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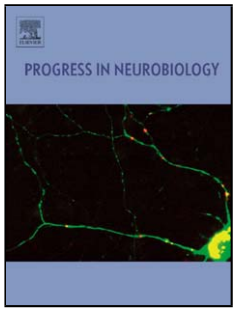

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Authors: Arun L.W. Bokde, Michael Ewers, Harald Hampel

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Assessing Neuronal Networks: Understanding Alzheimer's Disease

Arun LW Bokde PhD, Michael Ewers PhD, and Harald Hampel* MD, MSc

Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neuroscience (TCIN), Laboratory of Neuroimaging & Biomarker Research, Trinity College Dublin, The Adelaide and Meath Hospital incorporating the National Children's Hospital (AMiNCH), Dublin, Ireland

and

Dementia and Neuroimaging Research Section, Alzheimer Memorial Center and Geriatric Psychiatry Branch, Department of Psychiatry, Ludwig-Maximilian University, Munich, Germany

* Corresponding Author

Running Title: Connectivity in AD

Corresponding Author:
Harald Hampel, MD, MSc
Discipline of Psychiatry
School of Medicine
Trinity College
Trinity Centre for the Health Sciences
The Adelaide and Meath Hospital
incorporating The National Children's Hospital (AMiNCH)
Dublin 24
Ireland
Tel.: +353-1-896 3706
Fax.: +353-1-896 1313
Email: Harald.Hampel@tcd.ie

Abstract

Findings derived from neuroimaging of the structural and functional organization of the human brain have led to the widely supported hypothesis that neuronal networks of temporally coordinated brain activity across different regional brain structures underpin cognitive function. Failure of integration within a network leads to cognitive dysfunction. The current discussion on Alzheimer's disease (AD) argues that it presents in part a disconnection syndrome. Studies using functional magnetic resonance imaging, positron emission tomography and electroencephalography demonstrate that synchronicity of brain activity is altered in AD and correlates with cognitive deficits. Moreover, recent advances in diffusion tensor imaging have made it possible to track axonal projections across the brain, revealing substantial regional impairment in fiber-tract integrity in AD. Accumulating evidence points towards a network breakdown reflecting disconnection at both the structural and functional system level. The exact relationship among these multiple mechanistic variables and their contribution to cognitive alterations and ultimately decline is yet unknown. Focused research efforts aimed at the integration of both function and structure hold great promise not only in improving our understanding of cognition but also of its characteristic progressive metamorphosis in complex chronic neurodegenerative disorders such as AD.

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1.0 Introduction

Functional neuroimaging studies in humans and animals suggest that particular brain regions are necessary for specific cognitive functions. The activations of different brain regions, however, do not appear to occur independently from each other but may occur in a sequential spatio-temporally ordered fashion (McIntosh et al., 1994; Murphy et al., 1993). The involved regions integrate into a large-scale network which forms the basis of cognition and closely relates to its complex underlying systemic structural architecture (Horwitz et al., 2005; Lee et al., 2006; Luria, 1973; McIntosh, 2004; Rogers et al., 2007). For example, successful associative learning has been shown to correlate with a change in the effective connectivity, i.e., the influence of activation of one brain region onto another, within a specific neuronal network (Buchel et al., 1999). From the neuroanatomical perspective, connectivity of brain activity is predicted to be confined towards pathways of neuroanatomical connections between specific brain regions (Greicius et al., 2008; Toosy et al., 2004). These neuroanatomical constraints allow generating useful predictive models, specific working hypotheses concerning the effect of localized lesions on specific network functions in complex chronically progressive neurodegenerative system disorders such as Alzheimer's disease (AD).

Thus a failure of the regions of a network to interact at a high level of coordination may underpin the cognitive disorders which are present in AD. The failure of network function may be due to interaction failure among the regions of a network, which is denoted the disconnection hypothesis. In other words, a disruption in the temporal-spatially coordinated activity among different regions in the brain rather than isolated changes in particular brain regions may underlie cognitive impairment in

AD. The breakdown is thought to be due to chronically progressive AD neuropathology with underlying molecular mechanisms leading downstream to neuronal and synaptic dysfunction and ultimately to neuronal loss. Such AD-characteristic structural and functional changes are hypothesized to reflect at least partially the progressive impairment of fiber tract connectivity and integrity (Meguro et al., 1999; Morrison and Hof, 2002; Morrison et al., 1986; Stoub et al., 2006), suggesting that the disconnection in AD is evident at both the functional and structural level.

The aim of the current review is to characterize neural network changes with regard to (a) the characteristics of AD-related neuropathology, the distribution within the brain and association with dementia severity, (b) functional breakdown, both within the functional and structural domains of the brain, of specific networks associated with impaired cognitive function such as memory, (c) possible applications to the clinical domain, and (d) future approaches for understanding the multi-dimensional nature of network changes and the behavioural and cognitive changes that they produce. The associations between brain pathology and indices of functional and structural connectivity may help our understanding of the role of connectivity in brain function. We will review studies investigating the neuroanatomical spread of AD-related pathology, and studies using functional magnetic resonance imaging (fMRI) and electroencephalographic (EEG) data to investigate functional networks, as well as studies utilizing diffusion tensor imaging (DTI) to investigate structural changes.

2.0 Neuropathology and its spread in the brain

Current understanding of the effects of focal damage on neural networks is rudimentary, even though such understanding could provide greater insight into important neurological and psychiatric disorders. AD is characterised by chronically progressive neurodegenerative mechanisms that translate clinically into multi-domain cognitive decline, complex psychopathological and behavioural disturbances with subsequent loss of function to perform day-to-day tasks. One key mechanistic molecular and histopathological hallmark is proposed to relate to intracellular hyperphosphorylation of micotubuli-associated tau protein, progressive neurofibrillary changes such as formation of paired helical filaments (PHF) and neurofibrillary tangles (NFT), dystrophic neurits, and extracellular neuritic plaques (NP) (Braak and Braak, 1995; Khachaturian, 1985; Mirra et al., 1991). Another major mechanistic strand is described in the amyloidogenic cascade hypothesis with pathological cleavage of the amyloid precursor protein (APP), leading to non-neuritic deposition of fibrillar Aβ and production of toxic oligomers, dimmers and trimers within the brain regions (Selkoe, 1994). The development of NFT, leading to microstructural degeneration within the axon and cell body (Grundke-Iqbal et al., 1986), is associated with neuronal death (Gomez-Isla et al., 1996), and downstream global cognitive decline (Arriagada et al., 1992b; Berg et al., 1998, Arriagada, 1992 #220) early in the course of AD.

The location and distribution of AD-related molecular mechanisms and neuropathological lesions lend support to the hypothesis that AD is in part a disconnection syndrome characterized by the loss of afferent and efferent connections of regional allo- and neocortical areas associated with the death of pyramidal neurons (Morrison and Hof, 2002; Morrison et al., 1986). The earliest regions affected by AD

pathology are the transentorhinal cortex, the parahippocampal gyrus and the hippocampal formation. It has been found that the projections among the hippocampal formation, entorhinal cortex, and amygdala contained NFT and the ends of the projections contained amyloid deposition (Hyman et al., 1990). The location of the neuropathology is such that it affects intracortical property neurons specifically (Armstrong, 1993; Mann, 1996; Pearson et al., 1985; Van Hoesen et al., 1991). The NFT predominate in layers III and V of the association areas in the frontal, temporal and parietal lobes as well as in layers II and IV of the limbic periallocortex. The pyramidal neurons are located within these layers, enabling cortico-cortical connections between the cerebral hemispheres. It has been suggested that the distribution of the NFT across the AD brain exhibits a pattern where the most vulnerable cortical regions are those that have connections to the ventromedial regions of the temporal lobe (Arriagada et al., 1992a). Thus AD pathology may spread in a stepwise manner from the medial temporal lobes through the cortico-cortical connections (Bancher et al., 1993; Braak et al., 1993; Buckner et al., 2005). The hypothesized mechanism is that NFT would be present in the body of long cortico-cortical pyramidal neuronal cells so that there would be a loss of efferent and afferent connections to the neocortex (Morrison et al., 1986). Thus brain areas that are the least affected by NFT in the early stages of AD are those that are far removed, in terms of cortico-cortical connections from the ventromedial temporal lobes (Arnold et al., 1991).

3.0 fMRI and PET findings: revealing connectivity in functional brain networks

3.1 Cognitive Function Domain

There is growing evidence that brain activity to support a cognitive function occurs within large-scale brain networks rather than within single isolated brain regions. The volume of studies on brain connectivity between brain regions has increased steadily since the earliest studies reported about 15 years ago (McIntosh et al., 1994; Murphy et al., 1993). For the definition of connectivity of brain activity between brain regions, two major concepts have been applied (Horwitz, 2003). The first concept refers to functional connectivity, i.e., the correlation between neuronal changes within one brain region related to another (Friston, 1998). This approach does not allow for a causal interpretation of the influence among different brain regions, but is purely correlational in nature. Functional connectivity has been applied to explore the correlative pattern of brain activity (Bokde et al., 2001; Horwitz et al., 1987). In contrast, effective connectivity refers to the influence of one brain region onto the other where that direction of influence can be explicitly modelled, using approaches such as structural equation modelling (McIntosh and Gonzalez, 1994), autoregressive correlation, or dynamic causal modelling (Friston et al., 2003) (for review see (Ramnani et al., 2004)). These approaches are especially well suited to test specific hypotheses about the function of a particular neuronal network (McIntosh et al., 1994).

Another approach to investigate the networks activated by a task is demonstrated by Sperling and colleagues who utilized independent component analysis (ICA) to examine the networks that activate or de-activate during an associate memory task (Celone et al., 2006). The memory network across groups included the visual areas, hippocampus, bilateral dorsolateral prefrontal cortex and posterior parietal cortices supporting the hypothesis that a specific large-scale network underpins associative

encoding. The study included healthy controls, mildly cognitive impaired subjects (MCI) and AD patients, and they found a continuum of activation in the hippocampus from healthy controls to hyperactivation in more mildly impaired MCI subjects to hypoactivation in more severe MCI subjects to no activation in AD patients. The nonlinear changes in activation in the network across the various groups provided further evidence of an initial study suggesting this non-linear dynamic in the hippocampus (Dickerson et al., 2005). A study using resting measures of glucose metabolism found medial temporal lobe hypometabolism to be associated with memory encoding impairments, but the study also found significant correlations to parietal-temporal association cortices and frontal areas that may be part of a compensatory process in the AD patients (Desgranges et al., 1998). Decreased activation of the medial temporal lobe was also found in an encoding task in both MCI subjects and AD patients compared to healthy controls (Machulda et al., 2003). To investigate the early changes in networks is not only possible through the examination of brain activation changes but also by examination of the transition phase between activation and rest (Fox et al., 2005a). Rombouts and colleagues (Rombouts et al., 2005b) found that the transition phase between blocks of an encoding task and fixation led to significant differences between healthy controls, MCI subjects and AD patients over a network of regions that included the medial temporal lobe areas as well as visual processing areas, and frontal cortices. Even though the first indications of AD neuropathology may be present in the medial temporal lobe, it affects a significant number of regions outside of this initial area due to the high interconnectivity of the brain.

In AD, working memory is also significantly impaired at an early stage of the clinical manifestation of the disease. Patients with AD are severely impaired in a delay response task of visuo-spatial memory (Simone and Baylis, 1997; Stuart-Hamilton et al., 1988) and both visual and visuospatial short-term memory are impaired even in predementia subjects with MCI (Alescio-Lautier et al., 2007), where impaired visuospatial processing contributes significantly to deficits in every day skill in AD (Perry and Hodges, 2000). fMRI and PET-based studies showed that impaired visual working memory correlated with brain activity within the posterior parietal association cortex, prefrontal cortex, and thalamus (Collette et al., 1997; Desgranges et al., 1998, Collette, 1997 #2) in AD. Only few studies have examined changes in network-related changes in activity in relation to visual working memory breakdown in AD. Functional connectivity analysis of PET-data showed that patients with AD exhibit, in comparison to elderly healthy controls, reduced functional connectivity between the prefrontal cortex and hippocampus and the prefrontal-occipital areas during a delayed-matched to sample task of face stimuli (Grady et al., 1993). The reduced connectivity between the prefrontal cortex and visual occipital areas was consistent with findings for a perceptual matched-to-sample task of face stimuli in AD (Horwitz et al., 1995). In another study examining a delay-match-to sample- task with different duration of the delay interval, the age-matched healthy controls showed increased activity in the bilateral prefrontal and parietal cortex with increasing delay, whereas the patients had increased activity in the right prefrontal, anterior cingulate and left amygdala. Task performance in both groups was correlated with the right prefrontal cortex with the addition that performance in the AD patients was also correlated to the left amygdala (Grady et al., 2001). Taking the right prefrontal cortex as reference for functional connectivity analysis, Grady and colleagues found that in

healthy controls there was strong functional connectivity to a network of other frontal areas and posterior cortex regions while the AD patients had strong functional connectivity only to other frontal regions. It was found that the left amygdala in the AD patients had strong functional connectivity to the left prefrontal cortex and other posterior brain regions whereas the healthy controls has strong functional connectivity only to other posterior cortices. Grady and colleagues suggested that the results show a functional disconnection between the hippocampus and the frontal cortices in the AD patients, and that the disconnection was underlying the memory deficit in the AD patients. A further study in AD patients demonstrated that the recruitment of additional regions in the prefrontal cortex in AD patients was correlated with performance in a semantic and episodic memory task while the healthy controls utilized a different network with the networks correlated to task performance (Grady et al., 2003).

Insert Figure 1 near here

Not only are memory networks affected as shown by another study that examined a the functional connectivity between the fusiform gyrus and a wide cortical network across the brain (see Figure 1) (Bokde et al., 2006b). In this study, the task was to decide if two faces presented simultaneously were identical, and the reference region for the functional connectivity was the right fusiform gyrus, a key region in the perception of faces. Of interest in this study was that the activation in this task was not altered between the MCI subjects and the healthy controls (Bokde et al., 2008), suggesting that connectivity within a network is first altered due to the putative AD neuropathology and then changes in activation occur in the brain. It may be that

before recruitment of compensatory regions for a cognitive task, functional connectivity would be the first step leading to increased activation in a region that would activate as a compensatory mechanism. These issues would have to be examined within a longitudinal study framework to be able to answer these questions in more detail.

Effective connectivity can also be quantified using electrophysiological measures of brain activation (Astolfi et al., 2005; Massimini et al., 2005; Moran et al., 2008; Ursino et al., 2007) and initial work has been done in AD (see review (Uhlhaas and Singer, 2006)). Connectivity in resting state EEG was increased in the theta and delta bands and it was associated with a decrease in power in the alpha and beta bands (Babiloni et al., 2006; Jelles et al., 2008). The changes across the brain are not only frequency specific but also vary according to the spatial location and reflect the remaining connectivity pattern in the AD brain (Stam et al., 2007; Stam et al., 2003). There have been few studies using EEG with cognitive paradigms in AD and one study found reduced synchronization in the alpha and beta bands during the delay phase (maintenance) of a working memory task (Pijnenburg et al., 2004).

One of the best delineated neuronal networks in humans is the visual system of the human brain. The ventral pathway has been thought to underlie object identification whereas the dorsal pathway has been associated with processing of the spatial location of objects (Haxby et al., 1991; Ungerleider and Mishkin, 1982). Analysis of effective connectivity assessed by structural equation modelling showed evidence for the correlated activity within each pathway (McIntosh et al., 1994) specific to object vs location matching. Such results of connectivity analyses were central to identify an important feature: connectivity analysis supports the notion of distinct functionally

integrated networks. For example McIntosh and colleagues (McIntosh and Gonzalez, 1994) showed that the differences in effective connectivity of the ventral and dorsal visual pathways, as well as the inter-hemispheric effective connectivity, were different as a function of the cognitive task performed by the healthy elderly subjects. This approach has been applied to investigating the changes in healthy aging (Della-Maggiore et al., 2000) and in AD patients (Horwitz et al., 1995). In the study by Horwitz and colleagues they found that there was a functional disconnection between the dorsolateral prefrontal cortex and regions in the occipital-temporal lobes. The AD patients as a compensatory process for the disconnection recruited additional regions in the frontal lobes (Horwitz et al., 1995).

3.2 Coherent Resting Networks in the Brain

Recent developments on the functional and structural organization of the brain have demonstrated that there are large-scale networks across the brain that are defined through a coherent low frequency signal (Damoiseaux et al., 2006; Fox et al., 2005b). This spatial temporal structure extends throughout the brain and has been found also in non-human primates (Vincent et al., 2007). The findings of Vincent and colleagues (Vincent et al., 2007) suggest that fluctuations of spontaneous activity across anatomically interconnected brain regions constitute a fundamental principle of brain organization. Such an interpretation is supported by the fact that organized patterns of brain activity are present in both humans and non-human primates. The resting networks have generated new issues when examining brain activation due to a cognitive task, such the relationship between the task-associated network and the resting networks in the brain (Buckner and Vincent, 2007; Greicius and Menon, 2004).

The most investigated network among the spontaneous fluctuation networks that has been investigated is the default mode network (DMN) which is of particular interest for AD research because it includes the medial temporal lobes and the posterior cingulate – two key areas supporting memory function as well as affected very early in the disease – as well as lateral inferior parietal cortex and medial frontal areas. It is hypothesized that the DMN is active when a person does not do a goal oriented task, and it is hypothesized to mediate awareness of the internal state of the person as well as awareness of the external environment surrounding the subject (Gusnard et al., 2001; Raichle et al., 2001). The DMN is deactivated (suppressed) during performance of a cognitive task and it has been measured using two approaches: (a) comparing a cognitive task to rest condition and examining the regions deactivated during the task, and (b) analysis using only resting fMRI datasets to measure the DMN. In a study with young and old healthy controls and AD patients performing a semantic classification task (Lustig et al., 2003), it was found that the deactivation in lateral parietal regions was similar in all three groups, while the medial frontal areas showed it was reduced between young and old healthy controls with no further reduction in the AD group. The medial parietal region and posterior cingulate showed decreased deactivation between young and old, with much less deactivation in the AD group compared to both groups. Further examination of the temporal profile of the activation in this medial parietal region/posterior cingulate found that the healthy subjects deactivated this region during the task but that the AD patients had a constant level of activation across the semantic task and the control task. Another study that examined the deactivation during a cognitive task (Rombouts et al., 2005a), in this case a visual encoding and a working memory task in MCI, AD and healthy controls,

found that the deactivation in the medial frontal areas discriminated between the HC and the MCI (medial frontal) and AD (anterior cingulate) groups. In addition, the precuneus significantly discriminated between the healthy controls and the MCI and AD groups.

When utilizing only resting state fMRI data sets, Greicius and colleagues (Greicius et al., 2004) found significant differences in the DMN between AD and healthy controls in the hippocampus and posterior cingulate region. Another study found decreased functional connectivity between the right hippocampus in AD patients to cortical regions across the brain compared to healthy controls (Wang et al., 2006). In particular, the regions with disrupted connectivity comprised in part the DMN showing further support to the network-related nature of brain function disruption.

3.3 Interaction among networks

Given that the DMN is deactivated during a cognitive task, it is of high interest to examine if there is an interaction between the task-related network activated and the DMN. In a study using associate encoding, Celone and colleagues (Celone et al., 2006) found that the deactivation in the lateral and medial parietal regions was reciprocally related to the activation in the task related activation in the hippocampus. Across the 3 groups in the study, the activation in the hippocampus (bilaterally) was strongly inversely linearly correlated to the deactivation in the bilateral parietal regions. Further evidence that an impaired deactivation contributes to impairment in the task related activation and task performance is a study in AD patients that found a linear correlation between increased activation in medial temporal areas in the patient group during an associative memory paradigm to the impaired deactivation in the

parietal areas (Pihlajamaki et al., 2008). In AD patients the level of deactivation in the medial parietal areas was correlated with memory performance with less deactivation correlated with less successful encoding. Further support for the role of the DMN in cognitive tasks was found in a visual perception study with MCI subjects who showed decreased negative functional connectivity between a visual perception area and the medial frontal areas of the DMN compared to healthy controls (Bokde et al., 2006a).

Thus initial evidence from functional imaging studies indicate that not only do networks mediate cognitive function but also that the interactions among networks, among them the default network, have a linear association with performance. The role of the default network in cognition and how it might underpin it is unresolved.

3.4 Connectivity Dysfunction due to Changes in White Matter

White matter lesions (WML) are prevalent in AD with about one-third of autopsy-confirmed cases of AD (Mirra et al., 1991) but are frequently found in ageing as well (Erkinjuntti et al., 1994; Scheltens et al., 1992). WML including microstructural changes may be related to factors such as microvascular damage leading to hypoperfusion and white matter degeneration (Bailey and Kandel, 1993; de la Torre, 2004). The significance of white matter lesions alone for cognitive decline is not clear. This may be partially explained by the fact that for the assessment of macrostructural white matter changes, including presence of lacunae and white matter hyperintensities, lesion ratings were often averaged across large brain areas in previous studies, thus compromising the sensitivity to detect a correlation between the white matter changes and the decline in specific cognitive functions (Burns et al., 2005; Snowdon et al., 1997). Importantly, conventional T2-weighted MRI is sensitive

towards macrostructural lesions but less so for the assessment of microstructural white matter changes that could remain undetected in so-called normal appearing white matter areas (Bozzali et al., 2001). Such microstructural changes that are common in AD, however, can be detected with diffusion tensor imaging (DTI).

Damage of the membrane and degeneration of intra-axonal microtubules are associated with neurofibrillary changes that may lead to axonal microstructural damage (Grundke-Iqbal et al., 1986). DTI is sensitive for the detection of microstructural alterations, even though it is not clear which specific intra-axonal changes lead to changes in the DTI-assessed diffusivity (Beaulieu, 2002). The reduction of cellular integrity of nerve fibres as observed in AD may result in less constrained motion of the water molecules and thus higher diffusion and lower anisotropy values (Basser and Jones, 2002). If the integrity of neuronatomical connectivity between brain regions is an important determinant of neuronal network activity, damage to neuronal connections within a network should have a specific impact on the effective connectivity within the network, as often found in neurodegenerative diseases (Au Duong et al., 2005a; Au Duong et al., 2005b; Grady et al., 2001).

The apparent diffusion coefficient (ADC) can be calculated per voxel, where the intensity value is proportional to the diffusion of protons. Differences in the spatial orientation of diffusivity are expressed by fractional anisotropy (FA). Based on the assumption that the diffusivity is maximal in the direction of fibre tracts, the voxel-by-voxel determination of FA can be used in order to tract fibres at the macroscopic level (Mori and van Zijl, 2002). A number of DTI-based studies in AD patients have

demonstrated decreased FA and increased diffusivity in temporal lobes of the brain, a key area in AD. ROI-based DTI studies have shown increased ADC in patients with mild to moderate AD within the temporal stem (Hanyu et al., 1998; Kantarci et al., 2001), anterior and posterior cingulate gyrus (Kantarci et al., 2001; Rose et al., 2000; Takahashi et al., 2002; Zhang et al., 2007), and the corpus callosum (Bozzali et al., 2002; Duan et al., 2006; Sydykova et al., 2006; Teipel et al., 2007b; Xie et al., 2006).

Insert Figure 2 near here

Using a multivariate factor analysis approach to analyze the FA maps obtained from AD patients and healthy controls, Teipel and colleagues (Teipel et al., 2007b) found that there was a spatially correlated pattern of decreased FA in intracortical fibers that included key tracts in the temporal lobes (see Figure 2). The intracortical fibres with lower FA in the AD group included the anterior corpus callosum, white matter of the parahippocampal gyrus and fornix, left fasciculus longitudinal inferior, white matter areas in left inferior and middle temporal gyri, white matter areas in bilateral frontal lobes, right posterior cingulate and right middle occipital gyrus. The decreased FA in these areas is consistent with previous findings of grey matter structural changes, such as decreased FA in the parahippocampal white matter would indicate neurodegeneration of the white matter fibers that connect to the allocortical areas of the temporal lobes, which are affected early in AD (Price et al., 2001). The FA decreases in the fornix probably correspond to the loss of neurons in the hippocampus, as the fibers from the hippocampus project via the fornix to the mamillary bodies. Thus it can be seen that the decreased FA values occur within white matter fibres that connect to medial temporal areas. It is consistent with the

hypothesis that the changes produced by AD neuropathology within the brain follow a network of connections that arise from the medial temporal areas (Arriagada et al., 1992a; Morrison and Hof, 2002; Morrison et al., 1986). The association cortices located in the parietal lobes have long cortical-cortical connection to the medial temporal areas and these areas in the parietal lobes are also one of the first areas affected by AD. Furthermore, the decline in the corpus callosum, whose fibers connect both hemispheres, is consistent with atrophy of these areas due to grey matter declines on the cortex (Hampel et al., 2000; Hensel et al., 2002; Teipel et al., 2003; Teipel et al., 2002; Teipel et al., 1998; Teipel et al., 1999). It was found that left cingulum fibers, which connect the anterior thalamus, the cortical cingulum, and the association cortices in the frontal, temporal and parietal cortices and the hippocampus to each other, were correlated with free recall, verbal recognition and Boston Naming test performance in AD patients (Fellgiebel et al., 2008). The various regions that the cingulum fibers connect have been shown to be involved in the various tasks of memory such as encoding (in the hippocampus), retrieval and recognition (in the posterior cingulate, the retrosplenial cortex, and posterior and medial parietal cortex).

4.0 Future Perspectives of Research in Connectivity in AD

The studies reviewed here suggest that AD is in part a disorder caused by disconnection within cognitive networks and the failure of the brain to integrate the functionality of the various regions into an effective and efficient network. The assessment of the integrity of specific fibre tracts can be used in order to assess its association with the degree of functional brain activity (Toosy et al., 2004). If the integrity of neuroanatomical connectivity between brain regions is an important

determinant of neuronal network activity, damage to neuronal connections within a network should have a specific impact on the effective connectivity within the network (Au Duong et al., 2005a; Au Duong et al., 2005b; Grady et al., 2001). One approach to investigate the effects of structural changes on function would be to integrate effective connectivity and structural connectivity measures together using a multiple regression technique. It would allow testing for associations between the various connectivity measures and task performance. Given the initial changes within the temporal lobes and the memory domain in AD, a possible starting point for integration of function and structure would be in memory tasks and a neural network that would include the temporal lobes (see Figure 3).

Insert Figure 3 near here

The proposed integration of effective connectivity can also be done using EEG-based measures of effectivity connectivity and DTI. Thus one study examined the changes in the resting-state EEG inter-hemispheric connectivity between MCI subjects and healthy controls and changes in diffusivity across the brain (Teipel et al., 2008). It was found that the temporal-parietal coherence in the alpha band was correlated with FA and MD values in the white matter in posterior regions of the brain in both MCI and HC. In the frontal lobes coherence in the alpha band was correlated with diffusivity in the frontal lobes, anterior corpus callosum, and thalamus only in the MCI group. Thus, they showed an association between inter-hemispheric coherence changes and alterations in the alpha and beta bands of resting-state EEG.

In addition, methodological advancements in time series analysis would allow for a more detailed understanding of the changes in the phase-related changes in the fMRI-related signal. In addition, the coherent resting networks will provide another avenue for investigating neural networks and their breakdown, as well as plasticity processes, as from the available evidence it seems that the resting networks do not have compensatory processes, at least, as would be manifested by the recruitment of other regions. Thus the task-related networks and the resting coherent networks seem to have different properties and the compensatory processes are different between these networks. The interaction of networks and the dynamics of the resting coherent networks is a rich area of current research.

Future studies should also examine the multi-modal nature of networks, both the structural and functional components that define a network. Given the large changes that the brain undergoes with the presence of AD-related neuropathology, the changes will manifest themselves not only in the functional and structural domains but also in how the changes in the two domains interact with one another. For example, one study examined how brain activation in the fusiform gyrus during a perceptual task was dependent upon grey matter density along the ventral and dorsal visual pathways (Teipel et al., 2007a). Thus not only local grey matter atrophy may influence activation, but also atrophic changes at other nodes of the network. These issues need to be further investigated.

5.0 Clinical Applications

Assuming that cognition requires a high level of interaction among regions of a network, it may be that alterations in the interaction among these regions may be the

first biological indicator of active cellular molecular mechanisms and related neuropathology in the AD brain and that changes in connectivity would be followed by changes in activation. A multi-modal approach to investigating neural networks would inform the sequence of events that would lead to a breakdown of cognitive function at the earliest stages of the disease process. These issues have not been investigated and may play a critical role in the development of disease modifying compounds for AD.

Early detection of AD is of dramatically increasing importance since many new compounds claiming disease-modifying effects are currently being tested in phase 2 and 3 clinical trials. These drug candidates for secondary AD prevention would preferentially be investigated in patients during earlier presymptomatic stages since it is hypothesized that these compounds would be more effective when less damage to the brain has occurred. With this objective in mind, a recent position paper (Dubois et al., 2007) proposed that the research criteria for the diagnosis of AD should be refined and updated to be able to detect the earliest clinical stages of AD. The new criteria would be centred on clinically significant deficits in episodic memory and an abnormal measure on one or more biomarkers among structural MRI, molecular PET imaging, or cerebrospinal fluid amyloid beta or tau protein analysis. The greater use of biological based information such as the implementation of mechanistic biological markers of action (MoA) is particularly important in order to reflect safety and outcome induced by mechanistically active and potentially disease modifying compounds, such as amyloid lowering agents, amyloid immunization strategies, gamma and beta secretase inhibitors, or approaches targeting inflammation, oxidative stress or tau hyperphosphorylation and tangle formation. Understanding network

changes as early as possible within the chronically progressive AD disease course holds promise to provide an effective indirect means for early presymptomatic detection of AD pathology and to help create enriched and stratified early target populations for presymptmatic trials, as the disease modifying strategies could be potentially preventive of further progression to irreversible damage to brain structure and function. This notion is currently strongly supported by regulatory authorities, such as the FDA and the EMEA, searching for more suitable drug trial designs and biological safety and outcome measures in the development of therapies in the field of neurodegeneration.

The proposed integration of both structural and functional connectivity, as illustrated in Figure 3, would help increase our understanding of the underlying biological processes in AD but also could be applicable to investigation of early prodromal stages of AD. In the medium to long term perspective, a specific application of the proposed methods would serve as an effective and dynamic tool for enrichment of pre-symptomatic treatment trials so that the inclusionary criteria for the trial are more specific to AD. The proposed approach could also be implemented as a secondary outcome variable in phase 3 confirmatory clinical trials in which the outcome does not depend upon specific neuropathology or mechanisms in the brain.

6.0 Conclusions

Experimental data across a wide variety of approaches suggest that connectivity plays a critical role in mediating cognitive function and that the breakdown of connectivity, both in the functional and structural system domain, plays a major role in the development of AD. One critical element in understanding the disconnection

hypothesis in AD is that the spreading in the brain of the AD-related neuropathology as disease severity increases is through the large cortical-cortical pyramidal neurons. The location of the AD-related neuropathology in the mild stage of the disease is in the medial temporal lobes. Thus one sees the development of AD-related neuropathology in very specific regions of the cortex that are structurally connected while adjacent regions remain free of AD neuropathology. In addition, the studies using structural and functional imaging methodologies showed that networks mediated cognitive performance and their breakdown was correlated to decreased cognitive performance. In particular, compensatory networks in patients were shown to linearly correlate to cognitive performance. Thus the various approaches to understanding networks could be valuable tools in developing new approaches for early diagnosis of AD and for predicting the effectivity of possible treatment strategies.

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Figure 1. Map of the regions showing statistically significant differences in the linear correlation coefficient between healthy control and MCI groups. Figure from (Bokde et al., 2006a).

Figure 2. Projection of the positive and negative components of the canonical image into voxel space—3D-reconstruction. The canonical image in voxel space projected on a 3D-reconstruction of the T1-weighted template brain. A block has been cut-out from the anterior right hemisphere, opening the view on the internal capsule in height of the central sulcus at Talairach–Tournoux *y*-coordinate − 17. Red to yellow: components of the canonical images that are reduced in AD relative to controls. Blue to green: components of the canonical images that are increased in AD relative to controls. Figure from (Teipel et al., 2007b)

Figure 3. Integration of fMRI and DTI results into a picture of network connectivity over the two domains. The image on the upper left illustrates a hypothesized network, on the right side tehre are two images of activation, where the activation occurs in areas indicated by the network. The other images show some of the tracts that connect the various regions on the network.

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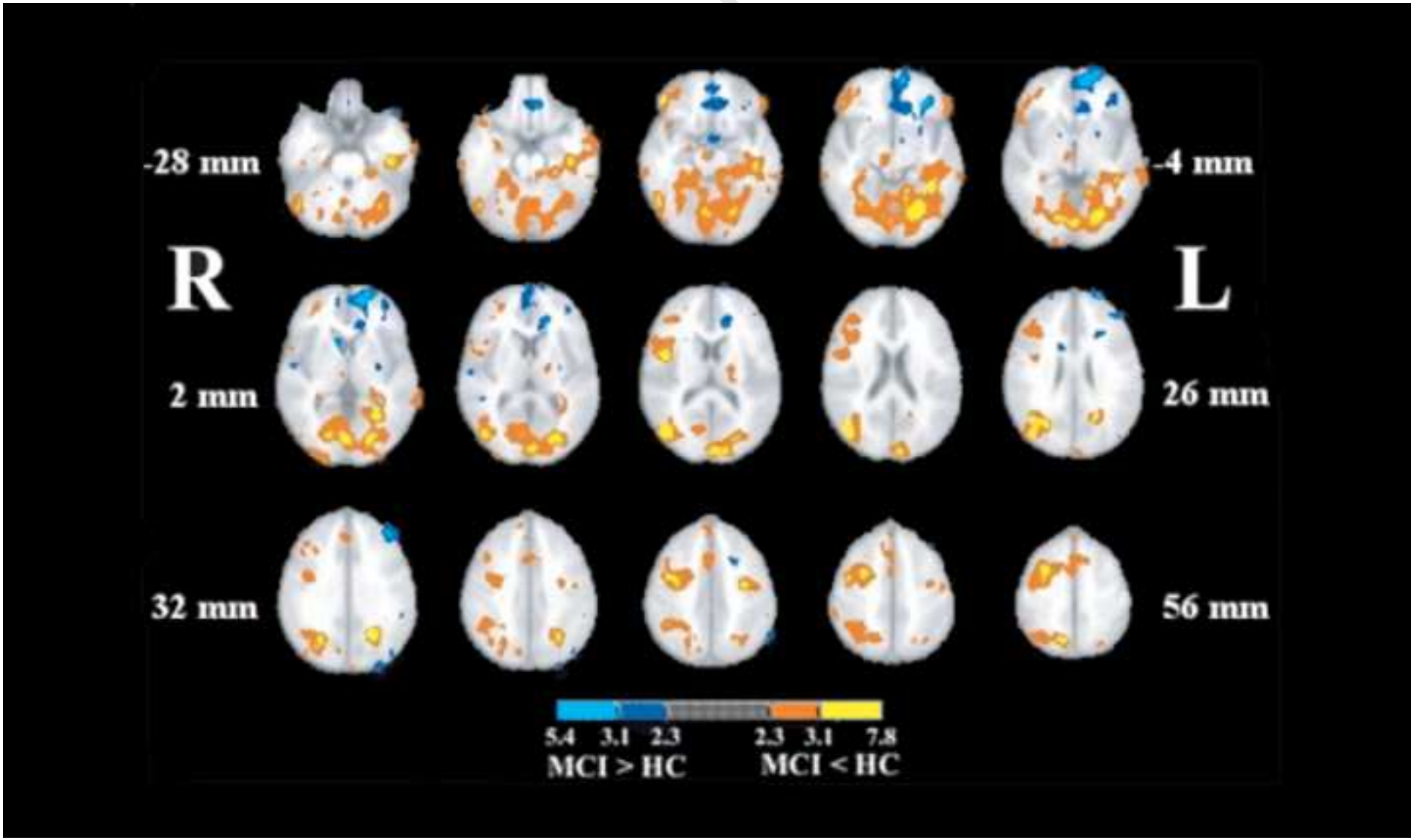
Figure_1



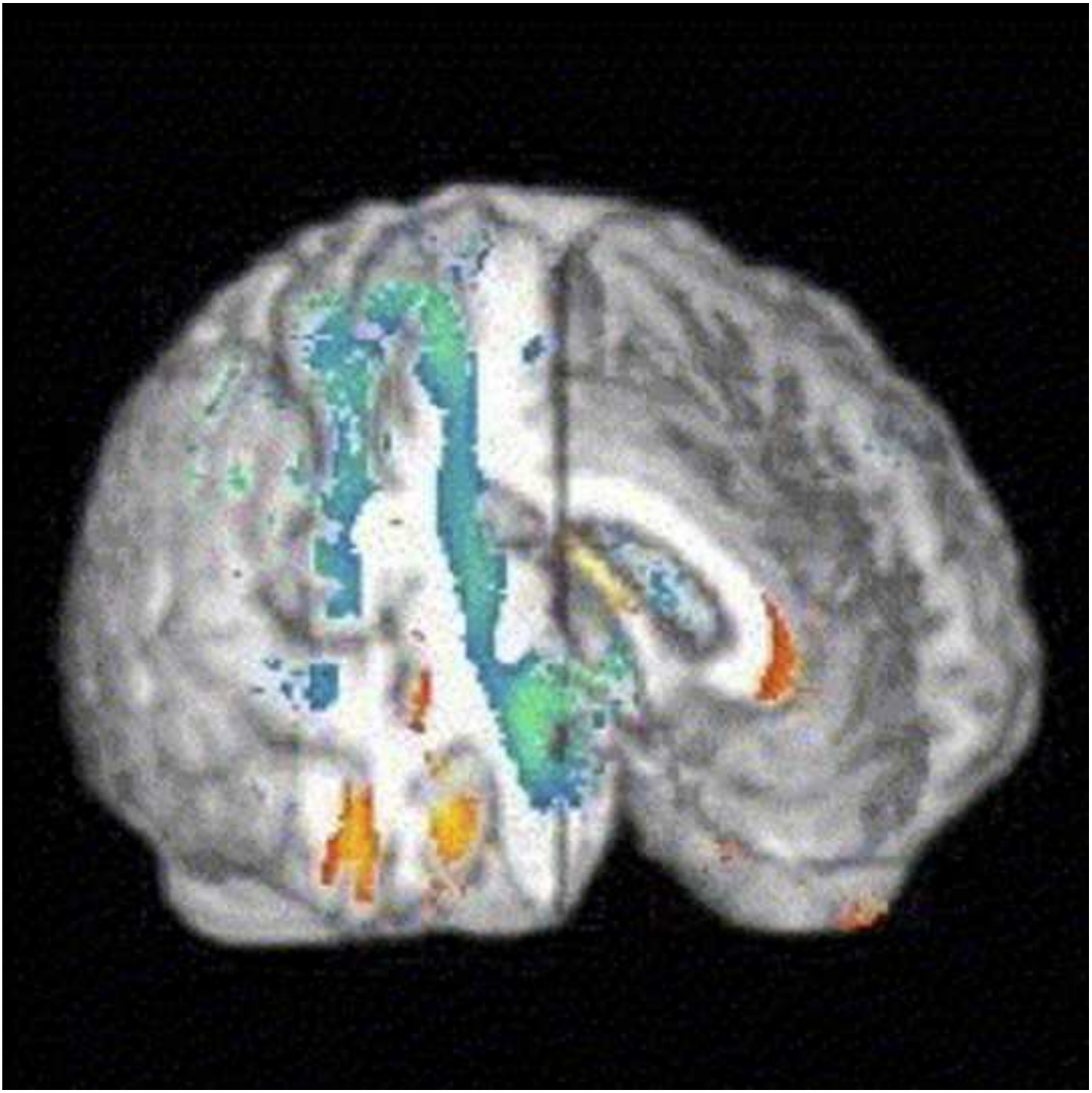


Figure_3