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Structural networks in Alzheimer's disease

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Abstract
Alzheimer's disease (AD) appears to be a uniquely human condition, which is possibly attributable to our expanded longevity and peculiar capacity for episodic memory. Due to a lack of naturally-occurring animal model for investigating AD pathogenesis, our knowledge about the disease must be derived from correlational observation of humans, or from animal models produced by genetic manipulation of known risk factors in humans. Advances in neuroimaging, cellular and molecular science, and computational methods have proven useful for the improvement of such techniques, but the general limitation persists; as a result we remain without clear answers to some of the fundamental questions posed by AD. On the other hand, much progress has been made in characterizing the longitudinal progression of AD pathology, which includes the formation of "plaques and tangles", a distinct topological pattern of atrophy of grey and white matter, and the concurrent decline of specific cognitive functions, beginning with mild memory impairments and ending with general debilitating dementia. In this review, we first discuss the existing literature which characterizes AD etiology, pathology, and pathogenesis, with the intention of framing the disease as primarily a "disconnection syndrome". We next describe methodologies for investigating the topological properties of human brain networks, using graph theoretical techniques and connectivity information derived from anatomical and diffusion-weighted MR imaging. Finally, we discuss how these methodologies have been applied to systems-level analyses of AD, to help characterize the network changes underlying the disease process, and how these patterns relate to specific cognitive outcome measures.

1. Alzheimer's disease as a disconnection syndrome

1.1. Neuropathology

AD has been characterized by two well-investigated pathological features called neuritic plaques (NP), comprised of abnormal extracellular deposits of amyloid beta (Aβ) protein, and neurofibrillary tangles (NFT), comprised of intracellular aggregated hyperphosphorylated tau protein (Braak and Braak, 1994;

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Corder et al., 2000). The distribution of NFT occurrences in the neocortex has been shown at earlier stages of the disease to be largely restricted to association regions, primarily in temporal, parietal, and frontal lobes, while largely sparing motor, somatosensory, and primary visual areas until late in the pathological progression; NPs, on the other hand, appear to have a less selective distribution (Lewis et al., 1987; Pearson et al., 1985). Interestingly, the relative amount of NFT accumulation in a given cortical region (measured postmortem in humans) has been observed to increase in proportion to its position in the visual hierarchy (i.e., as described by Felleman and Van Essen, 1991).NFTs and NPs are also arranged in specific laminar patterns, with NFTs clustering mainly in layers III and V, and NPs occurring more predominantly in layers III and IV (Lewis et al., 1987). The same authors report that NFT accumulation displays a shift in its laminar distribution depending on the cortical area in which it is observed, and further note that this shift "parallels the laminar shift in the distribution of long corticocortical projection neurons in homologous regions of monkey cortex." They suggest that NFTs selectively occur within large pyramidal cells which give rise to long-range corticocortical projections, a proposition which has since been confirmed by quantitative analyses in superior frontal, inferotemporal, and primary and secondary visual cortex (Hof et al., 1990; Hof and Morrison, 1990).These observations provide an intriguing first clue that (1) AD pathology may propagate "stepwise" along long-range corticocortical projections; and (2) the corresponding disruption of this long-range structural connectivity may figure prominently in the longitudinal pattern of cognitive dysfunction observed in AD patients. These propositions modelADas a "disconnection syndrome" (reviewed in De Lacoste and White, 1993; Delbeuck et al., 2003), or alternately as a "system degeneration" (Saper et al., 1987).

Both NFTs and NPs are associated with neuronal degeneration (particularly of large pyramidal cells), but the mechanisms for these changes are still poorly understood and possibly numerous (reviewed in Dickstein et al., 2007). AD-related pathology has been characterized in terms of discrete stages by Braak and Braak (1994), and expanded upon by Corder et al., 2000. It occurs in a predictable sequence, with putative origins in subcortical structures with diffuse neocortical connectivity, including locus coeruleus and dorsal raphe nucleus (Braak and Del Tredici, 2011), and progresses to the entorhinal cortex (EC) (Braak stages I and II), spreading via the perforant pathway to the hippocampus and amygdala (Braak stages III and IV), and eventually affecting other cortical and subcortical regions (Braak stages V and VI). The clinical progression within neocortex appears to be mediated by the cortical connectivity structure, its sequence being: "temporal medial > parietal > frontal medial > occipital secondary > occipital primary" (Corder et al., 2000).NPs do not appear to directly associate with cell death, and estimates of NFT association vary greatly (84–87%, Giannakopoulos et al., 2003; 43%, Gómez-Isla et al., 1997; 2–8%, Kril et al., 2002). Proximity to NPs is, however, related to substantial alterations in dendritic morphology, including increased curvature and curvilinear length (Knowles et al., 1999), and decreased spine density and shaft diameter (Tsai et al., 2004). According to computational simulations of neuronal activity, these morphological changes should result in nontrivial disruptions to signal processing – and likely effective connectivity – in these neurons. Knowles et al. further speculate that such morphological changes to dendrites might lead to the hyperphosphorylation of tau and eventual formation of NFTs, which proposes a causal link between the two forms of pathology. This causal hypothesis is supported by evidence that soluble Aβ (see below) can induce tau toxicity and cell death in wild-type mice, via an NMDAR-dependent pathway (Tackenberg and Brandt, 2009).

Synaptic loss may be another important consequence of NPs and NFTs. Electron microscopy has been used to demonstrate the loss of synapses in the frontal lobes of AD patients with mild to moderate dementia (DeKosky and Scheff, 1990) and in the dentate gyrus of early AD patients (Scheff and Price, 2006), and this loss was strongly associated with both Mini-Mental State Exam scores (MMSE, a measure of clinical dementia) and delayed recall performance. Using synaptophysin-like immunohistochemistry, Masliah et al. (1991)reported a loss of presynaptic terminals in AD patients, which was most severe in frontal and parietal cortex (45%, compared to a 35% loss of large neurons), with smaller effects in hippocampus, EC, visual cortex, the nucleus basalis of Meynert, and the locus coeruleus. While the precise timing of synaptic degeneration is not known, the presence of Aβ has been demonstrated to result in synaptic loss and a marked decrease in dendritic spine density in both humans and mouse models of AD, so it can reasonably be concluded that the presence of NPs substantially aggravates synaptic loss, whether or not they are its sole cause (reviewed in Knobloch and Mansuy, 2008). More recent evidence suggests that a soluble, oligomeric form of Aβ, rather than NPs themselves, is the more important neurotoxin in AD pathology. Oligomeric Aβ has been isolated from the brains of AD patients and introduced into normal rat hippocampi, producing deficits in synaptic plasticity, as well as impairing recall for a previously learned avoidance task (Shankar et al., 2008). In purely animal models, soluble Aβ has been shown to have a number of detrimental effects upon neuronal function. It appears to act directly upon a number of neurotransmitter receptors, including AMPA, NMDA, and nicotinic acetylcholine receptors, and alter their presence in the postsynaptic membrane (Lacor et al., 2007). NMDA in particular is critical for Aβ toxicity, as the effect of Aβ on spine density can be prevented with application of an NMDA antagonist (Shankar et al., 2007). This relationship and corresponding electrophysiological evidence suggests that Aβ can alter synapses and dendritic morphology through mechanisms similar to long-term depression (LTD), via calcium-dependent signaling cascades; indeed, oligomeric Aβ has been demonstrated to facilitate LTD in hippocampal slices of mouse brain (Li et al., 2009). The end result of such changes appears to be altered cytoskeletal configurations, spine shrinkage and loss, endocytosis of AMPA and NMDA receptors, and impaired plasticity and learning. However, these changes may also result in a paradoxical *hyper*excitability, and even epileptiform activity (Palop et al., 2007), corresponding with numerous reports that human AD patients have an increased susceptibility to epilepsy (reviewed in Palop and Mucke, 2009).The nature of this paradox may involve a reorganization of local inhibitory circuitry, but this has not yet been clearly demonstrated. In any case, it is evident that the presence of NPs and particularly oligomeric Aβ has dramatic consequences for synaptic transmission and plasticity that can at least partially account for the network disconnection and cognitive decline observed in AD.

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