable at the level of population-wide correlations between regions. Patterns of atrophy

in temporal lobe epilepsy, the most common drug-resistant epilepsy in adults, recapitulate patterns of structural co-variance and known white matter connections in healthy individuals[168], a convergence similar to that observed in age-related neurodegenerative disease. It has been reported that the strength of positive inter-regional correlations is increased on average in temporal lobe epilepsy[169]. In addition, graph theoretical analysis of structural co-variance networks reveals decreased efficiency, increased clustering and an altered distribution of network hubs[169]. Longitudinal analysis suggests that network alterations become more apparent over time in the same group of patients[169], indicating that inter-regional neuronal synchronization may progressively alter structural covariance networks.

Because the onset of autism occurs before the age of 3 years during a critical period of brain development that includes the maturation of structural co-variance, it is unsurprising that inter-regional correlations found in healthy individuals may be disrupted in autism. Parts of the brain related to social cognition and behaviours that are abnormal in people with autism and other autism spectrum disorders may be particularly targeted. For example, one study showed that the structural covariance between the fusiform gyrus and the amygdala is decreased in autism spectrum disorders[170], which could relate to deficits in face processing, especially in social contexts. There appears to be a widespread disruption of positive inter-regional volume correlations in children with autism, particularly in brain regions that subserve social function[171]. This disruption could reflect an early developmental insult that prevents coordinated brain maturation of social cognition networks.

Various other disorders show altered patterns of structural co-variance, including but not limited to multiple sclerosis, chronic pain syndromes and mood disorders. Cortical thickness networks in multiple sclerosis are altered in proportion to the extent of white matter lesions[172]. Patients with chronic pain syndromes show altered spatial properties of structural co-variance, with a disruption of the inverse relationship between correlation strength and anatomical distance between brain regions that exists in healthy individuals[173]. Carriers of a *5-HTTLPR* polymorphism that has been associated with increased risk of depression have decreased correlations between the amygdala and anterior cingulate cortex[77]. In addition, there is preliminary evidence for structural co-variance alterations in bipolar disorder[174], Turner syndrome (usually associated with chromosome X monosomy)[175], cancer survivors with chemotherapy-related cognitive impairment[176], adolescents who had severely pre-term births[177] and grapheme–colour synaesthesia[178].

The variety of these conditions underscores the sensitivity of normative structural co-variance patterns to a range of developmental, genetic and environmental factors. However, it is difficult to interpret disease-related changes in structural co-variance, as we currently lack a clear understanding of the cellular and molecular mechanisms that normally drive the emergence of large-scale structural co-variance networks and their development during the life course.

Conclusions and future directions

Ongoing brain imaging research in animals should help to clarify the mechanisms underlying structural covariance and thereby contribute towards increasing the clinical utility of structural MRI for patients with neurological and psychiatric diseases and the capacity to test network hypotheses about disease mechanisms. When combined with the kind of controlled genetics and invasive experiments that are not possible in human subjects, animal brain imaging studies have the potential to yield a molecular and cellular understanding of inter-regional correlations in morphology[179–183]. Although few animal imaging studies to date have looked explicitly at covariance structure[180–182], the feasibility of such research has been demonstrated in non-human primates and in rodents. For example, a study of ageing rhesus macaques found inter-regionally correlated changes in grey matter volume with age that predicted working memory performance[182], which is consistent with studies of ageing in humans[124,125]. In addition, mice trained in different spatial navigation tasks showed task-specific alterations in grey matter density[183] that echo differences in human populations[5]. These alterations in grey matter density correlated with immunohistochemical markers of neuronal remodelling but not with variation in the size or number of neurons or astrocytes[183], suggesting the hypothesis that over time, synaptic changes can generate inter-regional structural correlations. In the future, animal models can be used to directly test such hypotheses.

Perhaps the holy grail of brain imaging is to increase its clinical utility for complex brain disorders such as schizophrenia and Alzheimer's disease. Classification studies have attempted to find MRI signatures that are associated with particular diseases or outcomes and that could be useful in diagnosis or treatment planning. Here, the inter-dependence of the anatomy of brain regions is both a hurdle (because many classification techniques are optimized for datasets of independent features) and an opportunity (because deviations from expected co-variance patterns provide additional information), and successful preliminary studies have explicitly or implicitly incorporated brain co-variance structure into their predictive models[184–186]. The complex mixture of developmental, genetic and environmental factors that influence anatomical structure and inter-regional dependence even in healthy individuals may be one reason why the clinical utility of MRI in psychiatry has yet to meet expectations. As the mechanisms of structural co-variance become better understood, and methods for measuring deviations from expectations in single scans become more securely validated, MRI data on structural co-variance in an individual patient could yield more useful information for clinicians.

The phenomenon of structural co-variance allows the exploration of network hypotheses about disease mechanisms. For example, patterns of atrophy in neurodegenerative disease appear to be consistent with the transneuronal spread of pathology through white matter tracts[135] and functional connectivity networks[134] that were previously shown to closely match structural co-variance networks in the same patient populations[36]. The importance of more research into functional connectivity and diffusion imaging is widely acknowledged. However, studies that explicitly target brain connectomics can be prohibitively expensive, whereas structural MRI scans that are acquired for clinical purposes as part of many large studies often remain unanalysed. The application of network analysis to inter-regional co-

variance patterns in existing datasets is a relatively untapped resource and could provide a window into the developmental relationships between different parts of the human brain.

Acknowledgments

Abbreviations

Correlation	When two sets of data are statistically inter-dependent or mutually predictive.
Topology	The pattern of connections or relations between nodes within a network.
Segregation	The existence, in the brain, of relatively distinct anatomical, physiological or functional units.
Modularity	The concept that a network has a community structure and can be decomposed into a set of modules, with each module comprising nodes (brain regions) that are densely connected to each other and sparsely connected to nodes in other modules.
Integration	The capacity of the brain to act as single, unified entity.
Hubs	Topologically important or central nodes.
Efficiency	A measure that is inversely proportional to the lengths of the shortest paths between nodes. In brain networks, the global efficiency is often used as a measure of the overall capacity for parallel information transfer and integrated processing.
Pleiotropy	When a single gene influences many phenotypic traits.

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## Box 1 | Measuring structural co-variance in human brain MRI data

An MRI scan images the hydrogen in water molecules throughout the brain as pulses of energy alter their alignment with the scanner's static magnetic field. The timing of these alterations depends on the specific kind of brain tissue and on magnetic gradients that are superimposed on the static magnetic field, enabling a three-dimensional picture of the brain. Analogous to a pixel in a two-dimensional digital photograph, the approximately cubic 'voxel' is the basic element of these images[187]. Further analysis of these brain images yields morphological information about regions of the brain, such as their volume, thickness and surface area.

Manual tracing of brain images by expert anatomists has given way to largely computer-automated analyses. In approaches such as voxel-based morphometry, voxels are segmented on the basis of their image intensity into one of three tissue classes: cerebrospinal fluid, white matter or grey matter. After registering all of the scans in a study into a common anatomical space, using an average brain as a template, the grey matter density (or 'volume') at each voxel can be compared across the brain and between subjects[188–190]. In contrast to these intensity-based approaches, surface-based analyses explicitly model the boundaries that separate the grey matter of the cerebral cortex from the deeper white matter and the surrounding cerebrospinal fluid[191–194]. This step enables the distinction between surface area and thickness contributions to cortical volume, which may have different genetic[195] and developmental[196] underpinnings. In addition, surface-based approaches can explicitly study cortical folding and curvature[197].

The simplest case of determining structural co-variance is to consider the relationship between the morphology of one brain region and that of another brain region, each measured in a large sample of human subjects (see the figure). Commonly, the linear dependence between these two datasets is indicated by the product–moment correlation coefficient, Pearson's r. The terms co-variance and correlation are often used synonymously, but only the correlation coefficient is normalized by the variance of the individual datasets, which makes it possible to compare correlations between datasets of different scales. Alternative statistics offer increased robustness to statistical outliers[198] and/or sensitivity to non-linear relationships[199]. Confounding variables that could affect correlation patterns within a sample, such as age and gender, can be corrected for by using partial correlation methods. Allometric relationships in the form of different brain regions scaling differently with total brain size[200,201] can also be incorporated into statistical models.

Outstanding methodological problems exist in structural MRI analysis in general, and in structural co-variance analysis in particular. Issues with in-scanner subject motion, spatial normalization and MRI tissue contrast make the reliable and accurate extraction of morphological properties in paediatric samples a particular challenge[202]. The cellular interpretation of MRI-based morphological properties is also non-trivial and difficult to compare across experimental contexts. For example, 'cortical thinning' during adolescence could reflect synaptic pruning or increased myelination[109], whereas it is associated with neuronal loss in neurodegenerative disease[203].

Although measures of grey matter volume and cortical thickness have been the subject of most studies to date and are therefore the focus of this Review, studies have begun to look at the co-variance of other structural phenotypes, including surface area[204], white matter volume[150,205] and diffusion imaging measures of tissue integrity[206]. Co-variance patterns need not be the same across structural phenotypes, and differences have already been demonstrated between cortical thickness and surface area co-variance[204]. Co-variance methods are theoretically applicable to any structural or anatomical phenotype, and including a larger array of brain imaging measures is a major target for future research. The figure is modified, with permission, from REF. 32 © (2013) Society for Neuroscience.
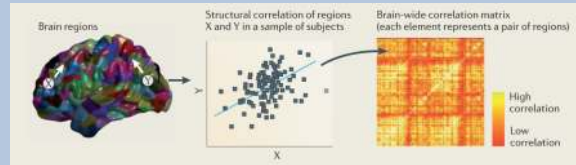
Box 2 | Structural co-variance networks

Studies that reveal structural co-variance networks generally use one out of three experimental approaches: seed analysis, principal component analysis or graph analysis. These methods are not unique to structural co-variance analysis, and they have analogues in the analysis of other brain connectivity and correlational data. For example, in functional MRI (fMRI) functional connectivity analysis, if correlations in brain activity are calculated between regions over time, then similar network methods can be applied. Brain structures measured in multiple subjects have the same statistical role for structural co-variance analysis as brain activations measured at multiple time points do for functional connectivity analysis.

Possibly the most straightforward of these methods is seed analysis. Here, the morphology in one seed region is compared with the morphology in the rest of the brain to generate a whole-brain map of structural co-variance (see panel **a** of the figure, which shows maps resulting from two different seed regions on the left and the right, respectively, with non-cortical areas blacked out). Maps created from different seed regions or from samples taken from different patient populations can then be compared.

Principal component analysis reduces the inter-regional co-variance across people to a small number of factors that are easier to visualize and interpret (see panel **b** of the figure, which shows brain maps of three components, with non-cortical areas blacked out). The principal components are like anatomical patterns composed of highly correlated brain regions: the different patterns are more strongly expressed in some people and less strongly in others, but together they explain a large portion of the variation across people. In principal component analysis, these different patterns are orthogonal to each other (perpendicular in multidimensional space); in addition, the first component explains as much of the total variance as possible, the second component explains as much of the remaining variance as possible and so on. Stressing other properties of the components, such as their statistical independence, yields different techniques, such as independent component analysis.

The graph theoretical approach tries to summarize complex global and regional co-variance patterns into biologically meaningful properties. A graph is a model that describes some basic elements (nodes) and the relationships between them (edges). In this case, nodes are brain regions, and edges represent significant morphological correlations between them. Graphs whose edges tend to form triangles have high clustering; graphs with dispersed edges such that short paths exist between most nodes have high efficiency; and graphs composed of communities with many within-community edges and fewer between-community edges have high modularity (FIG. 1). When applied to assess structural co-variance (see panel **c** of the figure), graph analysis performs pairwise correlations between every brain region. Thresholds are then applied, resulting in a small number of important correlations in a graph model, whose topological properties (such as clustering, modularity and efficiency) are measured. The properties of brain structural co-variance networks diverge sharply from simulated networks in which edges are drawn at random between nodes[15,207]. There are important and unresolved questions about graph construction and analysis[208–210].

One important point of difference between structural co-variance, fMRI and diffusion MRI networks is that fMRI and diffusion MRI networks can routinely be constructed from measures of inter-regional association or connectivity estimated for an individual image. By contrast, structural co-variance networks are constructed from inter-regional correlations estimated on the basis of a group of individual images. Methods for the construction of a network from an individual structural MR image have been reported[211] but not yet widely applied. This limits the opportunity to link structural co-variance metrics to inter-individual differences, for example, in cognitive function. Panel **c** is modified, with permission, from REF. 32 © (2013) Society for Neuroscience.
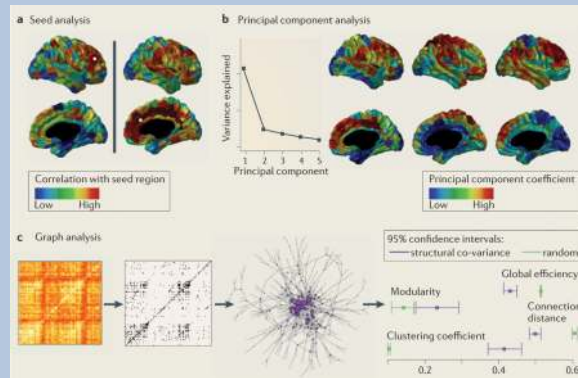
Box 3 | Anatomical and functional connectivities

Neuroimaging experiments explore the connectivity between anatomic parcels of brain matter using various methodological approaches. Diffusion MRI targets water molecules that diffuse preferentially along white matter tracts, which are groups of axons that are encased in layers of insulation and carry electrical signals across the brain. Unlike post-mortem dissection, microscopy and chemical tracing, which remain the gold standard for the determination of axonal connections, diffusion MRI can gather information about white matter tracts across the entire brain of a living person in a matter of minutes. However, crucial methodological issues remain unresolved[212–214].

By contrast, coordinated brain activity between regions is often labelled 'functional' connectivity. The magnetic properties of oxygenated blood, which fluctuate with regional brain activity[215], allow correlations between regions to be determined over time using functional MRI (fMRI). Electroencepholography (EEG) and magnetoencepholography (MEG) measure electrical signals directly as opposed to the (much slower) vascular response, but the spatial resolution of these methods is much lower than that of fMRI. A causal relationship between brain regions (as opposed to merely synchronized activity) is sometimes termed 'effective connectivity'[216]. Both functional and effective connectivity can be changed by cognitive, behavioural and emotional tasks, but 'intrinsic' inter-regional relationships may also exist[132].

As has been said of consciousness[217], brain connectivity is a mongrel concept: there are many different kinds of 'connectivities'. Even the arguably simplest kind of brain connectivity — the synapse between two neurons — has vastly different electrical, chemical, morphological and functional subtypes. It is therefore important not to simply conflate morphological co-variance across subjects — which itself is often described as structural or anatomical connectivity — with other kinds of brain connectivity. Studies comparing white matter and functional connectivity provide a template for such comparisons. These studies have demonstrated that if two regions are linked by a white matter tract, they tend to have high functional connectivity; however, functional connectivity also exists in the absence of direct white matter links, owing to indirect or emergent properties of white matter networks[34,35,218,219]. The relationships between brain connectivities must be explicitly tested.
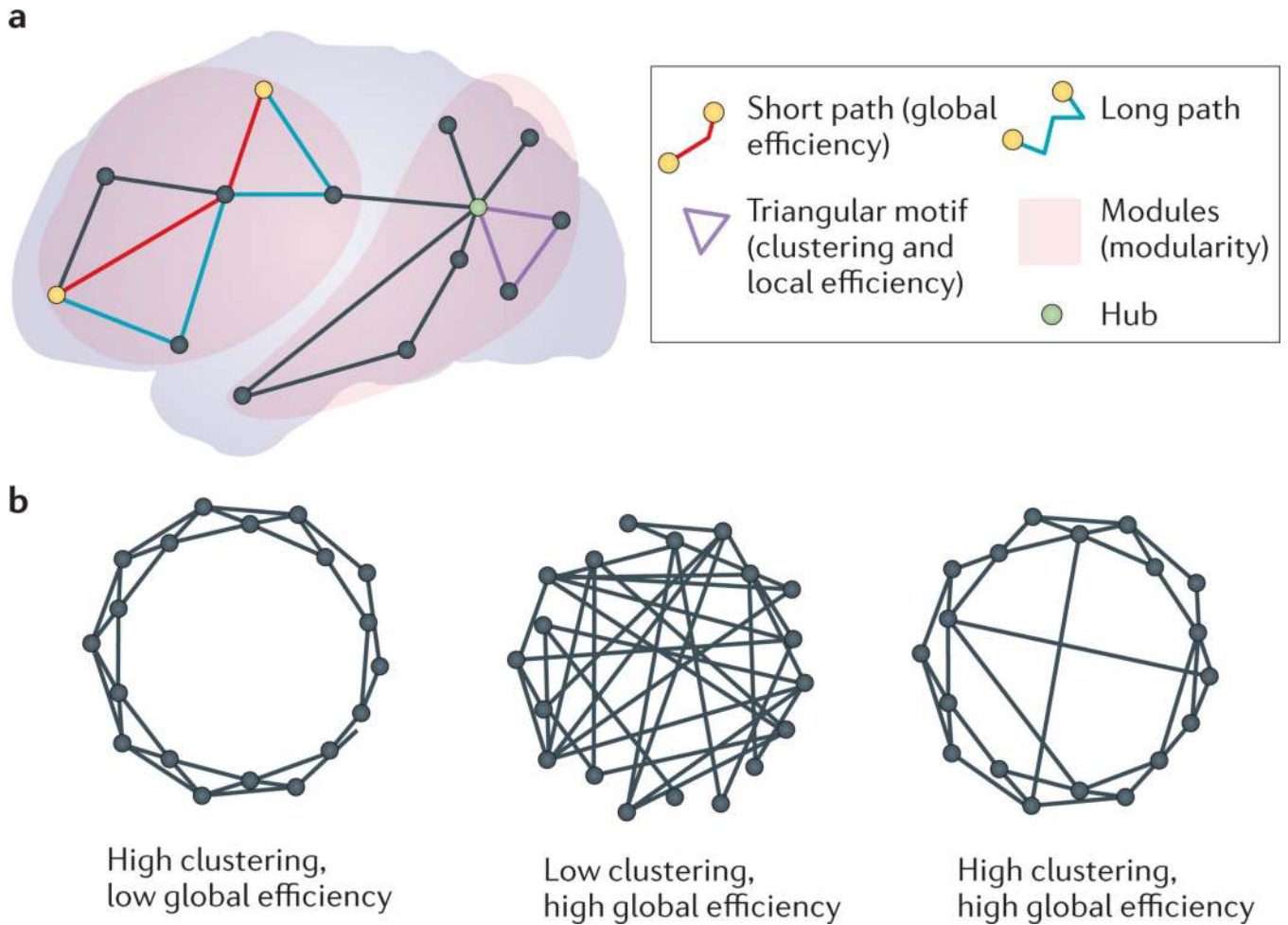
a

b

High clustering, low global efficiency

Low clustering, high global efficiency

High clustering, high global efficiency

Figure 1. Schematics of network properties

a | A simulated network is used to illustrate common terms in network analysis. Nodes are represented as circles, and edges are represented as lines. Networks with short paths between most nodes have high global efficiency. Networks with many triangular motifs tend to have high nodal clustering and local efficiency. A disproportionate number of paths between nodes pass through network hubs. Nodes within the same module are connected by many edges, whereas nodes in different modules are connected by relatively fewer edges. **b** | An example of a network with high clustering but low global efficiency is shown on the left, an example of a network with low clustering but high global efficiency is shown in the middle, and an example of an intermediate (small-world) network with both relatively high clustering and relatively high global efficiency is shown on the right[220].
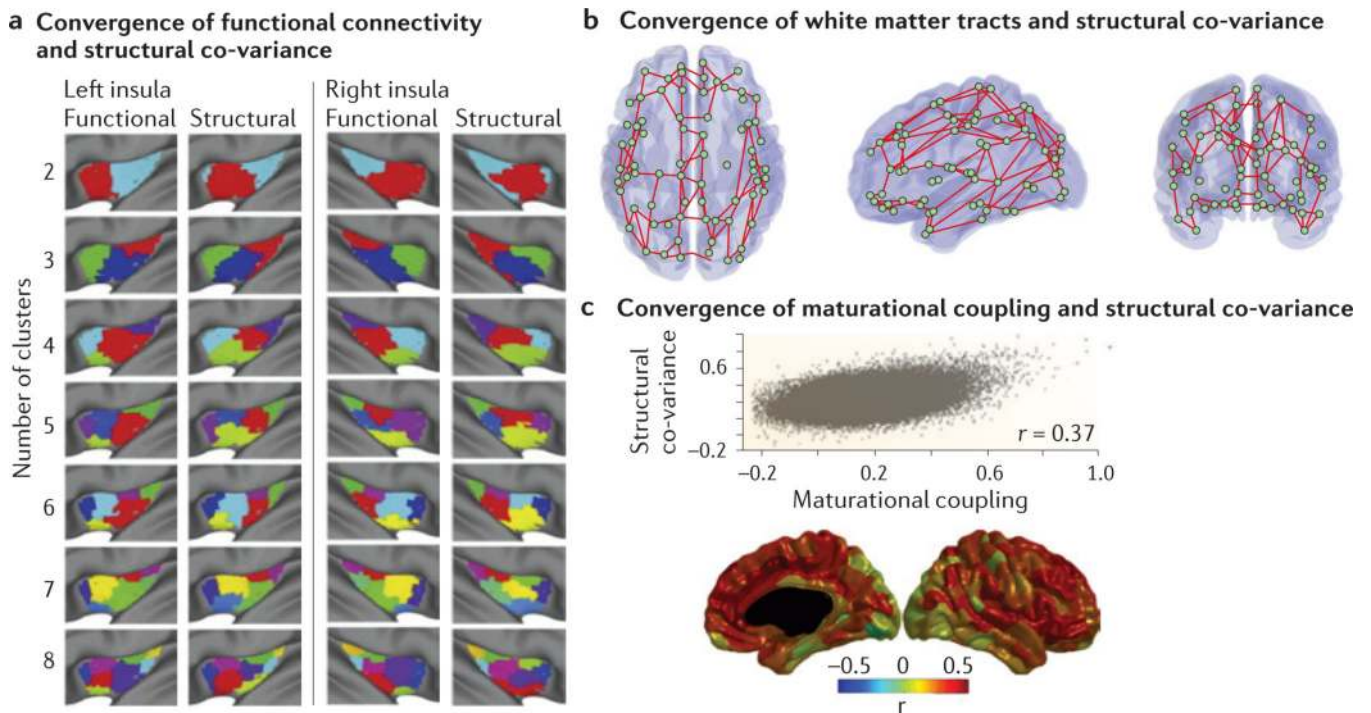
a Convergence of functional connectivity and structural co-variance

b Convergence of white matter tracts and structural co-variance

c Convergence of maturational coupling and structural co-variance

Figure 2. Co-variance may reflect connectivity

a | Clustering of the left and right insula into subregions reveals similar regional boundaries when the clustering is based on resting-state functional MRI functional connectivity data ('functional') as when it is based on grey matter co-variance ('structural'). The similarity of these 'clusters' (indicated by different colours in the figure) is consistent with the idea that functional connectivity influences patterns of structural co-variance. **b** | Pairs of regions that have both high cortical thickness co-variance (that is, structural co-variance) and white matter tract connectivity (based on diffusion MRI) in the same group of subjects are shown on a transparent rendering of the brain. Circles represent network nodes and lines indicate reliable convergence between diffusion MRI and structural co-variance. This convergence is stronger between regions that are close in anatomical space and weaker between regions separated by long distances, illustrating both similarities and differences between white matter connectivity and structural co-variance. **c** | Structural co-variance, which here is derived from inter-regional correlations in cross-sectional measurements of cortical thickness, may reflect 'maturational coupling.' Maturational coupling was defined via a two-step process: first, the linear rate of change in cortical thickness from the age of 9 to 22 years was estimated for a group of subjects with multiple longitudinal MRI scans; and second, inter-individual differences in these rates of change were correlated between regions across the cortex. The correlation between structural co-variance and maturational coupling ($r = 0.37$) — measured across all pairs of brain regions in the same group of subjects — indicates the inter-dependence of these measures (top panel). The brain maps (bottom panel) illustrate these correlations in a region-specific fashion, showing that the level of convergence (shown by the colour, a warmer colour indicating a stronger convergence) between maturational coupling and structural co-variance is anatomically heterogeneous (non-cortical areas are blacked out). Part **a** is modified, with permission, from REF. 38 © (2012) Elsevier. Part **b** is

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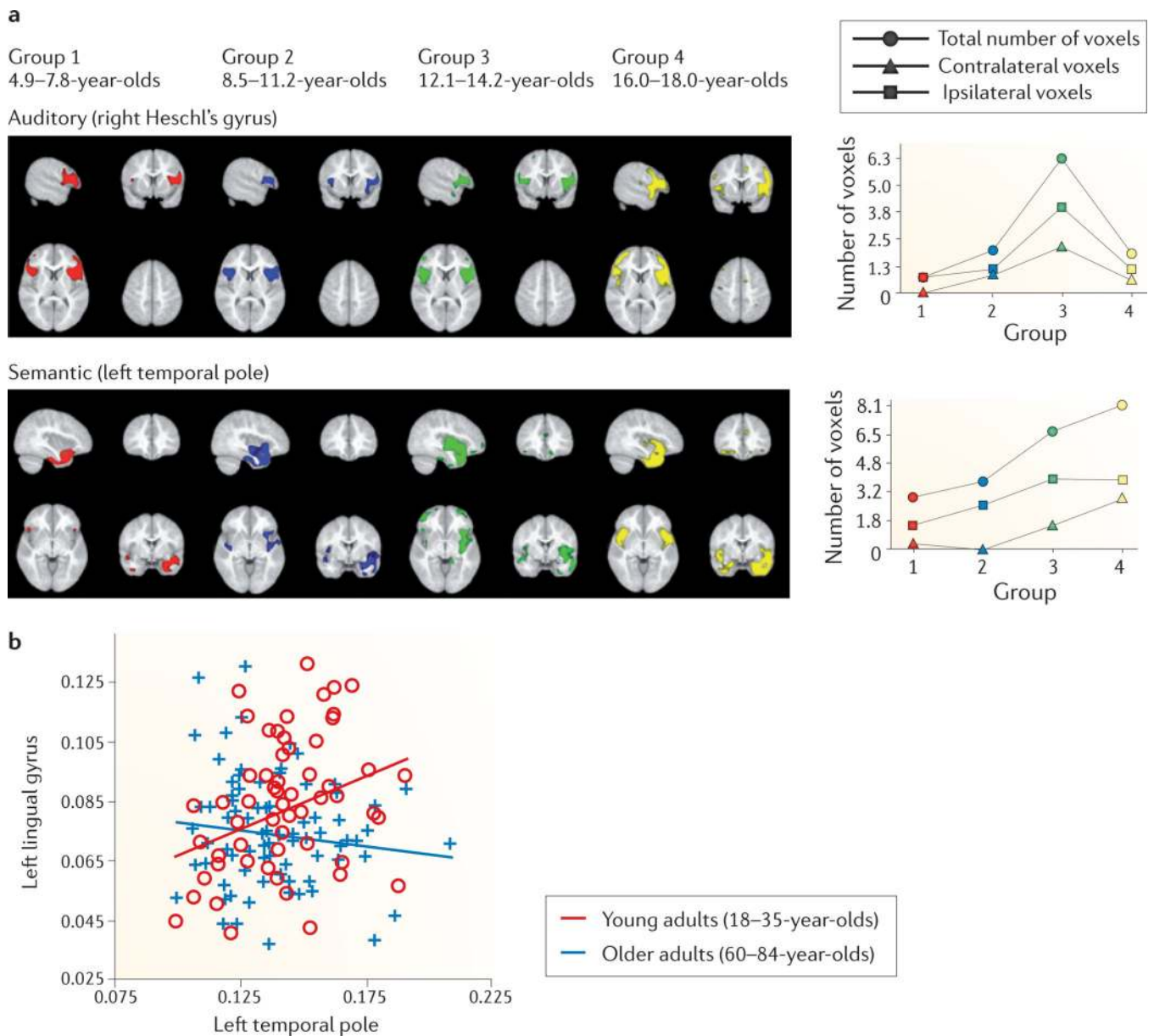
Figure 3. Structural co-variance networks change across the human lifespan

a | In 5–18-year-olds, certain seed-based grey matter co-variance networks, such as the primary auditory network (top, coloured areas) seeded from right Heschl's gyrus, peak during adolescence (in 12–14-year-olds) in terms of the total number of voxels, ipsilateral voxels and contralateral voxels that are correlated with the seed voxels. Other co-variance networks, such as the semantic language network (bottom) seeded from the left temporal pole, grow across the age range in terms of the number of other voxels correlated with the seed voxels. These different maturational trajectories may have functional significance, as primary sensory networks tend to peak in the number of voxels correlated with the seed voxels during adolescence, whereas many cognitive and language networks grow in the number of voxels correlated with the seed voxels through the eighteenth year of life. **b** | Correlations within the semantic language network and several other networks that tend to

grow in strength from 5 to 18 years of age show a reversal in later years. For example, structural co-variance between the left lingual gyrus and the seed voxel of the semantic language network in the left temporal pole is positive in younger adults (18–24-year-olds) but not in older adults (60–84-year-olds). Part **a** is modified, with permission, from REF. 6 © (2010) National Academy of Sciences. Part **b** is modified, with permission, from REF. 128 © (2012) Elsevier.
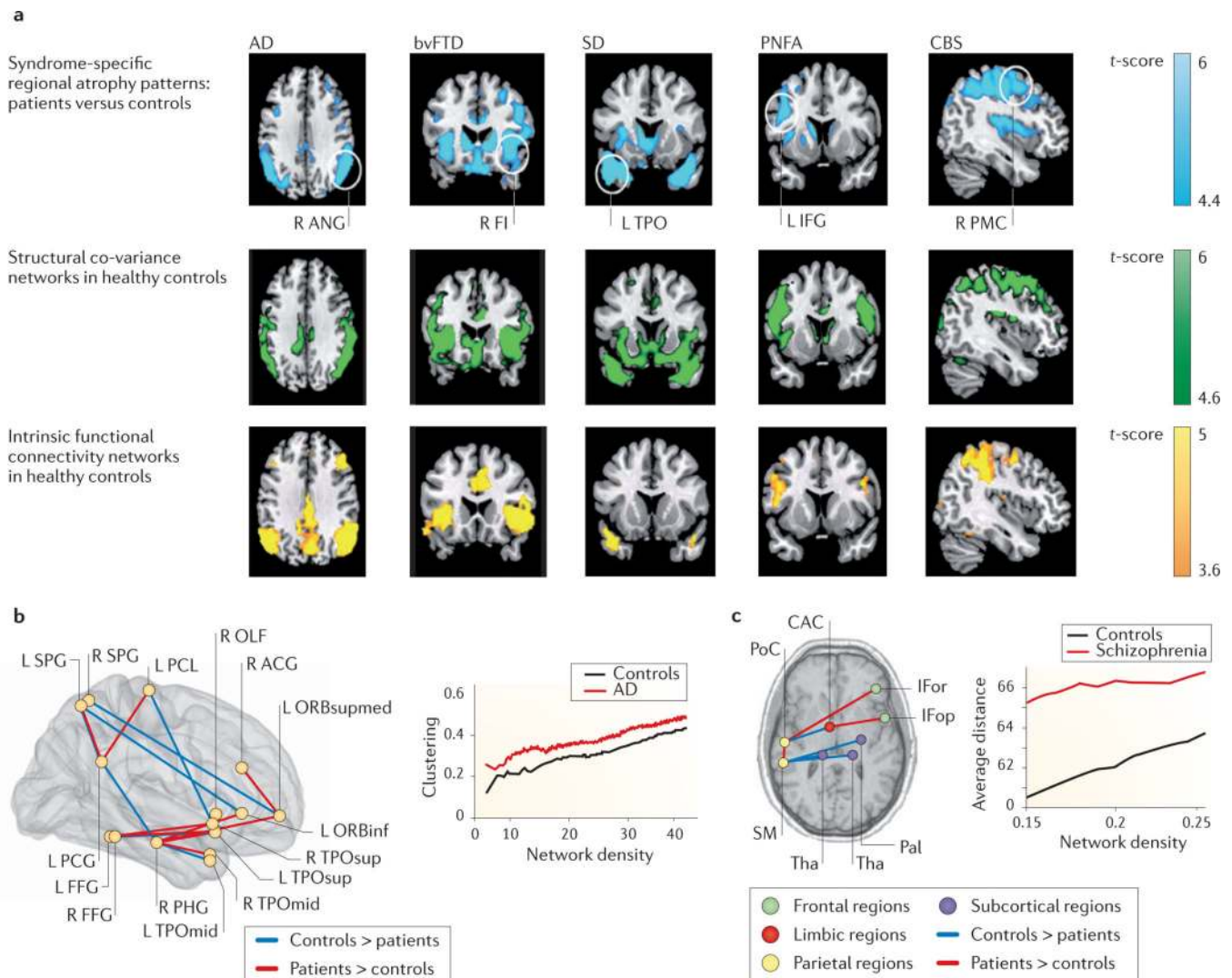
Figure 4. Structural co-variance networks are altered in disease

a | Seed-based structural co-variance networks (green) and intrinsic functional connectivity networks (yellow) in healthy individuals, using, as seed regions, the foci of grey matter loss in different samples of patients with five neurodegenerative diseases (blue). These include the right angular gyrus (R ANG) in Alzheimer's disease (AD); right frontal insula (R FI) in behavioural variant frontotemporal dementia (bvFTD); left temporal pole (L TPO) in semantic dementia (SD); left inferior frontal gyrus (L IFG) in progressive non-fluent aphasia (PNFA); and the right premotor cortex (R PMC) in corticobasal syndrome (CBS). The pattern of grey matter loss in patients recapitulates the patterns of structural co-variance and functional MRI functional connectivity in healthy individuals. This suggests that these diseases may target structural co-variance networks and that these structural co-variance networks are also functionally significant in the healthy brain. **b** | Structural co-variance alterations in AD. The brain map (left) shows specific regions whose structural correlations are higher (red lines) or lower (blue lines) in patients with AD compared with control subjects. These regions include the paracentral lobule (PCL), superior parietal gyrus (SPG), posterior cingulate gyrus (PCG), anterior cingulate gyrus (ACG), olfactory cortex (OLF),

inferior orbital cortex (ORBinf), superior medial orbital cortex (ORBsupmed), fusiform gyrus (FFG), parahippocampal gyrus (PHG), superior temporal pole (TPOsup) and middle temporal pole (TPOmid). At the network level (right), the AD network shows abnormally high clustering, indicating greater local agglomeration of connected nodes. **c** | Structural co-variance alterations in schizophrenia. The brain map (left) illustrates specific regions in which structural correlations are higher (red lines) or lower (blue lines) in patients with schizophrenia compared with control subjects. These regions include the postcentral cortex (PoC); supramarginal cortex (SM); inferior frontal cortex, orbital part (IFor); inferior frontal cortex, opercular part (IFop); caudal anterior cingulate (CAC); pallidum (Pal); and thalamus (Tha). At the network level (right), the average distance between connected nodes is longer in schizophrenia, suggesting that pairs of regions with the strongest structural co-variance are less close to each other in the patient group. Results are shown across a range of network 'density', which indicates the proportion of the strongest pairwise correlations included as edges in the graph models. Part **a** is modified, with permission, from REF. 36 © (2009) Cell Press. Part **b** (left) is modified from REF. 139. Part **b** (right) is modified, with permission, from REF. 136 © (2008) Society for Neuroscience. Part **c** (left) is modified, with permission, from REF. 157 © (2012) Elsevier. Part **c** (right) is modified, with permission, from REF. 22 © (2008) Society for Neuroscience.