Cognitive Decline Associated with Aging, Alzheimer's Disease and Cerebrovascular Risk: Advantages of Dynamic Imaging with MEG

Cheryl J. Aine, John C. Adair, Janice E. Knoefel, Lori Sanfratello and Julia M. Stephen

Abstract Recent studies examining Alzheimer's disease (AD) and aging have noted a strong association between cerebrovascular risk and cognitive decline, and suggest that AD may in part be attributed to vascular insufficiency. Based on our recent results we suggest that cognitive decline associated with cerebrovascular pathology should be characterized and if possible separated from neurodegeneration caused by amyloid plaques and neurofibrillary tangles (i.e., traditional AD-related pathology) since the progression of cerebrovascular pathology can be stopped or slowed down. Furthermore, because cerebrovascular pathology (e.g., hypertension and type 2 diabetes) co-exists in most AD patients, neuroimaging techniques dependent on 'uncompromised' neurovascular coupling (e.g., fMRI) will have more potential confounds to deal with in this area of study, in addition to difficulties associated with being an indirect measure of neural activity. We assert that functional measures (e.g., dynamic cortical networks, oscillatory activity and cross-frequency coupling), as opposed to structural measures (e.g., diffusion tensor imaging–DTI), will enable earlier diagnosis of AD and mild cognitive impairment (MCI) and that MEG in particular can make important contributions to this field. A new potential area of study that relates MEG single trial results to models of diffusion parameters in extracellular space is introduced.

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1 Introduction

One goal of our research effort is to accurately differentiate between Alzheimer's disease (AD), mild cognitive impairment (MCI), normal aging, and healthy successful aging. Interest in this area was motivated by our previous neuroimaging studies demonstrating that a majority of a sample of MCI and AD patients revealed moderate to severe MRI abnormalities [e.g., white matter hyperintensities (WMHs), suggestive of chronic white matter ischemia, and volume loss], as determined by a board-certified neuroradiologist (Aine et al. 2010). In addition, approximately 1/3 of our elderly control group also had moderate to severe MRI abnormalities and they generally performed worse on the behavioral tasks and neuropsychological tests of memory, compared to elderly with no or mild MRI abnormalities. Recent literature on WMHs indicate that their presence is typically associated with hypertension and/or type 2 diabetes (Inzitari 2000; Dufouil et al. 2001; Cook et al. 2002; De Groot et al. 2002; Awad et al. 2004; Kuo and Lipsitz 2004; Manschot et al. 2006).

Indeed, numerous epidemiological studies have recently linked cardiovascular risks in midlife (e.g., hypertension) with increased likelihood of developing dementia, including AD, later in life [see review by Qiu et al. (2005)]. DeCarli and colleagues (2001), for example, found that individuals with MCI had an increased prevalence of WMHs and elevated midlife diastolic blood pressure that increased the risk for MCI to at least the same degree as apolipoprotein E ε4 (APOE-4) genotype. Schmidt and colleagues (2000) showed that individuals who developed AD had higher systolic blood pressure than nondemented counterparts 10–15 years prior to disease onset. It has even been shown that antihypertensive medication can protect against dementia in some cases (Forette et al. 2002). And finally, recent results from a meta-analysis (Debette and Markus 2010) suggest that WMHs should be used as an intermediate biomarker of brain health since they are usually associated with small vessel disease. Consequently, careful documentation of brain health for studies of aging and AD is very important because: (1) we need to separate pathological aging (e.g., cognitive decline associated with cerebrovascular risk) from healthy successful aging in order to better understand aging processes per se; and (2) we need to sort out effects due to cerebrovascular pathology from those attributed to AD processes (e.g., plaques and tangles) in order to better understand and treat this disease. Cerebrovascular-related cognitive decline (e.g., due to hypertension and/or type 2 diabetes) can usually be prevented or controlled by changes in lifestyle (diet and exercise) or medication, thereby providing patients

with a possible opportunity to delay the progression of dementia-like symptoms or cognitive decline and enhance the quality of their lives.

The clinical syndrome called dementia consists of an acquired memory impairment and impairment in at least one other cognitive domain, which diminishes the sufferer's ability to cope with activities of daily living for at least 6 months (Eschweiler et al. 2010). AD, the most common form of dementia, ranks among the top public health problems confronting developed countries (Arrieta and Artalejo 1998), with an estimated 14.5 million people in the U.S. to become afflicted with the disease by the middle of next century. Although there is general consensus on the clinical course and neuropathology of AD, there is limited information on its causes and pathogenesis. Current data suggest that various possible causes and predisposing factors most likely reflect an interaction of biological and environmental influences (Small 1998). The gene coding for the amyloid precursor protein (APP), whose cleavage product (beta amyloid) forms the cores of senile plaques in AD, was localized to chromosome 21 (Walker 1997; Small 1998). However, it was soon discovered that APP mutations rarely caused AD. Other genetic mutations causing early-onset familial AD have been identified, but they account for a very small proportion of AD cases. For late-onset AD (dementia beginning after age 60), APOE-4 has been confirmed to be a major susceptibility gene for AD (Hof et al. 1992; Small and Leiter 1998; Small 1998). However, the genes identified thus far for late-onset AD account for only 50 % of the genetic variability in AD. More recently, AD and other dementias have been linked to cardiovascular problems since AD and other dementias typically co-exist with hypertension (60 %), coronary heart disease (30 %), congestive heart failure (28 %) and diabetes (21 %) [2008 Alzheimer's disease Facts and Figures, Alzheimer's Association].

Interestingly, when Alois Alzheimer first described AD, dementia was most often attributed to vascular insufficiency or syphilis (Iadecola 2010) and Scheibel (1989) even referred to AD as a capillary dementia. Regardless of its etiology, early detection strategies for AD are essential since any soon-to-be-developed anti-dementia treatments are not likely to reverse existing neuronal damage, but rather slow further progression. Unfortunately, many studies indicate that significant medial temporal lobe atrophy occurs before the diagnosis of mild AD and that neurofibrillary changes and plaque deposition may begin even before age 30 (Braak and Braak 1997; Price and Morris 1999; Petersen et al. 2006).

2 Neurobiological Changes in Normal Aging and AD

Normal Aging. There is a wealth of cross-validation studies relating measures of cognitive performance to neurodegenerative markers (e.g., changes in microscopic structure, decreases in synaptic density, neuronal density, mean neuronal size, the number of neuritic plaques, etc.), or rather, microscopic brain changes (Huttenlocher 1979; Anderson et al. 1983; Kemper 1984; Burke and Barnes 2006). However, a

broad range of similar neuropathological findings can also be observed in older people with normal cognitive performance (Klunk et al. 2004; Aizenstein et al. 2008; Jack et al. 2009). Generally speaking, brain weight declines with age (by about 10 % from early adult life to the ninth decade); the ventricles and sulci enlarge in volume; and both gray (GM) and white matter (WM) volumes appear to shrink [see review (Kemper 1984)]. Atrophic changes have been reported most frequently in the convexities of the frontal lobes, parasagittal regions and the temporal and parietal lobes. Although past studies reported substantial neuronal loss (Coleman and Flood 1987; Kemper 1993; Rosene 1993; Albert and Moss 1996) recent investigations suggest that there is only an overall loss of $\sim$9.5 % of neurons with age (Voytko 1998; Peters and Rosene 2003) and that it is a misconception to think that dramatic cell loss and morphological changes in neurons occur in normal aging (Burke and Barnes 2006). Instead, age-related changes result in myelin loss and structural changes within the myelin sheaths which has the potential to disrupt communication among neurons (Willott 1997; Peters et al. 2000). WM fiber tracts provide high-density connectivity between cortical and subcortical GM structures, thereby coordinating activity across disparate GM regions and creating widely distributed, functionally integrated circuitry. Similarly, a decrease in number of dendritic branches and reduction in dendritic lengths have also been noted in elderly humans (Scheibel et al. 1975), which affects the number of synaptic contacts that can be made with other neurons (Willott 1997).

AD. The pathologic hallmarks of AD are senile plaques and neurofibrillary tangles which are selectively distributed; their concentrations are highest in the temporal-parietal regions, hippocampus, entorhinal cortex, and the amygdala (Hyman et al. 1984; Katzman 1986; Van Hoesen and Damasio 1987; Hof et al. 1992; Steffens 1997; Willott 1997; Jack et al. 1998; Small 1998). Synaptophysin, a marker of neuronal connections, is decreased in areas that are affected by the disease (e.g., hippocampus) but not in regions that are behaviorally or neuropathologically uninvolved (Honer et al. 1992). Dementia severity of AD patients correlated with synapse counts in biopsy tissue and synaptophysin concentration in postmortem tissue (DeKosky and Scheff 1990; Terry et al. 1991) suggesting that synapse loss is the major correlate of cognitive impairment (Terry et al. 1991). Quantitative MRI studies in AD have documented a general increase in CSF volume in the sulci, ventricles and the combination of sulci and ventricles (Alavi et al. 1993). Other MRI studies showed a regionally specific decrease in volume of the medial temporal lobe and hippocampal formation (Kesslak et al. 1991; Jack et al. 1992; Murphy et al. 1993; Steffens 1997). MCI patients, who are at risk for developing AD (Petersen 2004), are believed by some to have AD neuropathology and that medial temporal atrophy in these patients predicts subsequent progression to AD (Jack et al. 1999).

Jack and colleagues (2010) recently summarized five of the most widely studied biomarkers of AD pathology and ordered the temporal relationships among the biomarkers with clinical disease stage. Amyloid (Aß) imaging (PET-PIB) abnormalities, for example, may precede clinical/cognitive symptoms by as much as 2–3 decades since approximately 20–40 % of cognitively normal elderly have evidence

of significant brain Aß deposition. Other biomarkers included CSF $Aß_{42}$, another index of Aß deposition, CSF tau, a putative marker of neuronal damage, and FDG-PET, an indicator of synaptic dysfunction. Unfortunately, these tests are either prohibitively expensive (i.e., requiring a PET scanner and cyclotron) or invasive (i.e., requiring lumbar puncture or exposing patients to ionizing radiation) so that their use is limited in clinical practice and restricted mainly to research studies. Structural MRI, listed as the 5th biomarker, provides a good measure of medial temporal volume loss that coincides with cognitive symptoms. While more clinically practical, structural MRI changes appear later in the temporal sequence than other biomarkers. Therefore, we need to identify neural signatures earlier, within the 2–3 decades that amyloid burden accumulates, in order to stop or defer disease progression.

3 Posterior Versus Anterior Patterns of Effects Differentiate Between AD and Normal Aging

Since AD is characterized by the presence of cortical amyloid plaques and neurofibrillary tangles in entorhinal and parahippocampal cortex in mild stages of AD, it is generally believed that the pathology has a more posterior distribution. The medial temporal lobe (MTL), a site where neurofibrillary tangles dominate first, is densely interconnected with posterior regions such as parietal cortex (Klunk et al. 2004; Buckner et al. 2005). Consequently, recall and recognition memory (e.g., recognizing a list of words) become increasingly impaired as the number of tangles increases. In contrast, there is a separate anterior pattern of changes associated with normal aging. Cognitive processes such as working memory and executive control are supported by the prefrontal lobes, and are among the first to decline with age [e.g. (Moscovitch and Winocur 1995; West 1996; Tisserand and Jolles 2003)]. Similarly, WM degenerates with an anterior-to-posterior gradient (i.e., prefrontal lobe dysfunction occurs first) (Head et al. 2005; Delano-Wood et al. 2012). Therefore, neuroimaging studies originally focused on differentiating between these anterior changes associated with normal aging (working memory/executive function deficits) versus posterior patterns associated with MCI/AD (word recall/recognition deficits).

However, a meta-analysis conducted by Gunning-Dixon and Raz (2000), along with other studies (Oosterman et al. 2004; Tullberg et al. 2004), have also shown that WMHs are: (1) more abundant in frontal regions; (2) associated with cognitive decline (e.g., executive dysfunction); and (3) associated with hypertension and type 2 diabetes (DeCarli et al. 1999; Gunning-Dixon and Raz 2000; Artero et al. 2004; Awad et al. 2004; Elias et al. 2004; Kuo and Lipsitz 2004; Schmidt et al. 2004; Qiu et al. 2005; Nordahl et al. 2006; Pantoni et al. 2007; Helzner et al. 2009). This cerebrovascular-related cognitive decline is believed to be due to demyelination and axonal degeneration (van Swieten et al. 1991; Taylor et al. 2003) in regions connecting frontal cortex and subcortical structures (Kuo and Lipsitz 2004).

Consequently, cerebrovascular-related cognitive decline also has an anterior pattern of changes since frontal areas are the first to reveal WMHs, followed by periventricular and parietal regions (Artero et al. 2004; Head et al. 2004). In each stage, the density of lesions increases until finally temporal and occipital regions are involved (creating an anterior-posterior gradient). Working memory and executive control functions are targeted first in this group. Since normal aging is also known to affect frontal lobe structures supporting working memory and executive functions, then cerebrovascular-related cognitive decline appears to be a serious confound for aging studies in general and certainly for studies attempting to differentiate between AD and normal aging.

In our most recent ongoing studies, we postulated that cerebrovascular risk factors (e.g., hypertension, hyperglycemia, hypercholesterolemia) underlie at least some of the apparent frontal lobe deficits seen in normal aging (Aine et al. 2011, 2013). This is similar to conclusions reached by Kennedy and Raz (2009) who suggested that: (1) elevation of arterial pulse pressure is linked to deterioration of WM tract integrity in frontal regions and (2) vascular risk may drive the expansion of WM damage from anterior to posterior regions. Burgmans and colleagues (2010) also examined effects of hypertension on white matter integrity (DTI, WMHs, WM volume) and concluded that diffusion-based indices of WM integrity may be more sensitive indicators of global and regional declines in the aging brain. Our initial results [behavioral and MRI/DTI; Aine et al. (2013)] show highly significant effects between cerebrovascular-related health status and cognitive decline. Cerebrovascular risk factors account for at least some, so-called normal aging effects. At least two issues remain: (1) how can we diagnose AD earlier in time; and (2) what do neuroimaging results tell us about the etiology of cognitive decline associated with aging and MCI/AD?

4 Advantages of Functional Neuroimaging with MEG

Currently, it is believed that neurodegenerative diseases and neuropsychiatric illnesses target specific networks, causing disruption and consequent cognitive decline (Seeley et al. 2009). Thus the elucidation of neuroimaging methods that can uniquely characterize these networks across anatomical and functional levels for each of the pathologies facilitates clinical diagnosis. While it is useful to know lesion localization via structural imaging, functional measures should be able to provide information about cognitive decline earlier than anatomical measures. The temporal evolution of biomarkers in AD discussed earlier asserts that changes in activity levels (e.g., FDG-PET hypometabolism) occurs months or years before structural changes within the brain are detectable. As noted above, structural MRI was listed as the 5th biomarker that provides a good measure of hippocampal volume that coincides with cognitive symptoms. However, we need to identify neural signatures prior to significant volume loss or symptom onset to maintain quality of life for those who are susceptible to AD-related cognitive decline.

Recently, Hedden and colleagues (2009) and Sheline and colleagues (2010) examined network connectivity in the default mode network (DMN) using fMRI in a group of cognitively normal elderly who were either classified as PIB+ or PIB− from the PET amyloid imaging exam (i.e., they either showed evidence of amyloid deposition when imaged with ^{11}C-labeled Pittsburgh Compound B or not). The PIB+ groups from both studies revealed a disruption of functional connectivity within the DMN that could not be explained by increased age or structural atrophy. The pattern of disruption was similar to that shown in AD patients in other studies (Greicius et al. 2004; Zhang et al. 2009). For example, connectivity between precuneus and hippocampus (i.e., a posterior pattern of effects) was significantly lower in individuals with amyloid deposition versus those without cerebral amyloid. We suggest that functional connectivity measures are far more likely to provide sensitive measures of disease processes, and earlier in time than structural measures. In addition, by using functional measures with enhanced timescales (i.e., milliseconds rather than seconds) that are less affected by neurovascular coupling issues (e.g., MEG/EEG) should increase the chances for successful differential diagnosis.

Issues Associated with Neurovascular Coupling for fMRI Studies of Age-related and AD Pathology. As mentioned previously even Alois Alzheimer attributed AD to vascular insufficiency or syphilis (Iadecola 2010). Later, AD was associated primarily with posterior degenerative pathology. Thus, it appears that views of AD are beginning to come around full circle since recently there are numerous studies indicating interaction between neurodegenerative and vascular factors in the pathogenesis of dementia (Farrall and Wardlaw 2009; Iadecola 2010; Warsch and Wright 2010) and some are outright suggesting that AD is a microvascular disorder [reviewed in (Jellinger 2002; Zlokovic 2005; Bell and Zlokovic 2009; Schneider and Bennett 2010)]. In a study of 300 AD autopsy cases, 98 % were found to have cerebral amyloid angiopathy (CAA) (i.e., deposition of Aß in arteries, arterioles, and less frequently in capillaries and veins) and 100 % showed microvascular degeneration (Kalaria and Ballard 1999). It is rather interesting that amyloid burden is most prevalent in frontal lobes even though AD is thought of as predominantly affecting medial temporal lobes. For example, a recent study examining cognitively normal elderly with PIB+ suggests that a frontal network associated with working memory was affected first by amyloid deposits (Oh et al. 2011). Theories that suggest cerebrovascular dysfunction precedes cognitive decline and the onset of neurodegenerative changes in AD [e.g. (Zlokovic 2005, 2008; Bell and Zlokovic 2009)] indicate that cerebral hypoperfusion impairs the clearance of Aß from the brain, which is normally performed by the cells in the neurovascular unit. Therefore, Aß accumulates on blood vessels (i.e., CAA) and in brain parenchyma. In support of this hypothesis, MR-based arterial spin labeling (ASL) showed widespread hypoperfusion in AD (Johnson et al. 2005). There is also increasing evidence that the effect of vascular lesions are more pronounced in the early stages of AD (Esiri et al. 1999) and that ischemic lesions and vascular risk factors accelerate disease progression of dementia (Helzner et al. 2009).

A recent meta-analysis covering aging, vascular dementia, AD, lacunar stroke, and leukoaraiosis indicates that the blood-brain-barrier (BBB) permeability in these conditions is altered (Farrall and Wardlaw 2009). In other words, the neurovascular unit itself is altered [e.g. Bell and Zlokovic (2009)]. Therefore, one potential barrier to using fMRI methods for examining AD is that neurovascular coupling may be altered in these groups and consequent interpretations of the BOLD changes may be incorrect (D'Esposito et al. 2003). Neurovascular coupling is defined as the relationship between a change in neuronal activity and the subsequent hemodynamic response reflected by a BOLD signal change. The primary determinant of the BOLD signal, deoxyhemoglobin within each voxel, is dictated by the venous blood volume, arterial blood flow and blood oxygenation, and any disease or medication that modifies the responsiveness or the baseline values of these parameters are likely to modify BOLD contrast even in absence of any modulation of neural activity (Iannetti and Wise 2007). Unfortunately, Lee and colleagues (2009) found patterns of hypo- and hyper-perfusion for their group of 38 healthy elderly leading them to believe that there are problems with neurovascular coupling in many elderly as well. Therefore, Iannetti and Wise (2007) offer several suggestions/steps for improving the interpretability of BOLD fMRI results in cases where the neurovascular coupling may be compromised. For one, they suggest acquiring an independent measure such as electrophysiological responses (e.g., EEG and MEG).

Figure 1 shows the utility of using MEG time-course information derived from inverse procedures to capture differences between diagnostic categories. As mentioned above, MCI and AD have a more posterior pattern of deficits (i.e., temporal lobe). Several recent studies have noted the importance of mapping anterior temporal (ANT) lobe activity as well. Studies monitoring cortical atrophy rates for MCI and AD in longitudinal designs consistently note early changes in the anterior MTL (Bozzali et al. 2006; Smith et al. 2007; Whitwell et al. 2007). Whitwell and colleagues (2007), for example, found changes in the anterior temporal lobe that occurred three years previous to a diagnosis of AD. At the time of diagnosis of AD, atrophy in the temporal lobes had spread to include the middle temporal gyrus and the entire extent of the hippocampus. Our auditory delayed verbal recognition task (Aine et al. 2010) is good for evoking activity in the anterior temporal lobe since this region has been identified as an auditory word form area (Cohen et al. 2004). Most healthy controls showed activation in ANT (blue tracing in top portion of Fig. 1 is the average time-course across participants which show ANT activity). MCI and some AD patients also revealed activity in ANT (red tracing), but they showed hyperactivity in this region. However, we could not localize activity in this region for some AD patients. Dickerson and colleagues (2008) reviewed three fMRI studies that also demonstrated greater MTL activation in MCI patients compared to controls. They consider hyperactivation as a predictive marker in MCI. Hypoactivation of MTL occurs at a later stage of the disease resulting in an inverted U-shaped curve describing blood oxygenation changes in MTL with progression from MCI to AD [(Dickerson and Sperling 2008) see also Maestú et al., this volume]. That is, hyperactivation of MTL circuits occurs early in the course of MCI

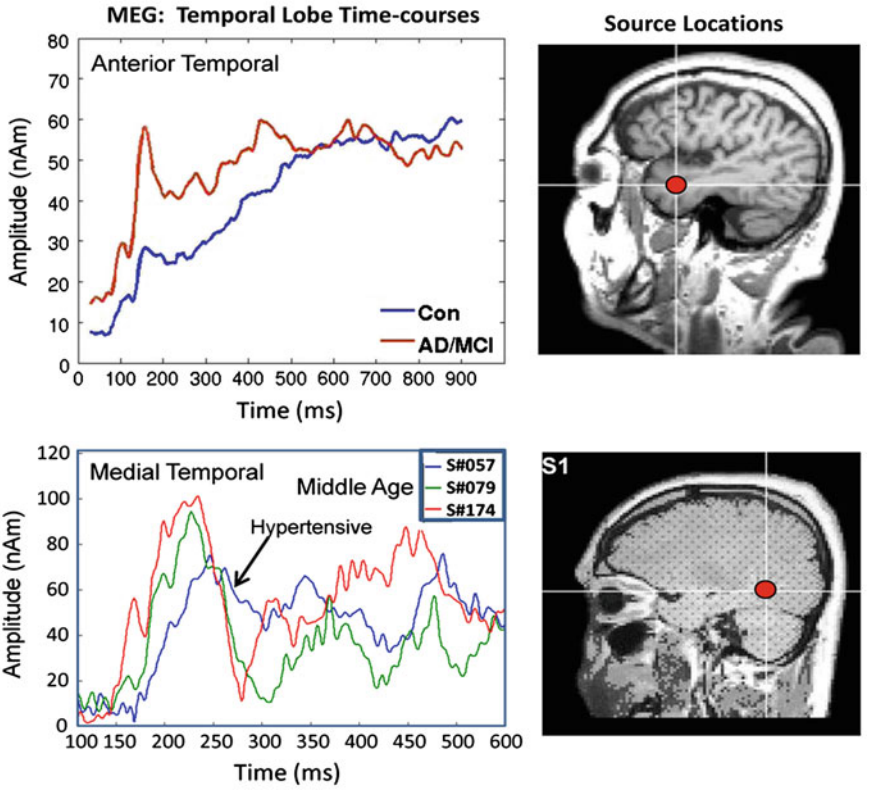

Fig. 1 *Top* MEG time-courses of sources localized to anterior temporal lobe, averaged together for the healthy controls (*blue* tracing) and MCI/AD patients (*red*) tracing. MRI at right reveals anterior temporal lobe. *Bottom* Time-courses of sources for 3 middle-aged participants localized to medial temporal lobe (see MRI at the *right*). Participants denoted by *red* and *green* tracings were healthy controls. *Blue* tracing denotes a hypertensive participant. These time-courses appear noisy because we did not want to eliminate high frequency activity (e.g., gamma band) superimposed on the slower activity

while these same regions failed to activate in AD. It was suggested that entorhinal and perirhinal cortices were most likely devastated by neurofibrillary pathology and cell loss early in the course of AD, effectively disconnecting the hippocampal formation from neocortical afferents and efferents. Our averaged MEG evoked response data corroborate these fMRI findings.

The bottom portion of Fig. 1 shows time-course effects associated with hypertension. In this case we used a visual working memory task (Sternberg variant) to evoke activity in MTL. Single-subject data are shown for two healthy middle-aged controls (red and green tracings) and one middle-aged hypertensive patient (blue tracing). All participants were 35–45 years of age. In contrast with

the ANT activity shown above, the hypertensive patient, representative of our hypertensive group, revealed lower amplitude signals and prolongation of peak activity. In this case, MCI and hypertension appear to operate in opposite directions (MCI have greater amplitude signals and no peak delays in ANT), at least initially, but AD and hypertension may have a similar trajectory (reduced amplitude, delayed peaks until activity in this region can no longer be localized). This is just one example of how MEG source locations and time-courses can be used to characterize various diseases and disorders. It should also be emphasized that MEG easily permits the examination of single subject data, a necessity for clinical intervention.

MEG/EEG: Oscillatory Activity and Frequency Domain Analyses. Certainly, we are interested in finding alternative ways of analyzing data for our clinical research on aging and dementia, that may be faster and/or geared toward very specific questions (e.g., slowing of activity in temporal regions). Characterizing altered neural oscillations and synchrony in pathophysiology as a potential biomarker provides an additional way to achieve classification specificity for brain disorders (Uhlhaas and Singer 2010). Recently, there has been increased interest in understanding oscillating networks since they appear to provide important links between single neuron activity, population activity, and behavior. The existence of an oscillatory hierarchy, which controls neuronal excitability (Buzsaki and Draguhn 2004; Lakatos et al. 2005), has been described in animal studies where higher frequency oscillations are nested within lower frequencies. Lakatos and colleagues (2005), for example, nicely show in monkey auditory cortex that a succession of negative and positive voltage fluctuations, comprising the oscillation, reflected an underlying 7 Hz alternation of net inward and outward transmembrane current flow, which produced extracellular current sinks and sources, respectively. The corresponding multiunit activity indicated that current flow alternation reflected shifts between net depolarized and hyperpolarized states in the local neuronal ensemble (i.e., increases in firing and decreases in firing). Studies on cross-frequency coupling in the hippocampus and other brain regions suggest that these nested oscillatory patterns may be capable of storing multiple memories within a single network (Lisman and Idiart 1995). In addition, there is a correlation between the distance over which synchronization is observed and the frequency of the oscillations such that higher frequency oscillations (gamma band activity) are believed to be confined within small neuronal space (i.e., shorter distance) whereas slower oscillations such as beta band activity carry information over longer distances (e.g., large networks) (Kopell et al. 2000; Buzsaki and Draguhn 2004; Uhlhaas et al. 2010). Only coherently oscillating neuronal groups (i.e., phase locked) can interact effectively across distance. In sum, oscillations constitute rhythmic modulations in neuronal excitability that affects both the likelihood of spike output and sensitivity to input, which also permits coherently oscillating neuronal groups across regions to communicate effectively and efficiently with each other (Fries 2005).

Unfortunately, after decades of research on oscillatory activity there is no unified theory on oscillatory activity as seen in surface EEG or MEG, although

there have been numerous studies attempting to determine the role of oscillations in perceptual binding (Engel et al. 1992; Singer and Gray 1995; Roelfsema et al. 1997). However, MEG recordings are better suited for examining oscillatory activity for two reasons. First, the abnormal MEG patterns noted for AD are very specific to sensor groupings (e.g., temporal regions) rather than being generalized across the head (EEG). This is important since much of the abnormal activity is in the same frequency range as muscle and other related artifacts. MEG can separate out abnormal brain activity from muscle artifact based on different spatial patterns. Second, we have noticed bursts of high frequency signals associated with WMHs and bursts of slow-waves associated with volume loss. Luckily, the skull does not act as a low-pass filter for MEG as it does for EEG (Hamalainen et al. 1993). Clearly this is an exciting area where MEG/EEG studies have a definite advantage over fMRI measures. For those interested in learning more about oscillatory activity and frequency domain analyses, please see chapters (this volume) by Schoeffelen and Gross, Brookes and colleagues, and de Pasquale and Marzetti.

What makes cortical frequencies change? Some frequency changes are associated with development [see Uhlhass et al. for a review (2010)]. But, pathology can also affect regional frequencies. For example, Fernandez and colleagues (2002) found abnormal slow wave activity for AD patients in temporoparietal regions (see a review by Maestú and colleagues—this volume). In general, diffusion parameters of the extracellular space such as volume fraction and diffusion barriers modulate neuronal signaling, neuron-glia communication and extrasynaptic volume transmission (Sykova 2004). Significant decreases in extracellular space volume fraction (e.g., due to astrocytosis) and increases in diffusion barriers (e.g., plaques) may occur in AD as the result of pathology. If ion homeostasis is not maintained in the extracellular space, increased neuronal excitability and synchronization may occur, as noted in epileptiform spike generation (Broberg et al. 2008). Interestingly, several neurodegenerative diseases such as AD are associated with increased incidence of seizures (Palop et al. 2006). Cell swelling and concomitant reduction of extracellular space volume occurs in a number of pathologic conditions, causing an imbalance in the neuronal environment. Plaques, in contrast, disrupt the synchrony of convergent inputs thereby reducing the successful integration and propagation of information by neurons (Stern et al. 2004); it affects network properties and causes an increase in response variability with a net result of reduced synchrony of converging synaptic inputs.

It is clear that pathology affects neuronal signaling but how exactly the deposition of plaques, cell volume changes and changes in the extracellular ion concentration affect signal generation and propagation remain unclear. Our single-trial MEG data shown in Fig. 2 suggest at least 3 different patterns of activity associated with pathology: (1) bursts of slow-wave activity some of which are time-locked to the stimulus; (2) bursts of high frequency spike-like activity that is not time-locked to the stimulus; and (3) abnormal rhythmic patterns (see Fig. 3: a fronto-temporal dementia case). High frequency bursts were often seen in single-trial data from participants who revealed moderate to severe WMHs on their MRIs (bottom panel of left column) resulting in source time-courses that were extremely

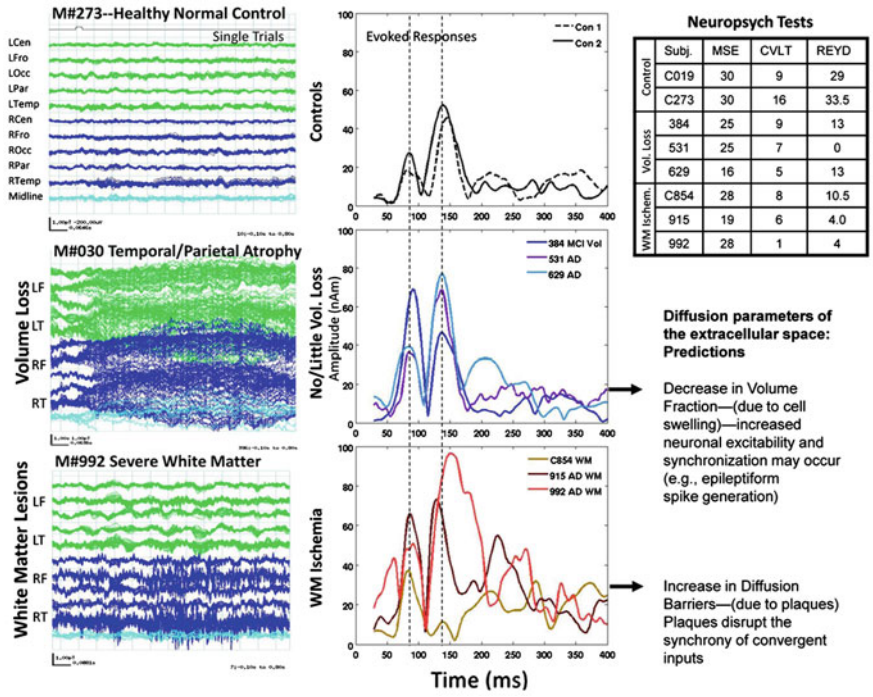

Fig. 2 *Left Column* (*Top*) Single-trial MEG responses from a healthy control evoked by a tone. This 1,000 ms segment (100 ms pre-stimulus and 900 ms post-stimulus) shows low-amplitude, de-synchronized activity from 275 sensors grouped by head regions; *green* and *blue* tracings represent *left* and *right* hemispheres, respectively. *Middle* Slow-wave activity is evident for this participant with MR abnormalities. *Bottom* High frequency activity over right temporal and frontal regions for another participant with MRI abnormalities. *Middle Column* Averaged time-courses localized to the superior temporal gyrus (STG) for (*Top*) 2 healthy controls and (*Middle*) 3 patients revealing moderate-severe volume loss and (*Bottom*) for 3 patients revealing moderate-severe white matter ischemia. *Right Column* (*Top*) Sample neuropsychological test results are shown for each patient and control. *Bottom* Predictions relating diffusion parameters of extracellular space to characteristics seen in the MEG data. *MSE* mini-mental status exam; *CVLT* Trial 5 of the California Verbal Learning Test; *REYD* Delayed recall on the Rey complex Figure Test

variable across participants in terms of peak latencies and amplitudes (bottom panel of middle column). In contrast, bursts of slow-wave patterns were evoked by auditory stimuli from participants with evidence of volume loss on their MRIs (middle panel of left column "M#030 Temporal/Parietal Atrophy"). Their corresponding averaged time-courses showed enhanced amplitudes, but the peak latencies were similar to those seen in normal controls (compare middle and top panels of middle column). As this longitudinal study progressed across years, it became possible to predict the MRI and neuropsychological results based on the number of epochs evidencing slow-wave bursts or high frequency activity in the

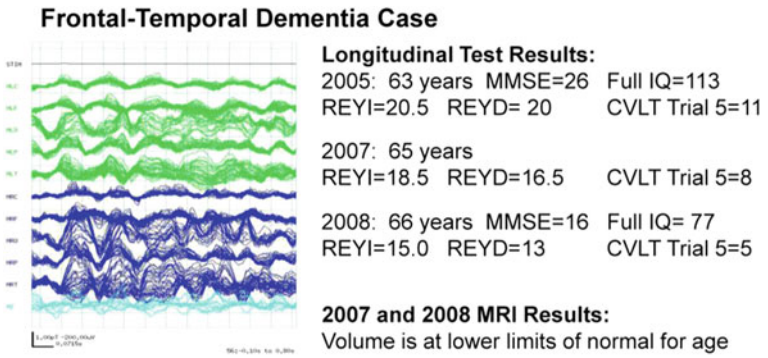

Fig. 3 Abnormal Rhythmic Patterns in Frontal-Temporal Dementia. *MMSE* Mini-mental status Exam; *REYI* Immediate recall on the Complex Figure Test; *REYD* Delayed recall on the Complex Figure Test; *CVLT* Trial 5 of the California Verbal Learning Test. MRI results were still within normal limits

single-trial data (unpublished results). We also see cases where both high frequency bursts and slow-wave activity are present within the same individual and their MRIs show the presence of both WMHs and volume loss. Relating single-trial data to models of diffusion parameters in extracellular space is likely to provide new information on the etiology of cortical pathology and cognitive decline associated with aging, MCI and AD. This is an untapped area of research that is uniquely suited for MEG.

5 Conclusions

If various causes and predisposing factors of AD reflect an interaction of biological and environmental influences (Small 1998), then health of the elderly, in addition to those suspected of probable AD, should be documented in research studies. Yet, most research participants do not complete neurological exams, blood tests, and even when the protocol requires the acquisition of MRIs, they are often not read by a neuroradiologist nor are subjects excluded from the study when MRIs reveal abnormalities for studies of healthy aging. Certainly, many more insults could have occurred in the brains of the elderly group, compared to the young, and in the brains of those suffering from cognitive impairment compared to normal elderly. At minimum, perhaps a structured interview could help determine the suitability of potential applicants for each study by asking a standard set of questions (e.g., have you ever experienced loss of consciousness for greater than 5 min? Did your doctor ever tell you that you have high blood pressure?).

As mentioned earlier, several recent studies found that WMHs associated with cardiovascular disease (e.g., hypertension and diabetes) target prefrontal cortex and affect working memory (DeCarli et al. 1999; Gunning-Dixon and Raz 2000;

Artero et al. 2004; Jeerakathil et al. 2004; Kuo and Lipsitz 2004; Schmidt et al. 2004; Tullberg et al. 2004; Nordahl et al. 2006; Pantoni et al. 2007; Burgmans et al. 2010). WM lesions, for example, affect performance on higher cognitive tasks via the disruption of neural transmission in functional networks (Peters and Rosene 2003; Filley 2005). The use of MEG-derived oscillatory characterizations should help tease out subtle differences in the spatio-temporal patterns of connectivity noted between cerebrovascular-related cognitive decline, neurodegenerative cognitive decline and normal cognition in healthy elderly. For example, it is likely that frequency differences associated with the nodes of the networks and cross-frequency coupling between nodes in the circuit will be evident earlier in time than structural or hemodynamic changes. Appropriate timing within the circuit is critical for proper functional connectivity. This is an area ripe for new studies, particularly if it can be related to models of diffusion parameters in extracellular space. In addition, this new area of research represents a unique niche for MEG methods.

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