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Human Cortical Anatomical Networks Assessed by Structural MRI

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Abstract Mapping the structure and function of the brain with non-invasive brain imaging techniques has become a world-wide enterprise in the last 20 years. The core concept that drives this rapid growth has been the use of a standardized 3D coordinate space for combining data from many subjects and/or time-points. This has allowed geographically-separated laboratories to reproduce experiments in precise detail, to share data or to perform meta-analysis in ways that go far beyond the traditional reviewing of summary results in journal publications. A further corollary of the brain mapping approach is the natural fostering of multi-center collaboration among distant sites. This article describes recent progress in trans-Pacific collaboration between Canadian and Asian laboratories in the study of neuroanatomical networks obtained from MRI data, both in the normal brain and in neurodegenerative disorders.

Keywords Brain mapping · Cortical thickness · Brain networks · Small-world · Pacific rim · Alzheimer's disease · Multiple Sclerosis · Leukoaraiosis

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Preamble

Brain mapping, the marriage of 3D brain imaging technology (MRI, fMRI, PET, MEG etc) and sophisticated computational analysis within a standardized (stereotaxic) coordinate space has become a global industry over the last 20 years. Brain mapping is ideally suited to an emerging scientific method based on information technology, due to its inherent digital nature and, most importantly, the concept of stereotaxic space. This somewhat trivial notion has had, and will continue to have, a profound impact on the way brain science is conducted and how brain scientists around the world interact. Although the dizzying technical advances in imaging hardware (signal type, sensitivity, spatial resolution, temporal resolution) and computation (compute power, storage capacity, web-based distribution of resources and information) are of course the building blocks of brain mapping, the use of the stereotaxic principle stands apart as the essential concept that binds together the global brain mapping community. It allows for the digital integration of data across subjects, across time and across laboratories such that a virtual "co-laboratory" of geographically distant scientific groups becomes an effective mode of scientific advancement.

The International Consortium for Brain Mapping (ICBM, Mazziotta et al. 1995, 2001), first established in 1993, was an early example of global brain mapping initiatives. Originally established by 3 centers at UCLA, McGill/MNI and the U. of Texas to create a probabilistic digital atlas of the human brain, ICBM expanded to include new centers in North America, Europe and Japan. Within ICBM, many multilateral, multinational collaborations have emerged around specific projects. Moreover, many groups in the Far East have developed similar but independent programs for the mapping of brain structure and function.

In this article, we describe recent collaborative work between neuroimaging scientists in Canada, China, Japan and Korea in the study of cortical anatomy with structural MRI. Scientists from Montreal and Seoul jointly developed an algorithm, CLASP, for automatic extraction of the cortical surface from 3D MRI. A collaboration between the Montreal and Beijing scientists used raw cortical thickness measurements as the basis for a network analysis of correlated changes of cortical thickness in neurodegenerative disease. Finally, a collaboration between Montreal and Sendai researchers, as part of ICBM, has conducted similar studies of aging and neurovascular disorders.

In the following sections, we will summarize this work, emphasizing cortical anatomy networks, and offer some perspectives on the future evolution of trans-Pacific collaboratory initiatives.

Introduction

The human brain is a large, interacting, complex network with nontrivial topological properties. Characterizing the architecture of such a network is an important issue in neuroscience. It can reveal general principles of structural and functional organization in the human brain and increase our understanding of how the human brain generates and integrates information from multiple sources (Sporns et al. 2000, 2004; Sporns and Tononi 2002). Most studies have focused upon functional connectivity. For example, recent EEG or MEG (Micheloyannis et al. 2006; Stam and Zwi 2004; Stam et al. 2006, 2007) and fMRI (Eguiluz et al. 2005; Salvador et al. 2005a, b; Achard et al. 2006) These studies have consistently demonstrated that human brain functional networks have "small-world" properties, a feature shared by various social, economic, and biological networks (Strogatz 2001). In small-world architectures the minimum path length between any pair of nodes approximates that of a comparable random network but the nodes have greater local interconnectivity or cliquishness (Watts and Strogatz 1998).

Little is known about the network of neuroanatomical connections. Connection models of the human brain are usually inferred from primate research (Stephan et al. 2000, 2001; Penny et al. 2004). That procedure is problematic, however, partly because of our poor understanding of the evolutionary discrepancies. Direct evidence for the underlying architecture of human brain anatomical networks is still lacking (Tootell et al. 2003). Characterizing such networks would reveal intrinsic structural organizational principles and clarify how functional brain states are associated with structural substrates. Recently, Sporns et al. (2005) referred to the comprehensive, detailed structural description of the network of elements and connections forming the human brain as the "human connectome".

In order to characterize the network properties of cortical anatomy, we developed a methodology for characterizing the regional correlation of MRI-derived cortical thickness. Thickness was chosen because it reflects the size, density, and arrangement of neurons, neuroglia, and nerve fibers (Parent and Carpenter 1995; Narr et al. 2005). The exact nature of cortical thickness correlations is still unknown but may arise from mutual trophic influences (Ferrer et al. 1995), heredity (Suddath et al. 1990; Steinmetz et al. 1994; Thompson et al. 2001) or common experience–related plasticity (Maguire et al. 2000; Draganski et al. 2004; Mechelli et al. 2004). Regions with correlated anatomy may be part of functional systems (Andrews et al. 1997; Wright et al. 1999; Mechelli et al. 2005; Mitelman et al. 2005). For instance, Andrews et al. (1997) observed that components of the visual system co-vary in volume across individuals. Significant regional gray matter volumetric or concentration correlations have been found in frontal–temporal (Woodruff et al. 1997; Bullmore et al. 1998; Mitelman et al. 2005) and frontal–parietal systems (Wright et al. 1999; Mechelli et al. 2005). Lerch et al. (2006) demonstrated a striking similarity between cortical thickness correlation map of Brodmann Area 44 and a diffusion tensor map of the arcuate, perhaps reflecting two aspects of the same underlying process. Ultimately, it is likely that all of these processes influence the pattern of anatomical connections in the brain.

Cortical surface analysis (CLASP)

Our algorithm for the fully-automated extraction of cortical surfaces (MacDonald et al. 2000; Kim et al. 2005; Lyttelton et al. 2007, Fig. 1) was first developed at the MNI and, as part of an ongoing collaboration between Hanyang University and the MNI, was further enhanced by Dr. June Sik Kim from Seoul during a post-doctoral fellowship at the MNI. The algorithm has been extensively validated (Kabani et al. 2001; Lerch and Evans 2005). A comparison of surface extraction algorithms conducted at the Seoul laboratory (Lee et al. 2006) demonstrated that CLASP outperforms other well-known surface extraction algorithms Freesurfer and BrainVisa, in

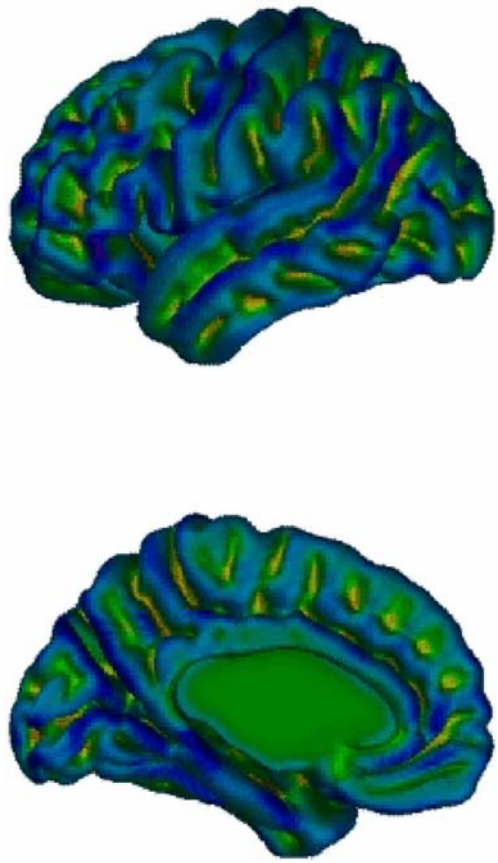

Fig. 1 Cortical Surface Extraction: CLASP surface average in stereotaxic space for N=152 normal adult subjects (ICBM data, Mazziotta et al. 2001; Watkins et al. 2001). Note extensive detail in the surface despite it being averaged across 304 (152×2) hemispheres, a consequence of iterative surface alignment (Lyttelton et al. 2007)

part due to the fact that a spherical topology is preserved throughout, i.e. no manual intervention to correct for "holes" or "handles" in the extracted surface. A simulation-based validation strategy compared quantitatively the performance of these algorithms, assessing geometrical accuracy and mesh characteristics such as the Euler characteristic (EC), fractal dimension (FD), total surface area, and local mesh density. CLASP showed the best accuracy in surface recovery, topology (EC, FD) and total surface area.

Graph theoretical network analysis (GRETNA)

Dr. Yong He, mediating a collaboration between the MNI and the Beijing Institute of Automation, recently developed a graph theoretical approach to the study of cortical morphology. This technique, GRETNA (Fig. 2) examines the correlation among morphological properties of different cortical regions. Specifically, it allows (i) a full-matrix analysis of CLASP-derived cortical thickness in all locations against all other locations, and (ii) a graph–theory analysis of the network properties of the correlated regions (He et al. 2007). The cortex is parcellated into N regions and the mean cortical thickness, T, across all intra-regional vertices, obtained. A linear regression of T_i versus T_j, across all subjects, is then performed for all pairs of regions i,j. Significant correlations define a graph of N nodes (regions) and K edges (connections) with parameters: a) *Degree k_i:* number of connections to node i, b) *Clustering coefficient Cp:* node average of $C_{i,}$ the number of connections between a node's neighbors divided by all possible connections (Watts and Strogatz 1998). Cp measures local clustering or "cliquishness", c) *Mean path length Lp:* average of L_{ij}, the smallest number of connections linking node i to node j, over all node pairs. Lp measures average connectivity or overall routing efficiency, d) *Wiring cost:* number of edges in a graph divided by the maximum possible number of edges.

GRETNA was first applied to brain MRI data from 124 right-handed normal adults (age 24.4±4.3), (linear regression removed the effects of age, gender, age-gender interaction and mean overall cortical thickness). The resultant brain network contained 45 nodes and 102 edges[2] (~7% of all possible pairs). It demonstrated significant short- and long-range correlations of cortical thickness, corresponding to known fibre connections (Table 1). C_p and L_p for the brain network were also compared with their average for 1,000 random networks, generated using the random rewiring procedure of Maslov and Sneppen (2002). Small-world networks fulfill the conditions: $\gamma = C_p^{real} / C_p^{rand} > 1$ and $\lambda = L_p^{real} / L_p^{rand} \sim 1$ (Watts and Strogatz 1998), summarized as "small worldness", $\sigma = \gamma/\lambda > 1$, (Humphries et al. 2005; Achard et al. 2006). The pattern of coordinated variation in the thickness of the cerebral cortex was neither regular nor random but "small-world" in nature, characterized by a high C_p and short L_p This small-world character suggests that human cortex has evolved in an optimally organized fashion to support both modularized and distributed information processing (Basset and Bullmore 2006; Basset et al. 2006; Sporns and Zwi 2004), minimizing wiring costs while maximizing the efficiency of information propagation (Achard and Bullmore 2007; Kaiser and Hilgetag 2004, 2006).

Network modularity in normal adult brain

We further used GRETNA to reveal a modular architecture in the normal **structural** brain network which reflects the known **functional** neuroanatomy (Chen et al. 2008). From a network topological perspective, a high C_p suggests modularity, where a module is a group of connected regions that subserve distinct brain functions. Each module should have denser intra-module than inter-module connections. The identification of modules by cortical thickness corre-

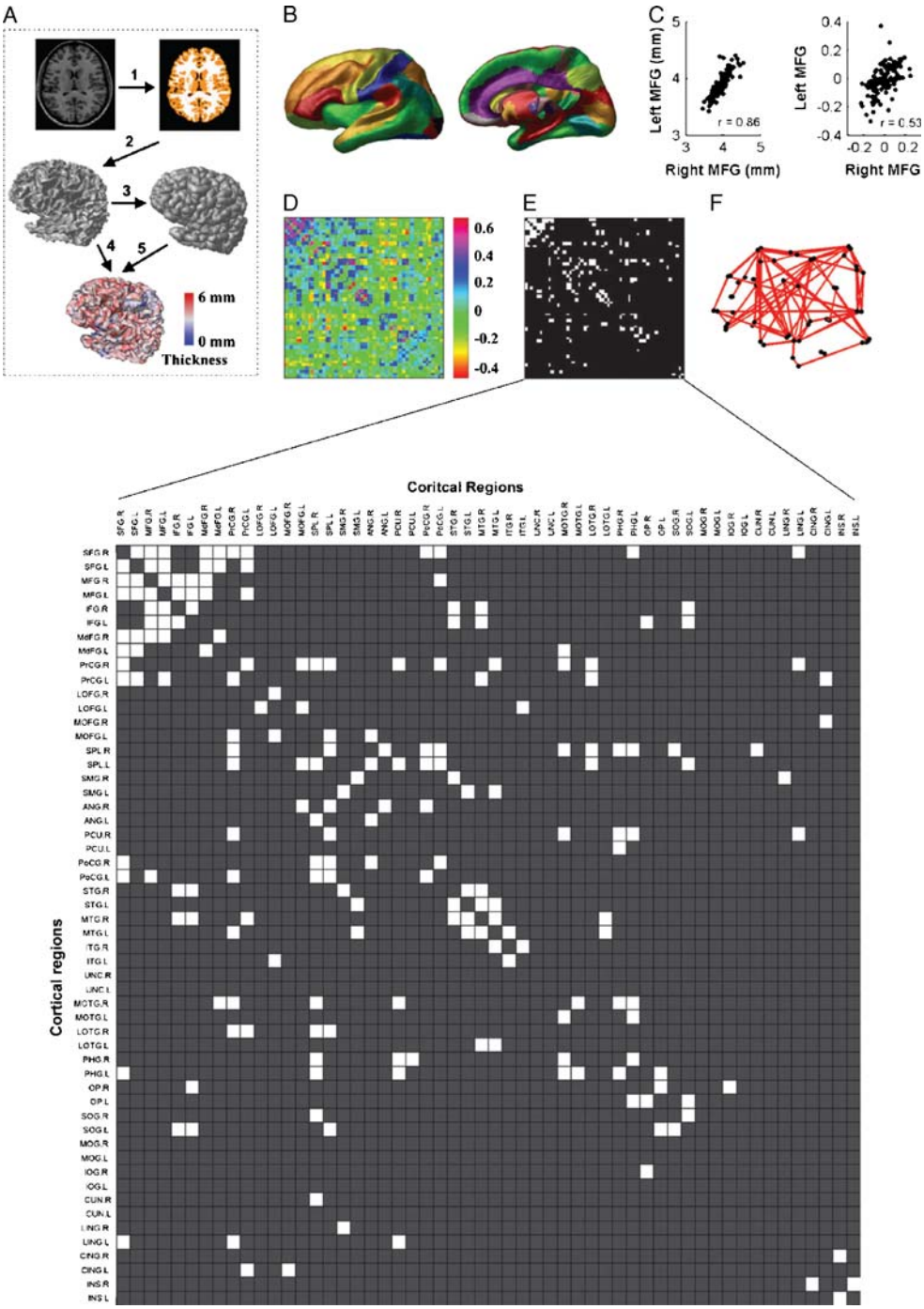

Fig. 2 Human brain anatomical networks using cortical thickness measurements from MRI. (**a**) Cortical thickness CLASP. Images are classified (1) to extract gray matter surfaces (*2*, *3*). Cortical thickness is measured at each vertex (*4*, *5*). (**b**) Cortex is segmented into 54 areas. (**c**) *Anatomical connection* is defined as statistical association in thickness of two areas across subjects, e.g. R. middle prefrontal gyrus has significant association with its L. counterpart. Left plot showed the associations using raw cortical thickness values, the right plot showed residuals after removal of mean thickness

lation was quantified by modularity analysis (Newman and Girvan 2004) and obtained **without any prior knowledge of regional functions**. The modularity Q (p) for a given network partition p is defined (Hilgetag et al. 2000; Sporns et al. 2005) as $Q(p) = \sum_{s=1}^{N} \left[\frac{l_s}{L} - \left(\frac{d_s}{2_L} \right)^2 \right]$ where N = # of modules, L = total # of network connections, l_s = # of connections between nodes in module s, and d_s = sum of the degrees of nodes in module s. Module "detection" finds the partition p that maximizes Q (Sporns et al. 2005). We used an algorithm (Danon et al. 2006) that allows for different module sizes, as observed in real networks, within

an agglomerative hierarchical cluster technique (Salvador et al. 2005a,b; He et al. 2007). Modules are joined in pairs, choosing the pair that yields the greatest increase in Q. We compared the cortical network modularity with that of 1,000 random networks. A z-score was defined as $(Q_{real} - Q_{rand})/Q_{std}$, with Q_{real} being the maximum modularity of the cortical network, Q_{rand} and Q_{std} its average and standard deviation over the 1,000 randomized networks. Q_{real} was significantly larger than for the randomized networks (z-score=7.9), implying that the modular architecture arises from non-random interactions. Six modules were identified (Fig. 3):

(i) **Auditory/language (A/L):** ten regions, including bilateral supramarginal gyri, middle temporal gyri, Wernicke's and Broca's areas (Mesulam 1990).
(ii) **Sensory/spatial (SS):** ten mostly parietal regions (bilateral superior parietal lobules, angular gyri and postcentral gyri) (Mesulam 1990).
(iii) **Executive (E):** nine mostly prefrontal areas (bilateral superior frontal gyri, middle frontal gyri and medial frontal gyri) (Duncan and Owen 2000).
(iv) **Visual (V):** five occipital regions specialized for visual processing.
(v) **paralimbic, hippocampocentric (PaH):** seven regions, including bilateral parahippocampal gyri, precunei and medial occipitotemporal gyri, involved in mnemonic/emotion processing (Mesulam 1990).
(vi) **paralimbic, olfactocentric (PaO):** bilateral lateral orbitofrontal gyri and inferior temporal gyri, regions connected through the uncinate fasciculus (Kier et al. 2004).

This segregation into six modules with apparent functional significance suggests that functional organization of human brain networks may have a modular anatomical correlate. This modularity also reveals the anatomical constraints underlying functional organization since symmetrical links between most bilaterally homologous regions are predominantly found together in the same module. These findings are compatible with clusters discovered in the mammalian cortical systems (Hilgetag et al. 2000) and human functional networks (Salvador et al. 2005a, b) from tract-tracing and fMRI.

Network analysis in neurodegenerative disease

Having established the GRETNA method in normal adults, we next examined putative network changes in degenerative disease: Alzheimer's Disease (AD), Multiple Sclerosis (MS) and Leukoaraiosis.

Alzheimer's disease (AD) AD is a progressive, neurodegenerative disease characterized by the impairment of memory and other cognitive functions. Current theories (Delbeuck et al. 2003; Buckner 2004; Buckner et al. 2005) posit that this arises from structural and functional disconnection within distributed neural systems. Establishing a structural disconnection pattern in AD will clarify how brain function is affected by disruption of underlying structural substrates (Sporns et al. 2005). Diffusion MRI studies have found white matter abnormalities in AD (Rose et al. 2000; Medina et al. 2006; Teipel et al. 2007),

Table 1 Strongest cortical thickness correlations and associated fibre tracts (He et al. 2007)

Region A	Region B	Corrected p	Associated fibre tract
PoCG.R	PoCG.L	1.96×10^{-13}	Midbody of corpus callosum[a, b]
MTG.R	MTG.L	1.63×10^{-10}	Splenium of corpus callosum[b]
SFG.R	MdFG.R	2.73×10^{-10}	Superior lateral fasciculus[c, e]
MdFG.R	MdFG.L	2.78×10^{-09}	Genu of corpus callosum[a, b]
SPL.L	PoCG.L	2.78×10^{-09}	Superior lateral fasciculus[c, e]
PrCG.R	PrCG.L	6.47×10^{-08}	Midbody of corpus callosum[a, b]
MFG.R	MFG.L	2.82×10^{-07}	Genu of corpus callosum[a, b, d]
LOFG.R	LOFG.L	4.20×10^{-07}	Rostrum of corpus callosum[d]
PHG.R	PHG.L	6.04×10^{-07}	Splenium of corpus callosum[b]
IFG.R	IFG.L	7.85×10^{-07}	Genu of corpus callosum[a, b]
SFG.L	PrCG.L	1.03×10^{-06}	Superior lateral fasciculus[c, e]
STG.R	MTG.R	4.25×10^{-06}	U-fibers[c]
PrCG.R	SPL.R	4.79×10^{-06}	Superior lateral fasciculus[c, e]
SFG.R	SFG.L	5.16×10^{-06}	Genu of corpus callosum[a, b, d]
SFG.L	MFG.L	7.25×10^{-06}	U-fibers[c]

Region pairs with most significant cortical thickness correlations. Significance p-values were all <0.0001 after FDR-correction (Genovese et al. 2002). Associated fiber tracts for each correlation are also listed. Cortical thickness correlation among regions was calculated after removing the effects of age, gender, age–gender interaction and mean overall cortical thickness. a) Hofer and Frahm 2006; b) Zarei et al. 2006; c) Wakana et al. 2004; d) Huang et al. 2005; e) Makris et al. 2005

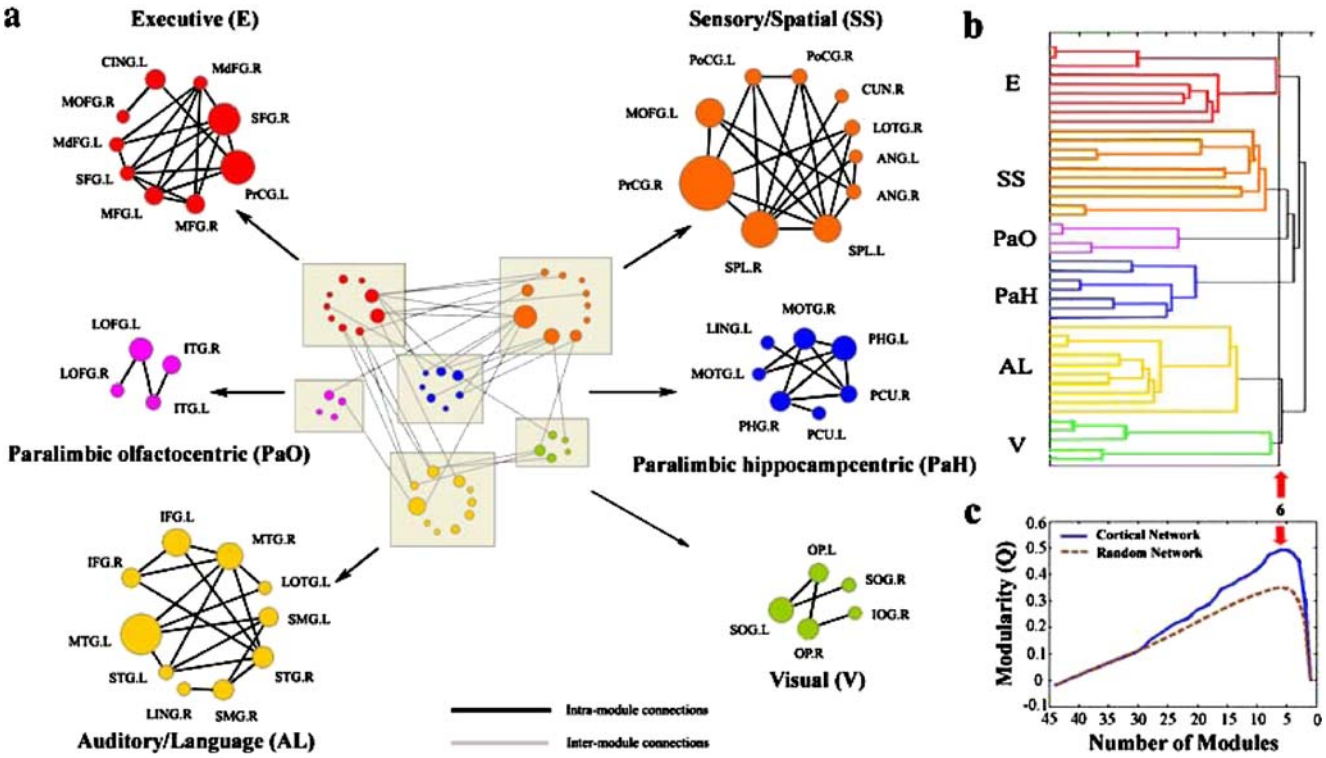

Fig. 3 Modular architecture of human cortical network. (**a**) Six network modules displayed in colour-coded groups. *Red: Executive (E)*; *Orange: Sensory/Spatial (SS)*; *Yellow: Auditory/Language (AL)*; *Green: Visual (V)*; *Pink: Paralimbic olfactocentric (PaO)*; *Blue: Paralimbic hippocampcentric (PaH)*. Inter-module and intra-module connections are shown in dark and gray lines respectively. The size of each node (*cortical region*) denotes the relative betweenness centrality of the node. (**b**) Dendrogram of the module-identification progress as determined by modularity Q^8. A maximum Q is reached when the network is separated into six modules (*red arrow*). (**c**) Progress of Q as regions are sequentially merged into modules for the human cortical network (*blue*) and 1,000 random networks (*dotted*). Red arrow indicates that Q is maximum for six modules (Z-score=7.9)

suggesting a disrupted structural connectivity. However, limitations in data acquisition and processing (e.g. crossing or intersecting fibers) has hindered this approach (Dougherty et al. 2005; Tuch et al. 2005). Focal cortical thickness changes in AD have been previously identified (Lerch et al. 2005, 2008; Singh et al. 2006) but the inter-regional correlation of those changes had not been examined. We therefore investigated this issue in AD patients and healthy controls using GRETNA (He et al. 2008). Both group networks exhibited small-world architectures (high C_p, short L_p). The AD network exhibited a more regularized configuration (i.e. increased clustering and path length) compared with the HC network, implying a less optimal topological organization in AD. The AD network exhibited changes in nodal efficiency, with significant decreases for temporal and parietal cortical regions and increases for frontal and occipital cortical regions. Intriguingly, the AD network was approximately as robust to *random* failures as the HC network but more vulnerable against *targeted* attacks (successive removal of the most connected node, Fig. 4, Albert et al. 2000), possibly due to decreased redundancy and capacity to engage compensatory pathways. Such alteration has implications for our understanding of how functional deficits relate to underlying structural damage.

Multiple Sclerosis (MS) MS is a multifocal inflammatory demyelinating disease affecting white matter (WM). Since WM lesions affect fiber pathways connecting cortical regions, the cortical network properties might show significant changes with MS disease progression. We used GRETNA to investigate the small-world efficiency of cortical networks in 425 relapsing–remitting MS patients (Charil et al. 2003, 2007). Using total WM lesion load (TWMLL) as a measure of disease severity, we defined six groups with TWMLL's of 0–2, 2–4, 4–8, 8–16, 16–32 and >32 cm^3. We used graph theory to calculate the local and global efficiency (Latora and Marchiori 2001) of each group over a range of wiring costs (0.1~0.4 The areas under these efficiency curves were obtained and correlated with the TWMLL by linear regression. MS network efficiencies were then compared with those of 1,000 random graphs and regular lattices. Both local and global efficiency showed significantly negative correlation with TWMLL (Fig. 5), suggesting a disease-associated alteration in network properties.

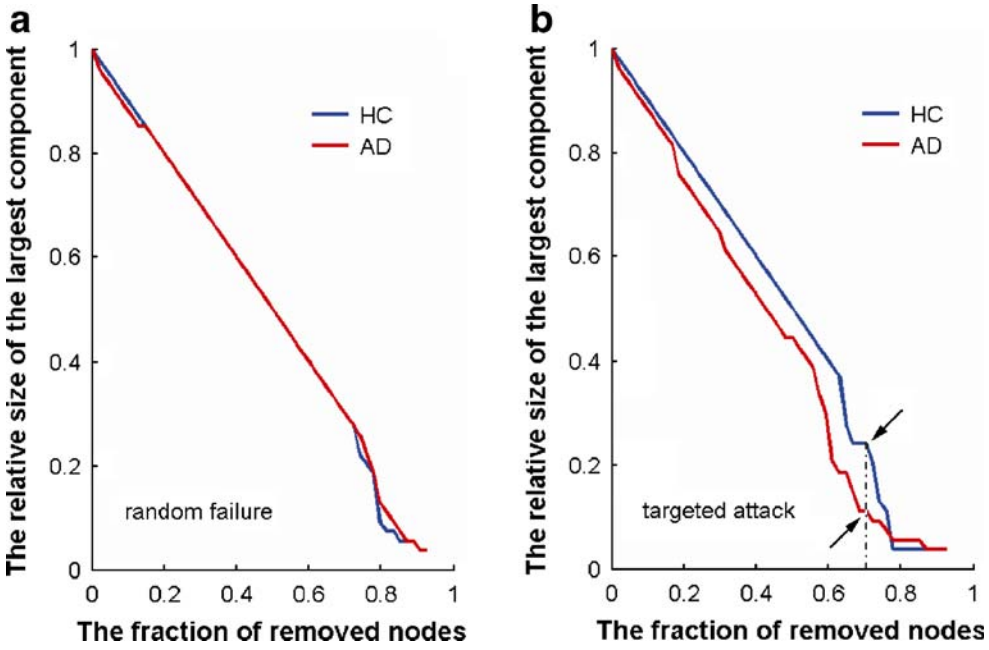

Fig. 4 Network robustness in Alzheimer's Disease. Graphs show the relative size of the largest component as a function of the fraction of nodes removed by *random* failures (*left* panel) or *targeted* attacks (*right* panel). The network for Alzheimer's patients (AD) is comparable to that of healthy controls (HC) in response to random failures. However, as indicated by the arrows, it is vulnerable to targeted attack, possibly due to decreased redundancy and capacity to engage compensatory pathways

Global efficiency of brain networks is associated with long-range connections that allow rapid transfer of information among remote cortical regions subserving cognition (Latora and Marchiori 2001; Sporns and Zwi 2004; Achard and Bullmore 2007). Local efficiency is associated with short-range connections between adjacent regions to support modularized information processing. Our results strongly suggest that widely distributed cortical networks exhibit reduced efficiency in MS, consistent with aberrant structural connections (WM tracts). GRETNA therefore provides a quantitative means to (i) monitor disease progression, (ii) characterize MS and its sub-forms (e.g. relapsing remitting or chronic progressive), and (iii) provide morphological substrates for the functional deficits seen in MS.

Leukoaraiosis An ongoing collaboration between the MNI and the Institute of Development, Aging and Cancer (IDAC) at Tohoku University is investigating white matter disorders of aging (Taki et al. 2004). Common white matter changes seen in aging are diffuse lesions observable in MRI as white matter hyperintensities (WHM) or *leukoaraiosis* (Hachinski et al. 1987). The pathogenesis is not well understood with several pathologies implicated, including white matter rarefaction, perivenous hypomyelination, small deep WM microcystic and discrete infarct, (Graham et al. 2006). While the etiology is uncertain, severe WMH incidence in deep white matter is known to be associated with neuropsychological changes (Tomimoto et al. 1996), suggesting an influence on cortical function. One hypoth-

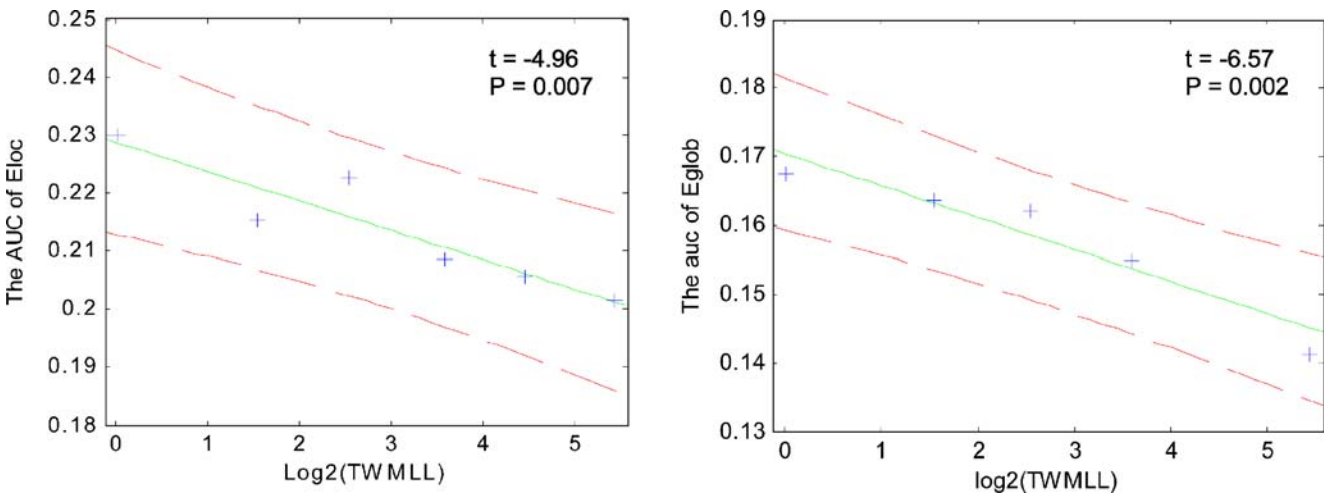

Fig. 5 Multiple Sclerosis brain network efficiency changes with the TWMLL. The Area Under the Curve (*AUC*) provides a stable measure of local efficiency (*left*) or global efficiency (*right*) across all wiring costs surveyed. Both are progressively degraded with increasing MS total white matter lesion load (TWMLL)

esis is that secondary cortical degeneration results from deafferentation (Hillis et al. 2002). The study of such changes in the living human brain remains challenging. We therefore investigated changes in cortical correlation associated with white matter lesions. Data from 927 healthy Japanese subjects, 491 men (age 63.8±7.5) and 486 women (age 64.2±7.4), were included. Four hundred seventy-seven subjects exhibited mild leukoaraiosis, while 450 subjects exhibited no lesions. The results (Mok et al. 2008) demonstrate that the pattern of cortical thinning depends upon specific lesion location, i.e. regional atrophy correlates with lesion location within a fiber bundle innervating that region, going beyond the general correlation of global cortical atrophy with total lesion volume.

Future perspectives

Cortical Anatomical Networks We have demonstrated, using network analysis with GRETNA, that coordinated variations in cortical thickness exhibit small-world attributes characterized by cohesive neighborhoods with high clustering and short mean distance between regions, a near-optimal network organizational pattern (He et al. 2007). Thus, GRETNA offers a new window for mechanistic modeling and interpretation of morphometry-based connectivity patterns of the normal subjects and patients with brain disorders. It allows for the investigation of: (1) biological mechanisms behind the correlations of cortical thickness; (2) the similarities and differences in cortical networks constructed from multiple morphological features (e.g. volume, density and thickness); (3) the relation between structural and functional brain networks; and (4) topological changes in cortical networks in normal aging and other brain diseases. We anticipate that the combination of (i) a novel graph theoretical analysis of network properties, (ii) various morphological indices (cortical thickness, area, volume, complexity etc.) and (iii) various behavioural measures will have wide utility in the study of normal brain development, developmental brain disorders, normal aging, neurodegenerative diseases and psychiatric disorders.

Pacific–Rim Organizational Networks The scientific work described in this article is the result of long-standing collaborations between scientists in Canada, Korea, China and Japan. It is evident that there is almost limitless potential for greater integration between brain mapping groups in the East and Western Pacific Rim. This arises from both the scientific advancement of these countries in brain mapping in their own right and the natural fit between brain mapping field and the rapidly expanding information technologies. Digital transfer of extensive brain imaging databases between remote locations is now commonplace. However, these initiatives are largely the result of bilateral initiatives rather than outgrowth of a larger multi-national, regional plan for fostering such inititatives. Different countries have put in place a range of mechanisms to stimulate their internal brain mapping programs (e.g. Korean Brain Mapping Initiative, US Human Brain Project, US Brain Imaging Research Network) but there is at the moment no international body specifically for coordinating Pacific Rim programs in brain mapping.

There are however, promising developments. In 2008, Canada funded the creation of a high-speed telecommunication infrastructure to link Canadian brain mapping groups (www.canarie.com). This will make use of Canada's CAnet 4 (equivalent to Internet2) network. Through a series of point-to-point optical wavelengths, most of which operate at 10 Gbps, CAnet 4 yields a total initial network capacity of 4–8 times that of CAnet 3 (equivalent to Internet). CAnet 4 embodies the concept of a "customer-empowered network" which will place dynamic allocation of network resources in the hands of end users. These applications are essential for the national and international collaboration, data access and analysis, and distributed computing. US, Chinese, Korean and Japanese agencies are setting up similar mechanisms. The next step will be to integrate these national networks into trans-Pacific networks. Governments are aggressively pursuing such integration and brain mapping programs will be direct beneficiaries of those efforts.

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