

Connectopathy in ageing and dementia

This scientific commentary refers to 'Regional amyloid burden and intrinsic connectivity networks in cognitively normal elderly subjects' by Lim *et al.* (doi:10.1093/awu271).

Connectivity in the brain is dynamic. From development through normal ageing or as a result of pathological processes, structural and functional connectivity are in a constantly changing state. Some changes may occur rapidly as a consequence of learning, for example, but others may take years or decades. Our ability to witness and measure changes in structural connectivity relies on the diffusion properties of water (e.g. diffusion tensor imaging, DTI). As for functional connectivity, detected as active regions with temporal contiguity, this relies on changes in blood oxygenation (e.g. resting state functional MRI). In this issue of *Brain*, Lim *et al.* (2014) examine the effects of amyloid deposition on the intrinsic functional connectivity networks in cognitively normal elderly populations. They report that the presence of amyloid, as measured with the PET tracer Pittsburgh Compound B (PiB), is associated with changes in network connectivity and also with regional interactions within those networks.

These measures of connectivity are important in the quest to better understand normal and compromised brain function. Connectivity, when combined with other morphological and physiological measures, provides a far more comprehensive picture of the brain in health and disease than its shape alone. Anatomically, many fascicles, bundles and tracts have been mapped in exquisite detail in mostly normal populations and also in a number of cohorts with neurodegenerative diseases, psychiatric illnesses, and even infectious diseases. Although subpopulation variability is largely unknown, there are efforts underway to assess that and relate it to genetics and other factors (Jahanshad *et al.*, 2013; <http://www.humanconnectomeproject.org/>). Studies of structural brain connectivity in hundreds of subjects are beginning to reveal characteristic changes in brain networks with development (Dennis *et al.*, 2013), and more subtle differences with regard to sex and genotype. Early in life, short-range structural connections tend to mature more quickly than long-range connections, and the brain develops a relatively 'modular' organization. van den Heuvel and Sporns (2011) suggest that the brain also develops a 'rich club' organization, in which very highly connected 'hubs' integrate local information and communicate with other hubs via long-range connections, such as the language pathway, or interhemispheric commissures. Similar patterns of hubs arise in airline and other transport networks, and hubs improve the communication efficiency of the network as a whole. The gradual loss of structural connections in Alzheimer's disease may progress in the opposite sequence to normal development, in a first-in, first-out sequence, with gradual loss of characteristic features of efficient networks, such as 'small-world organization'.

Functional connectivity, as determined using resting state functional MRI, has revealed a number of networks of coordinated activity (Biswal *et al.*, 1995). Based upon either modelled or

model-free approaches, at least three canonical networks have been identified: (i) the default mode network (Raichle *et al.*, 2001), which includes the ventromedial prefrontal cortex and posterior cingulate cortex; (ii) a salience network, which includes the ventrolateral prefrontal cortex and anterior insula (sometimes called the fronto-insular cortex), as well as the anterior cingulate cortex; and (iii) a central executive network, whose key nodes include the dorsolateral prefrontal cortex and posterior parietal cortex. Figure 1 illustrates these three networks anatomically using tractography seeded with resting state functional MRI data. These networks have been examined in groups of patients with neurological diseases and psychiatric disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, schizophrenia and autism. One early landmark study mapped the emergence of functional networks in children, and found that the age of the child could be predicted surprisingly well from networks extracted from resting state functional MRI (Dosenbach *et al.*, 2010).

Numerous resting state studies suggest some overlap between the classical pattern of amyloid accumulation in the brain (Braak and Braak, 1991) and hubs of the default mode network (Hedden *et al.*, 2009). Using independent component analysis (ICA), Greicius (2008) found decreased connectivity across the default mode network in Alzheimer's disease—in frontal, parietal, and temporal cortices, and the hippocampus. In one multi-modal study of 93 adults aged 18–93 years, Andrews-Hanna *et al.* (2010) found a significant reduction in functional connectivity between anterior and posterior hubs of the default mode network (medial prefrontal cortex and posterior parietal cortex) with normal ageing, but this reduction was not solely explainable by increases in brain amyloid accumulation. Mormino *et al.* (2011) also used an ICA approach to investigate amyloid- β deposition, and found significant overlap with regions of the default mode network: elevated PiB was associated with decreased network connectivity in the ventral-medial prefrontal cortex, right angular gyrus, and left middle and superior frontal gyri. Lim and colleagues' study suggests a possible interdependency in network connectivity among the default mode network, salience network and central-executive network (Lim *et al.*, 2014). The attempt to determine how these networks respond to amyloid burden, and their relationship to episodic memory, is a more whole brain approach to age-related changes in cognition than that of earlier work. Their study suggests a complex cascade of changes with increasing amyloid, and that compensatory mechanisms or reserve capacity may have varying effects on different networks over time.

We do not yet understand the mechanisms whereby Alzheimer pathology affects the hubs of the brain's functional networks. Early cellular dysfunction, including vascular insufficiency, metabolic compromise, inflammation, and myelin degradation may disrupt the synchrony of brain networks, followed later by overt loss of neurons and their axonal connections to other parts of the

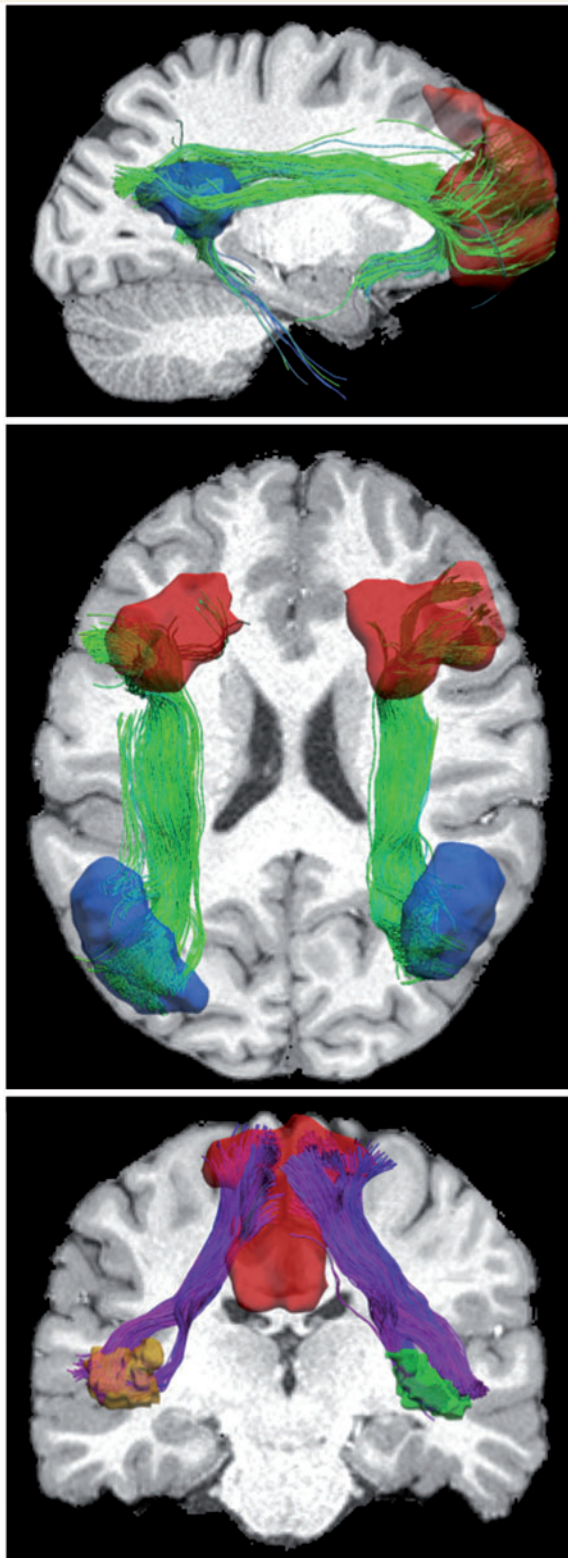


Figure 1 The anatomical substrate of intrinsic functional networks derived from tractography seeded with sites from resting state functional MRI. For each network, regions of interest were warped from the functional region of interest atlas to one random subject selected from the Human Connectome Project database. Note that because the regions of interest are generated from functional images (using ICA), there is no anatomical

brain, along with Wallerian degeneration. Some speculate that the highly adaptive systems involved in learning and memory—with their high metabolic activity—may be more vulnerable to neuronal loss due to amyloid and tau pathology than the heavily myelinated primary sensorimotor and visual systems that mature the earliest in childhood. Typically, the primary cortices show least atrophy in ageing and Alzheimer's disease, and appear functionally intact until the advanced stages of disease.

Balanced and symbiotic activity among the larger networks of the brain may also be important for normal functioning. Disturbance of equilibrium owing to pathological processes such as amyloid- β accumulation may produce increases and decreases in network connectivity as compensatory mechanisms. Agosta *et al.* (2012) examined the default mode, central executive, and salience networks in Alzheimer's disease and mild cognitive impairment. Surprisingly, they found increased mean connectivity in Alzheimer's disease in the central-executive component, and this was associated with cognitive scores. They suggested that the increased connectivity may be the brain's attempt to limit the functional consequences of continuing tissue damage.

Several large-scale initiatives are underway that seek to understand how brain connectivity varies with age and genetic factors over the lifespan. The Human Connectome Project (<http://www.humanconnectomeproject.org/>), for example, is scanning large cohorts of normal twins and advancing the power of imaging methods to assess brain connectivity, such as diffusion spectrum imaging, and ultra-high field imaging. The quest to identify genetic variants that affect brain connectivity has also begun in earnest; international collaborations such as ENIGMA (<http://enigma.ini.usc.edu/>) have begun to identify heritable measures of brain connectivity across cohorts scanned around the world, aggregating these data into large-scale genome/connectome-wide screens. At the same time, large-scale neuroimaging studies in ageing and dementia, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI; <http://www.adni-info.org/>), GAAIN (<http://www.gaain.org/>) and DIAN (<http://www.dian-info.org/>) are beginning to identify connectivity metrics that characterize and predict network breakdown as we age, along with prodromal changes in functional brain connectivity in autosomal dominant forms of Alzheimer's disease.

The sensitivity of resting state functional MRI to acute changes in brain networks has also attracted the attention of clinical trial

Figure 1 Continued

constraint. Using the fibre orientation distribution already computed, probabilistic tractography was performed between a pair of regions of interest to generate the fibre bundles. Outliers were removed with simple length-based thresholding. Finally, visualizations were generated to overlay the surface representation of regions of interest and fibre bundles. *Top*: Default mode network: ventromedial prefrontal cortex and posterior cingulate cortex. *Middle*: Central executive network: dorsolateral prefrontal cortex and posterior parietal cortex in both left and right hemispheres. *Bottom*: Saliency network: ventrolateral prefrontal cortex and anterior insula in both hemispheres. Only the part of the saliency network between insula and cingulate is shown here.

designers, who are keen to identify treatment effects over intervals that are as short as possible. Ultimately, defining which features of image acquisition and analysis promote reproducible studies and metrics of brain connectivity will make it easier to integrate, coordinate, and meta-analyse connectivity data across disparate studies that were initially designed independently.

The broad interest in methods to assess brain connectivity relative to other measures associated with ageing and dementia suggests that major advances are imminent, revealing new factors that influence brain network changes in the millisecond range, across the entire human lifespan and as a result of neurodegenerative disease.

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The hippocampus is essential for completely unconscious as well as conscious flexible memories

This scientific commentary refers to 'Unconscious relational encoding depends on hippocampus' by Duss et al. (doi: 10.1093/brain/awu270).

Several beliefs about the nature of organic amnesia were deeply entrenched by the early 1990s. It was believed that damage to the medial temporal lobe or its connections in the midline diencephalon and basal forebrain did not disrupt intelligence, perception, processing of information at input and immediate (short-term) memory, but selectively disrupted—following even a brief

distraction—recall and recognition of recently encountered personal events or facts/concepts. In other words, amnesia was thought to affect only episodic and semantic memory, whether for pre-morbid events (retrograde amnesia) or post-morbid events (anterograde amnesia). With these kinds of memory, not only is the remembered information consciously apprehended at input and at retrieval, but the person remembering is also consciously aware that the information is a memory. That is, the person feels that the information has been encountered before, often in a particular context. In contrast, it was believed that