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Development and Decline of Memory Functions in Normal, Pathological and Healthy Successful Aging

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Abstract

Many neuroimaging studies of age-related memory decline interpret resultant differences in brain activation patterns in the elderly as reflecting a type of compensatory response or regression to a simpler state of brain organization. Here we review a series of our own studies which lead us to an alternative interpretation, and highlights a couple of potential confounds in the aging literature that may act to increase the variability of results within age groups and across laboratories. From our perspective, level of cognitive functioning achieved by a group of elderly is largely determined by the health of individuals within this group. Individuals with a history of hypertension, for example, are likely to have multiple white matter insults which compromise cognitive functioning, independent of aging processes. The health of the elderly group has not been well-documented in most previous studies and elderly participants are rarely excluded, or placed into a separate group, due to health-related problems. In addition, recent results show that white matter tracts within the frontal and temporal lobes, regions critical for higher cognitive functions, continue to mature well into the 4th decade of life. This suggests that a young age group may not be the best control group for understanding aging effects on the brain since development is ongoing within this age range. Therefore, we have added a middle-age group to our studies in order to better understand normal development across the lifespan as well as effects of pathology on cognitive functioning in the aging brain.

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Keywords

Memory; Cognitive decline; White matter; Gray matter; Development; Memory strategies; Hypertension; White matter hyperintensities; Alzheimer's disease; Mild cognitive impairment; Magnetoencephalography (MEG)

Introduction

Traditional views of aging suggest that neurocognitive decline results from an inevitable loss of tissue and functional reserves (Bellamy 1997; Cabeza et al. 2002; Reuter-Lorenz and Lustig 2005; Tisserand and Jolles 2003). In support of this view, postmortem studies revealed microanatomical changes associated with aging such as changes in microscopic structure, and decreases in synaptic density, neuronal density and mean neuronal size (e.g., Anderson et al. 1983; Flood and Coleman 1988; Huttenlocher 1979; Terry et al. 1987). Similarly, studies using anatomical neuroimaging techniques (e.g., CT and MRI) have reported structural changes and some have correlated these changes with neuropsychological test results (Burgmans et al. 2009; Cardenas et al. 2009; Jagust 1994; Taki et al. 2010; Yue et al. 1997). Frequently, gray matter (GM) in prefrontal regions (dorsolateral and orbitofrontal) was shown to decline linearly after adolescence or young adulthood (Gogtay et al. 2004; Raz et al. 1997; Sowell et al. 2001, 2003) (see Fig. 1, solid line). Therefore, studies of aging typically viewed young adults in their twenties as being at their peak of neurocognitive functioning, followed by a steady linear decline. This view was further supported by lesion studies showing that lesions in dorsolateral prefrontal regions are associated with poor performance on executive control tasks such as working memory, selective attention, and inhibitory control (D'Esposito et al. 1995; Grasby et al. 1994; Muller and Knight 2006; Paulesu et al. 1993; Petrides 1994). The postmortem, structural imaging, and lesion findings were generally consistent with the frontal deficit hypothesis of cognitive aging, i.e., cognitive processes supported by the prefrontal lobes are among the first to decline with increasing age (Moscovitch and Winocur 1995; Tisserand and Jolles 2003; West 1996).

Functional neuroimaging studies of aging began contrasting behavioral performance and brain activation patterns between young adults (ages 20–29) and elderly participants (ages 60 years and older) since the young were presumed to be at their peak of cognitive functioning while the elderly were on the decline. Many of these studies showed no differences in memory performance between the age groups (often by design in order to keep error rates or cognitive effort the same across groups), but they did show different brain activation patterns, particularly in prefrontal regions, consistent with the frontal deficit hypothesis mentioned above. For example, a common finding in the neuroimaging research on aging was that during memory retrieval or recognition, older individuals showed bilateral prefrontal activity while the young showed right prefrontal activation. Different cognitive models for these age-related differences were evaluated, such as 'compensation' (i.e., additional recruitment of brain regions during memory retrieval such as prefrontal cortex to help maintain good performance; e.g., Cabeza 2002; Cabeza et al. 2002; Grady et al. 2006; Madden et al. 1999; Reuter-Lorenz et al. 2000) and 'dedifferentiation' (i.e., the tendency of the older brain to revert to the less specialized organization as seen in children; e.g., Colcombe et al. 2005; Park et al. 2010; Zarahn et al. 2007).

As noted by Craik (2006), in order to differentiate between these models it is important to determine whether those individuals showing the best behavioral performance within the elderly group are also those showing the greatest degree of bilaterality. It turns out, however, that the individual variability witnessed between levels of brain activation and performance

within age groups was considerable across studies. Even within the young group, some studies showed that faster performers revealed greater prefrontal activity than slower performers, while other studies showed the opposite effect (Rypma et al. 2006). In addition, some studies showed that the elderly group was not necessarily slower than a young group of subjects (Aine et al. 2006; Daselaar et al. 2003) and that some elderly participants within the elderly group outperformed some of the younger participants. Possible reasons for these discrepancies across studies range from: (1) differences in experimental designs (Daselaar et al. 2003); (2) analysis procedures differed (e.g., use of predetermined regions of interest (ROIs) vs. whole-brain analyses); (3) activation-performance associations varied by brain region (Rypma et al. 2006); (4) variations in strategies within and between age groups (Aine et al. 2006; Daselaar et al. 2003; Reuter-Lorenz et al. 2000; Rypma et al. 2005); (5) issues of reliability across fMRI results (Bennett and Miller 2010); (6) different activation levels may be due to differences in error rates or cognitive effort (Daselaar et al. 2003); (7) white matter (WM) tracts in prefrontal regions may be disrupted in the elderly due to cerebrovascular disease affecting activation levels (Aine et al. 2010; Nordahl et al. 2006); and (8) differences between young and old in fMRI studies of aging may be due to non-neural, vascular changes (i.e., issues of neurovascular coupling) (D'Esposito et al. 2003; Kannurpatti et al. 2011).

Here we share some of our results on aging obtained using magnetoencephalography (MEG), along with other methods. Our goal is not to determine which cognitive model fits our MEG data best but rather to discuss two issues that became important in our studies of normal aging, which need to be further addressed in aging studies. These two factors, related to the maturation of brain across the lifespan and degeneration due to pathological processes, are highly likely to affect both within- and between-group variability. We are in agreement with Rowe and Kahn (1987) who emphasized that the effects of the aging process itself have been exaggerated, while the modifying effects of external factors (e.g., diet, exercise) have been underestimated. For example, brain shrinkage has been shown in individuals with hypertension (Raz et al. 2010) while aerobic activity has been associated with greater task-related activation in regions of prefrontal/parietal cortices (Colcombe et al. 2004), greater GM volume (Erickson et al. 2010), and greater WM integrity (Marks et al. 2007). Few neuroimaging studies of aging exclude participants with hypertension which is known to adversely affect cognitive performance (there are some exceptions such as Cabeza et al. 2002, 2004) and few studies acknowledge that cognitive performance of the elderly can improve given certain conditions such as aerobic and cognitive training (e.g., Logan et al. 2002). Specifically, our goal at present is to focus on the development of WM tracts across the lifespan which leads to differences in how one may approach a task (i.e., strategies) and to examine effects of pathological processes such as hypertension and type 2 diabetes on WM tracts and brain volume, which also affect the strategies we utilize. In sum, from our perspective it is important to differentiate between "normal aging," usually associated with chronic pathological processes, and "healthy successful aging." In order to differentiate between healthy young, middle-aged and elderly groups, as well as healthy elderly and the not so healthy elderly groups, our current studies rely on diffusion tensor imaging (DTI) for assessing WM tract integrity and connectivity, MR morphometrics for determining WM and GM volumes, neuropsychological tests for characterizing overall level of cognitive functioning, MR scans specialized for imaging WM lesions (FLAIR), as well as blood tests/blood pressure measurements and neurological exams for characterizing physical health, in addition to MEG. We first present a brief section on why MEG methods are ideally-suited for studies of aging followed by results from two of our completed studies which laid the foundation for our current views, along with our progress in our ongoing studies which attempt to differentiate between healthy successful aging and the consequences of pathology on cognitive decline.

Rationale for and Brief Description of Our MEG Methods

One serious barrier to using fMRI methods for examining age-related cognitive decline is that the neurovascular coupling is most likely altered in these groups and consequent interpretations of the BOLD changes may be incorrect (Kannurpatti et al. 2011). Neurovascular coupling is defined as the relationship between a change in neuronal activity and the hemodynamic response that is reflected by a BOLD signal change (Iannetti and Wise 2007). The primary determinant of the BOLD signal, deoxyhemoglobin within each voxel, is dictated by the venous blood volume, blood flow and blood oxygenation, and any disease factor that modifies the responsiveness or even the baseline values of these parameters are likely to modify BOLD contrast even in the absence of any modulation of neural activity (Iannetti and Wise 2007). Rossini et al. (2004) examined the neurovascular coupling issue by comparing median nerve stimulation responses in stroke patients (a group with a predicted compromise in neurovascular coupling) and controls using MEG and fMRI. All of the patients showed clear MEG signals in both affected and unaffected hemispheres while some of the stroke patients did not reveal any fMRI activation in these regions (i.e., uncoupling). D'Esposito et al. (2003) cautioned researchers about neurovascular coupling issues since elders, for example, are more likely to have cardiovascular problems such as high blood pressure. In fact, according to the National Center for Health Statistics, 67% of adults aged 65–74 years have hypertension with percentages increasing thereafter with increasing age. However, not only has there been an increase in the number of fMRI studies on age-related effects on memory, but the number of studies of Alzheimer's disease (AD) in particular has increased dramatically. Some fMRI studies have attempted to deal with compromised neurovascular coupling (e.g., Rypma and D'Esposito 2000), while others have not. Given the above evidence, this area of research is ideal for MEG methods since neurovascular coupling issues are not a concern, but ironically, there are few MEG studies of aging and AD that attempt to localize networks of affected brain regions.

Our group has worked diligently over the past decade on methods of analysis that adequately characterize time-course activity, as well as source locations. MEG source locations, strengths and orientations are estimated using a semi-automated multidipole, spatio-temporal approach (Calibrated Start Spatial Temporal or CSST, Ranken et al. 2004) where estimation of time invariant parameters (locations) are conducted first, using nonlinear least squares minimization, followed by linear estimation of the associated time varying parameters (source magnitudes) (Mosher et al. 1992). CSST runs multiple instances of a downhill simplex search from random combinations of MR-derived starting locations from within the head volume on a Linux PC cluster. General steps for processing the MEG and MRI data using CSST are shown in Fig. 2. For details of our analysis procedures please refer to Aine et al. (2010).

Figure 3 shows how we rigorously assess the appropriateness of our algorithms. In this example of realistically simulated data, late activity (e.g., 400–600 ms) was synchronous across four cortical sites (primary visual cortex or V1, inferior lateral occipital gyrus or I.LOG, intraparietal sulcus or IPS, and dorsolateral prefrontal cortex or DLPFC), as is often seen in working memory studies. The upper left panel of Fig. 3 displays the locations of the cortical patches (yellow patches at the cross-hairs) that we created while the time-courses provided to the cortical patches are shown beneath. The lower left panel reveals the averaged waveforms (with signals embedded in 128 trials of real spontaneous noise) as seen across the 275 sensors. The table shown in the upper right panel from CSST output, shows the coordinates of the actual sources, the estimated source locations from CSST, and the errors using Euclidean distance. The lower right panel shows the estimated time-courses (inset) and source locations. In this example, the average error across all four sources was 0.67 cm with the greatest error for the I.LOG source. For more examples of realistic

simulated data and CSST fits to these data, including 6- and 7-source simulations, or for additional information on how we create these data for testing analysis algorithms, please see our web portal (http://cobre.mrn.org/megsim).

Development of Effective Cognitive Strategies

The healthy brain develops a host of large-scale, distributed neural networks to handle the many sensory and cognitive challenges encountered on a daily basis. Interactions within network nodes are mediated to a large extent by WM tracts, or the “superhighways” of the brain. WM contains fibers which connect various cortical and subcortical GM structures, thereby coordinating activity across disparate GM regions and creating widely distributed, functionally integrated circuitry. Maturation of WM tracts correlates with the development of language and memory strategies in adolescence and adulthood (Fuster 2003; Nagy et al. 2004; Paus et al. 1999), which may account in part for the different activation patterns often seen between young and elderly groups. There is strong evidence that brain development and changes in higher-cognitive functions continue throughout adulthood (Adleman et al. 2002; Huizinga et al. 2006; Klingberg 2006; Luna and Sweeney 2004; Zelazo et al. 2004) and that these changes are dynamic. For example, synaptic pruning or the elimination of unnecessary synapses, resulting in a reduction of GM volumes, occurs after puberty while myelination of axons continues to increase into the 5th and 6th decades of life (Benes et al. 1994; Lenroot and Giedd 2006). WM volumes are maximal in prefrontal and temporal regions around 47 years of age (Bartzokis et al. 2001; Sowell et al. 2003).

According to Fuster (2003), the development of representations in neocortex is a continuation of a process that took place during phylogeny and early ontogeny in primary areas. In other words, the phylogenetically oldest representations are those related to the simplest physical features of the world and motor adaptations to it (perceptual memories). These representations are present at birth in the structure of the primary and sensory motor cortex. In support of this view, developmental studies have shown that children tend to rely more on visuospatial processing to compensate for the immature access to widely distributed regions required to maintain appropriate response sets (Luna and Sweeney 2004). As children age, they switch from relying on visuospatial strategies to using the phonological loop to recode visual inputs into phonological form, via rehearsal (Gathercole et al. 2004). Rehearsal or inner speech become well-automated during adulthood and is considered to be a useful strategy to activate/retrieve currently relevant task-set representations (Emerson and Miyake 2003; Kray et al. 2004). Most participants will spontaneously cue themselves by silently repeating cues while engaged in working memory tasks (Nystrom et al. 2000; Walter et al. 2003) which helps them to regulate their behavior (Baddeley et al. 2001; Luria 1959). Linguistic abstraction in general allows adults to conserve their attentional resources (Tun et al. 1998).

One of our earlier studies examined spatial working memory by utilizing a delayed-match-to-sample (DMS) task with Walsh patterned stimuli. The task was designed to make it difficult for subjects to attach verbal labels to the stimuli, in order to prevent participants from using inner speech (Aine et al. 2006). Figure 4 shows the study design and time-courses from six cortical regions, averaged across 13 young adults (20–29 years—red tracings) superimposed on time-courses averaged across 11 elderly participants (≥65 years —blue tracings) during recognition. (Note time-courses extracted from localized source regions are averaged across subjects at similar cortical regions.) The red and blue “**” indicates a significant latency difference between age groups at Peak 3 ($F = 22.56$, $P < 0.0001$) for the lateral occipital gyrus (LOG) region. Although there was a main effect of age on the latency of the initial peak in primary/secondary visual cortex or the middle occipital region (MO—see “*”), consistent with age-related slowing of retinocalcarine signal

conduction, the older subjects' longer latency did not adversely affect their performance (accuracy and speed) since task performance measures were not statistically different from the young (see also Lindenberger et al. 2001 for a similar conclusion). Although contrasts did not reach statistical significance, this figure suggests greater amplitudes for the elderly over frontal and parietal regions [supramarginal gyrus (SMG), dorsolateral prefrontal cortex (DLPFC) and anterior cingulate (AC)—areas often associated with verbal processing] after about 200 ms. More importantly, correlations between MEG responses and neuropsychological tests suggested that young and elderly were using two different strategies to perform this task; the young relied on posterior brain regions (associated with spatial processing) while the elderly relied on inferior frontal and SMG regions, reminiscent of the phonological store or verbal processing (Henson et al. 2000). For example, correlations for the young clustered around visual memory (immediate and delayed recall on the Rey Complex Figure Test) and Performance IQ. In contrast, vocabulary and verbal IQ tests correlated with the MEG measures for the elders, suggesting that elders may have resorted to attaching verbal labels to the stimuli rather than using a "posterior" visual perceptual strategy (i.e., retaining the images in mind). Many of the older subjects endorsed employing such an approach at debriefing.

Other studies have reported a similar posterior-to-anterior shift in memory-related brain activation with advancing age. Grady et al. (2003) used line drawings of objects and words representing the names of objects in their PET study. They concluded that with age there is a shift in the cognitive resources used from a more perceptually-based to executive- and organization-based functions. Although they acknowledged that elderly revealed greater functional connectivity between hippocampus and DLPFC and parietal cortex than the young (the young showed greater connectivity between ventral prefrontal cortex, hippocampus and extrastriate regions), they did not suggest that connectivity between regions may still be developing across midlife which then allows different verbal-based strategies to be applied during the tasks. It is possible that this age-related alteration in hippocampal function may be a natural developmental change rather than a compensatory alteration. In another study, Meulenbroek et al. (2004) used a spatial navigation task and found a slight but significant decrement in navigation performance for the elderly (79.5% correct vs. 73.3%). More importantly, older subjects exhibited decreased task-associated activation of posterior, perceptually-related regions (i.e., parietal and posterior fusiform/parahippocampal regions) along with activation of anterior parahippocampal sites, which was not apparent in the young group. Both groups interpreted their results as reflecting the additional recruitment of regions to facilitate memory.

Similar to other neuroimaging studies, our comparison groups included young (20–29 years) and elderly (65 years and older) subjects. However, based on the previous literature discussed above WM development is protracted relative to GM development suggesting a better characterization of changes across lifespan is necessary. Unfortunately, neuroimaging studies do not generally compare brain activation patterns and task performance between young, middle-age, and elderly groups. To extend our work, we examined the MRIs from our young and elderly participants in addition to a separate group of participants intermediate in age between the young and older groups which we will refer to as middle-aged subjects, and compared GM and WM volumes between these groups. Based on the literature (e.g., Raz et al. 2005; Sowell et al. 2003), we hypothesized that the middle-aged group would reveal greater WM volumes than either of the other two groups. It was assumed that young subjects' WM was still developing while the elderly were beginning to show age-related degradation of WM tracts. Our morphometry results did reveal a decline in both GM and WM in frontal regions for the elderly relative to the young ($P < 0.004$ for GM and $P < 0.0002$ for WM; see Fig. 5 for WM results), consistent with the literature. But with the addition of middle-aged participants (31–43 years), it became apparent that the frontal

WM volume distribution followed an inverted U-shaped function. The young and elderly were at the two extremes, while middle-aged participants showed maximal WM volume ($P < 0.00005$ for middle-age vs. elderly and $P < 0.02$ for middle-aged vs. young). It is also interesting that although the elderly did not have greater temporal WM volumes than the young or middle-aged groups, the WM volumes in the temporal region correlated with verbal IQ scores (see bottom portion of Fig. 5; $r = 0.76$, $P < 0.02$) for the elderly, but not for the young. While conjectural, this finding may relate to how associative neocortical areas supporting receptive and productive language (such as temporal and frontal regions) are the last to mature in terms of myelination and dendritic branching (Fuster 2003).

These results are consistent with reports suggesting that WM maturation continues well into adulthood. Therefore, increased frontal activation with advancing age need not be viewed as reflecting a compensatory mechanism, but rather it may reflect the use of an effective strategy associated with normal maturational processes (e.g., WM maturation). Scherf et al. (2006), for example, found a four-fold increase in AC activity with age (up to 47 years). They claimed that adults' usage of AC and bilateral DLPFC is most efficient for preparing and organizing working memory behavior. They also consider the use of subvocal rehearsal strategies as a sophisticated strategy that develops with age. Bor et al. (2003) found a bilateral increase in prefrontal cortex when participants (aged 21–34) used an effective chunking strategy (i.e., reducing the amount of information to be retained into smaller, manageable pieces of information) during a spatial task which correlated with good performance. Data from studies examining the application of different strategies to working memory tasks suggest that bilateral frontal activity in the elderly may not reflect a compensatory mechanism. Instead, we suggest that the plastic nature of the nervous system, altered on the basis of development and experience throughout the lifespan (Casey et al. 2005; Poldrack 2000; Sakai 2005; Schlaggar et al. 2002), may not have been considered by some investigators. It is probable that the functional neuroanatomy underlying task performance differs between various age groups, and these developmental differences are associated with the adoption of different strategies for performing the tasks. Executive processes or more sophisticated strategies, for example, are apt to be utilized by middle-aged and elderly participants more than some young, since maturation of executive functions parallel the continued development of the frontal lobes (Romine and Reynolds 2004). Consistent with this position, our elder participants' responses to our structured interviews on the strategies they applied during the task indicate that they feel that their problem-solving skills for example, are better now than when they were in their twenties. It is noted that recent longitudinal/cross-sectional studies (Ronnlund et al. 2005) traced the course of episodic and semantic memory across 35–80 year old participants and found no episodic memory decline before age 60 while semantic memory improved up to this age. Similarly, it was recently shown that measures of deterioration of intracortical GM, along with subcortical WM signal intensity, weren't observed until the late 60s and early 70s in superior frontal areas (Westlye et al. 2010). However, to date there are still very few studies examining brain maturation, and the consequent emergence of executive functions (including strategies), across the adult lifespan. Hopefully a "systems" level approach (i.e., analyses focused on networks rather than single brain regions such as prefrontal cortex) will bring forth new information on the development of memory functions across the lifespan by showing the variety of strategies that can and are applied to working memory tasks.

Healthy Successful Versus Normal Aging

An additional factor that may account for some of the differences witnessed between young and elderly groups is the presence of chronic diseases in the elderly, such as hypertension and diabetes, which can result in premature memory decline. For example, WM lesions, associated with hypertension or type 2 diabetes, are considered as a surrogate marker of

small-vessel disease (Pantoni et al. 2007; Schmidt et al. 2004). Most neuroimaging studies typically attempt to exclude participants based on a history of neurological disease, head injury, seizure, stroke, substance abuse, and psychiatric disorders. This exclusion is typically determined by participant self-report rather than verification in medical records or actual documentation of blood pressure or blood sugar status, for example. However, because the description of exclusion criteria is usually not specific, it is unclear how many diseases that often affect the elderly are actually excluded. Although neuroimaging investigators of aging have access to MR scans, participants showing evidence of white matter lesions or volume loss are not typically excluded since the presence of white matter lesions and volume loss is often considered to be part of "normal" aging. In many cases, MRI scans are not read by a neuroradiologist (Illes et al. 2006). A finding from our most recent auditory word recognition study indicated that 28% of our elderly controls revealed moderate to severe abnormalities on their MRIs (e.g., consistent with chronic white matter ischemia or volume loss), as determined by a board-certified neuroradiologist who was blind to the diagnostic categories (Aine et al. 2010). This result is consistent with findings reported by Inzitari (2000) and Breteler et al. (1994). From our vantage point, health of the participants is a potential cohort difference between groups, which needs to be controlled.

Recent literature indicates that the presence of WM lesions often correlates with frontal lobe pathology (i.e., poor executive control and working memory performance). For example, a meta-analysis conducted by Gunning-Dixon and Raz (2000) and other studies (Oosterman et al. 2004; Tullberg et al. 2004) have shown that WM hyper-intensities (WMHs) are more abundant in frontal regions and are associated with frontal hypometabolism, prolonged processing times and executive dysfunction. There is also strong evidence that hypertension and type 2 diabetes are major risk factors for severe WMHs (Artero et al. 2004; Cook et al. 2002; de Leeuw et al. 1999; DeCarli et al. 2001; Dufouil et al. 2001; Inzitari 2000; Kuo and Lipsitz 2004) and there is ample evidence that the presence of WMHs is associated with cognitive decline. The severity and nature of decline relates to the density and locations of the lesions (Artero et al. 2004; Awad et al. 2004; De Groot et al. 2002; Inzitari 2000; Kuo and Lipsitz 2004; Manschot et al. 2006). Apparently, there is an anterior-posterior gradient in the occurrence of WMHs (Artero et al. 2004; Head et al. 2004) where frontal areas are the first to reveal WMHs, followed by periventricular and parietal lesions. In each stage, the density of lesions increases until finally temporal and occipital regions are involved. Therefore, WM lesions most likely act to perforate the WM tracts (i.e., "potholes" in the "superhighways"), which disrupt the synchronization of activity across large-scale networks that mediate effective neurocognitive functions.

In Aine et al. (2010), patients (mild cognitive impairment or MCI and mild AD) and controls with evidence of moderate to severe MRI abnormalities (WMHs or volume loss) performed significantly worse on the behavioral tasks and neuropsychological tests compared to healthy controls. Figure 6a shows their performance on the California Verbal Learning Test and a spatial memory test, the Rey Complex Figure Test, compared to the average performance of the controls without moderate to severe abnormalities on their MRIs (black lines). Figure 6b shows amplitude differences at select cortical regions as a function of MRI category. For the participants in whom parietal and anterior temporal lobe activity was identified, statistically significant hyperactivity in parietal and anterior temporal cortex was evident for participants with WMHs (red tracings), relative to controls (black tracings) or participants with volume loss (blue tracings). The term hyperactivity is used here since task and neuropsychological performance measures that were correlated with MEG time-course measures, indicated that moderate activity in anterior temporal lobe correlated with good performance, as long as it wasn't too much activity.

Our results have led us to the premise that age-related pathology correlates with cognitive decline. Therefore it is critical to parse out "normal aging," complete with pathological processes typically found in community dwelling elderly, from "healthy successful aging" (i.e., no or only mild pathology) in order to truly understand age-related changes in cognition. For example, effects of hypertension and type 2 diabetes may be a large contributor to the frontal deficits outlined by the frontal deficit hypothesis of aging and may add to the considerable inter-subject variability noted within elderly age groups. In order to rule out effects due to cohort differences between young and elderly groups, it is imperative to document the health of the participants at the time of study via MRIs, neuropsychological and neurological exams, blood tests (e.g., HbA1c and lipid panel) and blood pressure measurements.

A recent study in the literature provides a nice example of why careful characterization of health in aging studies is necessary. Persson et al. (2006) concluded after examining DTI-based fractional anisotropy (FA) measures and volume measures of the hippocampus that some members of their sample of older adults were not healthy. They examined a subset of older adults from an existing longitudinal study and split them into two groups. The groups did not differ when comparing their neuropsychological test results but they did differ on tests of memory obtained across a 10-year span (i.e., one group showed declines on memory performance). The elders who demonstrated a decline in memory tests also revealed either smaller hippocampal volumes or lower FA values, suggestive of disease processes, including early stages of AD. If the investigators did not have access to additional structural data, as well as longitudinal clinical data, they would not have known that some "normal" elderly were not healthy elderly.

The study from which Fig. 6 was obtained examined individual variability while participants performed a delayed, auditory word recognition task (for details see Aine et al. 2010). In this case, we reasoned that pathological processes (e.g., hypertension, type 2 diabetes, mild forms of cognitive impairment or dementia) typically encountered within the elderly population are likely to modify strategies applied to memory tasks as neural pathways become affected by a variety of insults. Therefore, we purposely examined a mixed group of elderly (n = 30); 12 were MCI or mild AD while others were healthy according to clinical readings from their MRIs and the study inclusion/exclusion criteria. By incorporating a wide range of abilities and health conditions, distinct strategies, both neural and behavioral should be identifiable within this group. We used the term strategies, to refer to different ways of conducting the same task and we operationally defined strategies as reflecting different patterns of brain activation that correlated with task performance. Effective strategies correlated with higher performance levels.

Since we were expecting to see a range of strategies in the present study we conducted a cluster analysis using the brain regions identified with MEG and then correlated the resulting networks with task performance and neuropsychological measures. (Note we did not use ROIs as commonly found in fMRI studies. Instead, we used an automated analysis that is conducted across the whole brain and identifies brain regions that are dominant in each individual case.) As Fig. 7 shows, there were three primary brain activation patterns found in the data. Group 1 pattern of activity, heavily weighted by activation in anterior temporal (ANT), parietal (PAR), and premotor (PRE) regions (the histogram bars reflect the percentage of individuals within a group who showed activity within each region), correlated positively with task and neuropsychological performance measures. This was the highest performing group and the neuroradiologist interpreted their MRIs as either showing no or mild abnormalities. Group 2, with no activity found in PRE, and Group 3, with no activity found in ANT, both revealed considerable activity in occipital regions as if they visualized objects that the words represented. Because different brain activation patterns

were found for each group which correlated differently with task and neuropsychological performance measures, we concluded that these groups used different strategies for conducting the task. Both Groups 2 and 3 performed worse than Group 1 on recognition, though reaction times did not differ, and all the MCI/AD patients were spread between Groups 2 and 3. Delayed recall on the REY Complex Figure Test (REY), a test of spatial memory, was very sensitive to group differences, more so than the California Verbal Learning Task (CVLT). We have found this to be true on our spatial working memory, versus verbal working memory tests as well. In general, it appears that the highly functioning Group 1 relied less on FRO in order to correctly recognize target words representing common objects from a longer list of target and foil words. In contrast, Groups 2 and 3 both appeared to rely on FRO and occipital regions in order to recall the object names. These types of differences in activity patterns, presumably associated with different strategies, are quite robust (i.e., they can be observed even at the level of raw isofield maps).

Current Study: Development of Strategies and Effects of Hypertension/ Type 2 Diabetes

Our current studies focus on WM tract development and degeneration via the use of DTI, morphometry, and FLAIR imaging. We hope to demonstrate that age-related changes in working memory parallels the development of WM connectivity, which is necessary for effective strategies (i.e., top-down processing), and that degeneration of WM tracts is associated with pathology and decline in memory functions. As discussed above, we hypothesize that middle-aged and elderly individuals use executive strategies (e.g., verbal abstraction or top-down processing such as chunking) more frequently when performing working memory tasks while the young rely more on a visual perceptual strategy, the phylogenetically oldest representations that are dependent upon bottom-up processing when engaged in spatial tasks (Davis et al. 2008; Fuster 2003). This is not to say that all elderly and middle-aged individuals use verbal or chunking strategies and all young adults use a visual perceptual strategy. Obviously, there will be a mixture of strategies in all age-groups and even among individuals, but we suggest that there will be a greater percentage of young participants using visual perceptual strategies and a greater percentage of elderly and middle-aged will use verbal-based or chunking strategies. The activity patterns can be described briefly as anterior- and posterior-based activity patterns, respectively. These differences are easier to show using spatial working memory tasks (Fig. 8). Below we present preliminary data from our spatial and verbal working memory tasks. The verbal task uses the same stimuli, only the task instruction changes (i.e., match the red digits' identity rather than position).

According to our hypotheses, the middle-aged group (35–45 years of age) will perform best (higher percent correct) on both spatial and verbal working memory tasks compared to the other age groups due to continued maturation of white matter tracts throughout middle age. If a "traditional" view is upheld, young adults should perform best, since ample literature shows a linear decline in GM across middle-age and old age (Fig. 1). Figure 9 shows the middle-aged group performing significantly better than the young group (Total Correct for spatial task $P < 0.03$; Total Correct for verbal task $P < 0.01$) and the elderly group (Total Correct for spatial task $P < 0.078$; Total Correct for verbal task $P < 0.05$). RTs did not show significant differences between middle-aged and young groups. We must point out that the elderly group in this example consisted mostly of hypertensives/diabetics with concurrent MRI abnormalities (all but 1 had either global volume loss and/or notable WMHs). RTs showed a large difference between young and old for the spatial condition only ($P < 0.004$).

Note that the variability for Total Correct is greater for both young and old groups compared to the middle age group (see standard deviation bars). Based on questionnaire responses,

there is no group where all members used the same strategy. In the young group, 12 out of 14 reported using a spatial strategy at some point during the spatial task (visual perceptual—keeping the locations in mind as presented), as predicted. For the middle-age group, 6 out of 7 reported using a verbal strategy at some point in time during the spatial task. The elderly reported using a mixture of strategies. The most interesting result is that the Total Correct and RTs for the middle age group are similar for spatial and verbal conditions suggesting that they used verbal abstraction (and chunking) for both conditions. Finally, elders with evidence of subclinical pathology performed worse on the spatial task altogether.

To investigate whether the MEG data would show different patterns of activity for young who reported using spatial versus verbal strategies during the spatial task, we examined MEG data from seven healthy young. Questionnaire responses indicated that one subgroup of young predominantly used a visual perceptual strategy (i.e., spatial strategy as determined from 22 questions using a 4-point Likert scale) and the other subgroup of young primarily used verbal coding or chunking to remember the locations of the digits (i.e., verbal strategy). For young subjects using a spatial strategy, predominantly bilateral occipital activation (n = 3) was evident, while the group using a verbal or chunking strategy (n = 4), demonstrated bilateral medial temporal lobe activity with some degree of occipital activation. Figure 10 (top middle panel) shows sequential onsets of occipital sources with primary/secondary occipital activity onsetting first (red tracing). This occipital activation pattern correlates with their affirmative responses indicating that they were holding the matrices with red digit locations in mind as they saw them. In contrast, for subjects reporting a verbal strategy (e.g., subvocalizing “upper left corner”), left medial temporal lobe appears to onset first (see red tracing in bottom middle panel at 100 ms) followed by activity in occipital and right medial temporal cortex. These preliminary data show different brain patterns associated with different spatial/verbal strategies for this spatial task. If this were an fMRI study using whole-brain analysis methods, data from both groups of young would most likely be averaged together, producing averaged areas of activity that are not representative of either group. If ROIs were used in this study then unique differences in brain activation patterns would probably not be found either. Miller et al. (2002; Van Horn et al. 2008) specifically discussed the issue of inter-individual variability in fMRI studies, including variability associated with different cognitive strategies (i.e., fMRI research has been heavily influenced by results based on population-level inference) and emphasized the unique opportunity and importance of understanding individual differences. Single subject analysis is one advantage of MEG methods and a necessity for clinical studies. We predict that more young will utilize a “posterior-based” visual-perceptual strategy while older subjects (and some of the young) will use executive strategies (including verbal labeling), thereby producing a more anterior rather than posterior distribution of activity. This study is ongoing and we have not yet performed this comparison.

As a first look at white matter integrity from our current study, preliminary DTI data from 22 subjects are shown in Fig. 11 where scalar diffusion parameters such as FA using dtifit (FSL) were calculated. The FA image was aligned to a FA template (normalized to the MNI space) with a nonlinear registration algorithm, FNIRT (FMRIB’s Nonlinear Image Registration Tool; FSL). The tract based spatial statistics (TBSS) method was used for group analysis (Smith et al. 2006). A mean FA image was calculated from the set of spatially normalized images. The TBSS algorithm was applied to the mean FA image to calculate a mean WM tract skeleton (Fig. 11b shows the mean FA image with a mean WM tract skeleton superimposed). The FA data of each subject was then projected on this mean skeleton to obtain a skelotonized image corresponding to each subject (Smith et al. 2006).

To examine preliminary age- (19–81 years) and pathology-related effects (four elders with hypertension or type 2 diabetes and 2 healthy controls), a voxel-wise linear regression was

done for each point on the skeleton. The values with significant correlations at $P \leq 0.01$ (uncorrected for multiple comparisons) were extracted. These significant voxels on the skeleton were then mapped on an atlas to identify WM tracts that had significant FA correlations with age. This atlas is based on the International Consortium for Brain Mapping template (Mazziotta et al. 1995) which consists of 50 regions and can be used for ROI analysis (Mori et al. 2008). Our hypotheses led to the selection of three midline ROIs from this atlas (Fig. 11a) consisting of the corpus callosum and eight bilateral ROIs in frontal, limbic, and association fibers.

The significant regions (i.e., FA was negatively correlated with age) found were in the anterior corona radiata (right and left ACR), the posterior thalamic radiation (right and left PTR), and the body of corpus callosum (BCC), and genu. Smaller regions were found in a number of other white matter tracts which will require more careful examination in a larger sample. Three regions with the greatest number of significant voxels are shown in Fig. 11c. This ongoing study will track the FA measures in healthy elderly in comparison to elder participants with a history of hypertension to determine if WM tract degradation accompanies normal or healthy aging, or both. In this example, we have mixed both healthy and hypertensive elderly.

This ongoing working memory study also examines participants with at least a 5-year history of hypertension (both middle-aged and elderly groups) and a separate group of middle-aged participants (35–45 years) with at least a 5-year history of type 2 diabetes. These groups are being compared with healthy young (18–25 years), healthy middle-aged (35–45 years), and healthy elderly control groups (60 years of age or older). Figure 12 shows preliminary behavioral data; performance from four elderly hypertensive (HT) and four elderly healthy controls (CON) while engaged in spatial and verbal working memory tasks are shown. MRI abnormalities were identified from five of the eight MRIs by a board-certified neuroradiologist who was blind to groups. Three HTs revealed WMHs while 1 HT revealed mild cerebral volume loss (i.e., greater than expected for age). One of four CONs showed mild WMHs on the FLAIR images.

Figure 12 shows effects of enhancers and distracters (presented during the delay interval) on recognition memory performance for CONs and HTs. When participants were instructed to remember digits (verbal working memory) or locations of digits (spatial working memory—refer back to Fig. 8 for design) and the same digits/locations were presented during the delay interval (enhancers) as those that the participants were asked to remember, participants achieved a higher percent correct during the recognition portion of the task (top row—Enhancers). In contrast, when the digits/locations presented in the delay interval were different from the ones they were instructed to remember (distracters), the percent correct decreased (top row—Distracters). HT participants generally revealed fewer percent correct and longer RTs than CON participants, except for the verbal RTs. When distracters were involved, HT participants performed much worse on the spatial task (fewer percent correct and longer RTs). Although these results are very preliminary, they already suggest that moderate to severe WM ischemic changes result in more global deficits. In conclusion, even though all of our participants had better than average IQs, specific tests of memory (particularly spatial memory) reveal poorer performance for HT participants. The MRI, neuropsychological, and behavioral results suggest that HT participants may not be aging as ‘successfully’ as some of the healthy controls. Our blood pressure measurements indicate that their medications are working well in three of four HTs, but behavioral performance is still compromised.

Concluding Remarks

Through our studies we have identified a number of potential confounds that affect the interpretation of studies of normal versus healthy aging. First, the health of the elderly is often based on self-report rather than documented with neurological exams, neuropsychological tests, or MRIs confirmed to be normal by a neuroradiologist. White matter lesions are frequently found in the MRIs of elderly and they have been shown to correlate with poorer performance on cognitive tasks, particularly working memory tasks. Second, there are very few neuroimaging studies of aging that have compared performance and active brain networks of middle-aged subjects with the elderly. There is ample evidence now that brain maturation is a dynamic process that does not stop in early adulthood, suggesting that a middle age group is another critical comparison group. Third, it is becoming increasingly clear that researchers should be cognizant of strategies participants use in order to understand the nature of the differences in neural circuitry patterns. Our studies, in general, suggest that one alternative explanation for the prefrontal differences typically noted between young and elderly adults is that brain maturation and consequent cognitive abilities continue to improve at least through middle age. There is now sufficient evidence to support this position. While it is acknowledged that there is some age-related decline in brain function, it is important to account for the dynamic aspect of brain development to better determine what changes are associated with ongoing brain development as opposed to brain dysfunction with increasing age. Finally, some of our elderly participants (including some in their late 70s) have not shown cognitive decline in our longitudinal study. These individuals are not necessarily “super normals” as some investigators have labeled similar entities. They are healthy normals. Therefore, our goal is to better define aging and to identify the additional modifiable risk factors that may lead to cognitive decline, previously attributed to normal aging. This information can help provide individuals with the knowledge that one may still be able to reduce the risk of cognitive decline by mitigating effects of metabolic syndrome and other age-related diseases.

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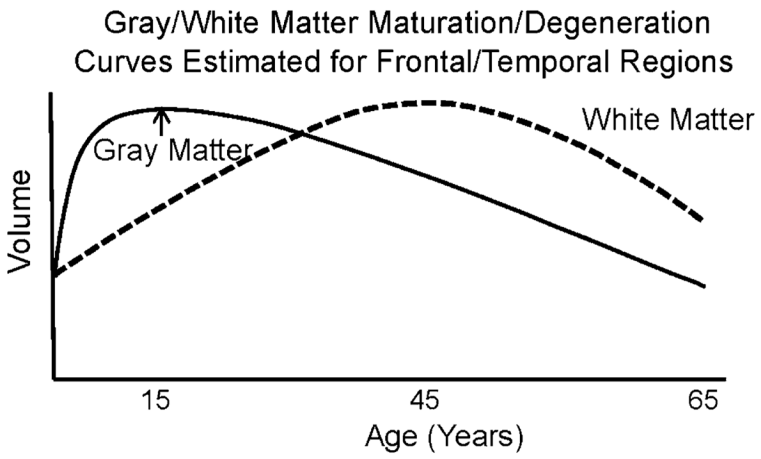


Fig. 1.

Estimated maturation/degeneration curves for peak volumes of GM (*solid line*) and WM (*dashed line*), collapsed across prefrontal and temporal lobe data, as a function of age. *Sources* Bartzokis et al. (2001), Benes et al. (1994), Giedd et al. (1999), Paus et al. (1999), and Sowell et al. (2003)

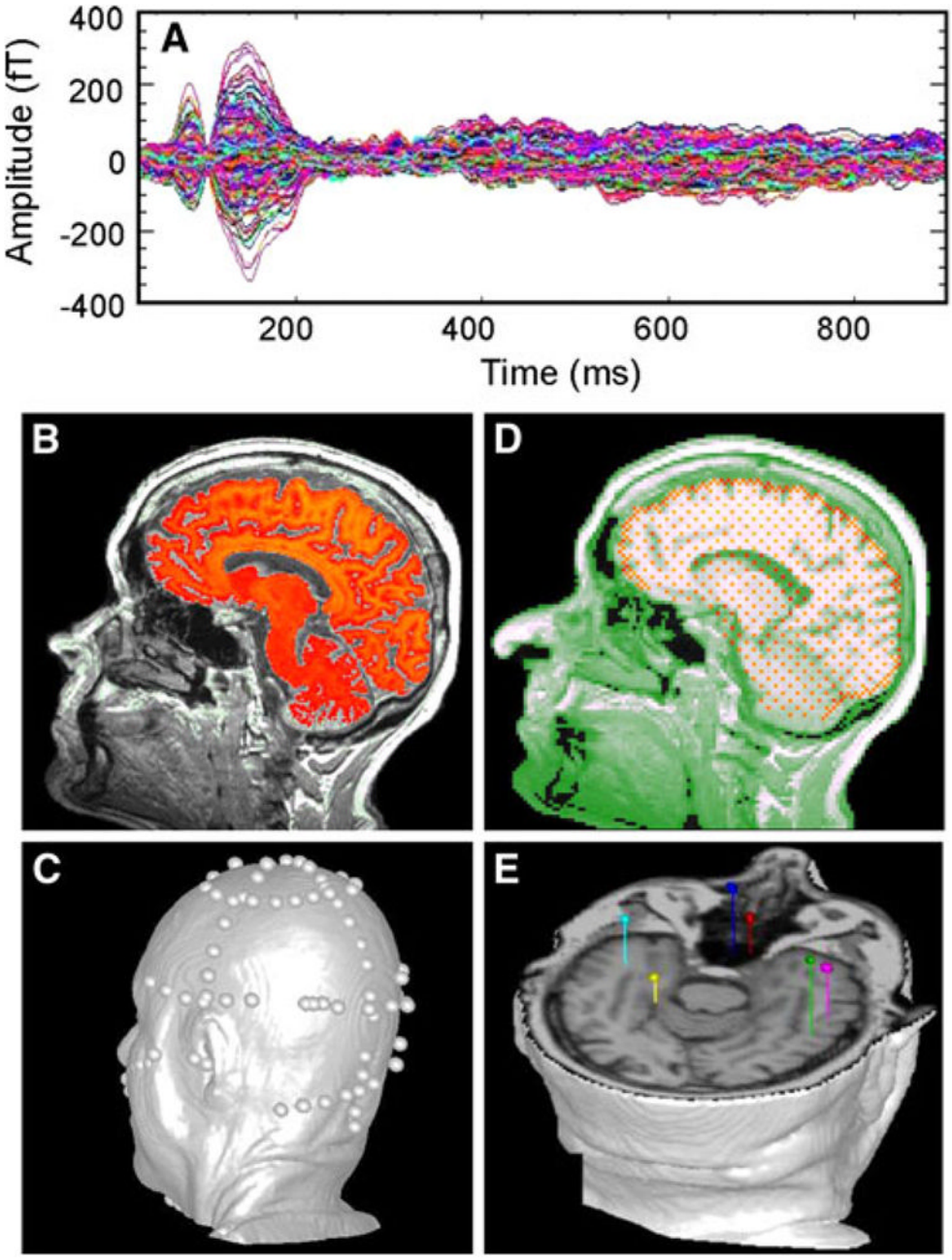
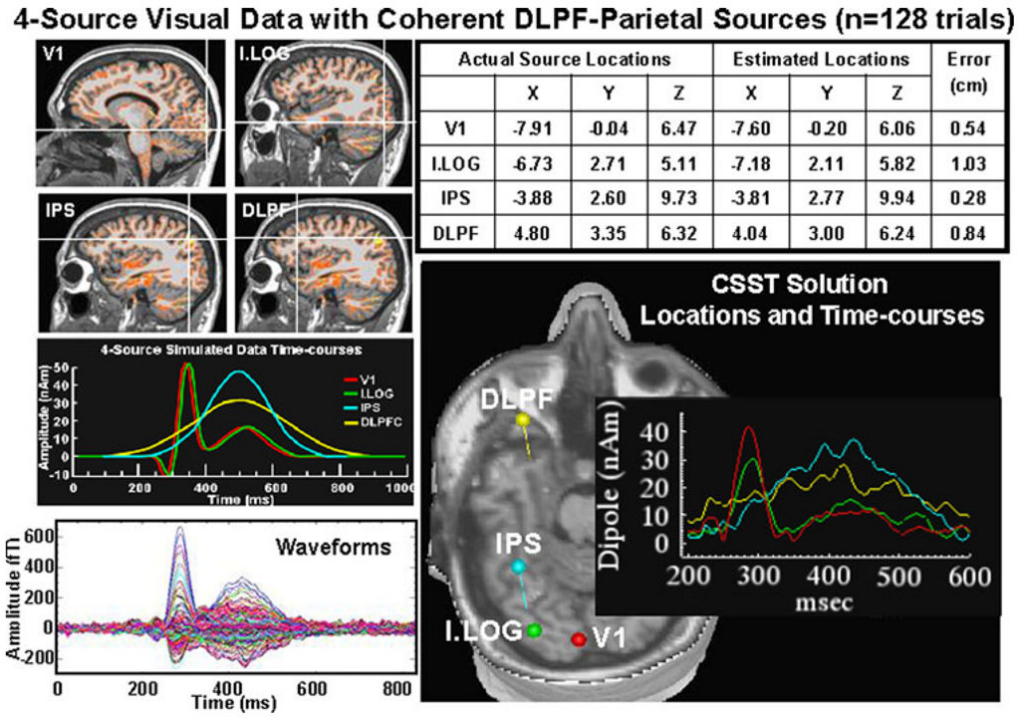


Fig. 2.

General processing steps for MEG analysis. (**a**) Averaged evoked responses to words shown superimposed across 275 sensor locations; this 30–900 ms interval of time was analyzed for each subject. MEGAN, a locally developed software package by E. Best, was used for preprocessing the data and formatting it into a netCDF format for CSST source localization analysis. MRIVIEW was used for: (1) segmenting the cortical volume (**b**); (2) conducting a least squares fit between ~150 points digitized on the head surface and the reconstructed MR surface (**c**); (3) determining the starting locations (*red dots*) and best-fitting sphere head model (**d**); and (4) setting-up the CSST fits and displaying the CSST source localization results (**e**). The CSST algorithm analyzes thousands of fits to the data, as opposed to a single fit, enhancing the probability of reaching the global minimum and obtaining statistically

adequate and accurate solutions (e.g., 20,000–25,000 fits to the data were conducted for 7- and 8-source models with fewer numbers of fits for lower-order models)



Actual Source Locations				Estimated Locations			Error (cm)
	X	Y	Z	X	Y	Z	
V1	-7.91	-0.04	6.47	-7.60	-0.20	6.06	0.54
I.LOG	-6.73	2.71	5.11	-7.18	2.11	5.82	1.03
IPS	-3.88	2.60	9.73	-3.81	2.77	9.94	0.28
DLPF	4.80	3.35	6.32	4.04	3.00	6.24	0.84

Fig. 3.

Simulation results for a 4-source model where all sources became synchronous during the later interval. Amplitudes and peak latencies were jittered across each of 128 single trials. *Upper left*: Actual source locations of the four 20 mm^2 cortical patches (*cross-hairs*) for primary visual cortex (*V1*), inferior lateral occipital gyrus (*I.LOG*), intraparietal sulcus (*IPS*), dorsolateral prefrontal cortex (*DLPF*). *Red–orange color* on the MRIs reflect segmented cortex which was used to help establish a grid of possible starting points for the CSST algorithm. *Left middle*: Time-courses of activity supplied to each cortical patch. *Lower left*: Reveals the averaged waveforms as seen from the 275 sensor locations (VSM/CTF Omega MEG system). *Top right*: Table of actual source locations, CSST solutions (locations), and resultant location errors. *Bottom right*: Locations of the CSST solutions and their time-courses (*inset*). Estimated time-course amplitudes differ somewhat from the current strengths assigned to the cortical patches (*left middle plot*) due to cancellation/summation between the individual current elements within each patch

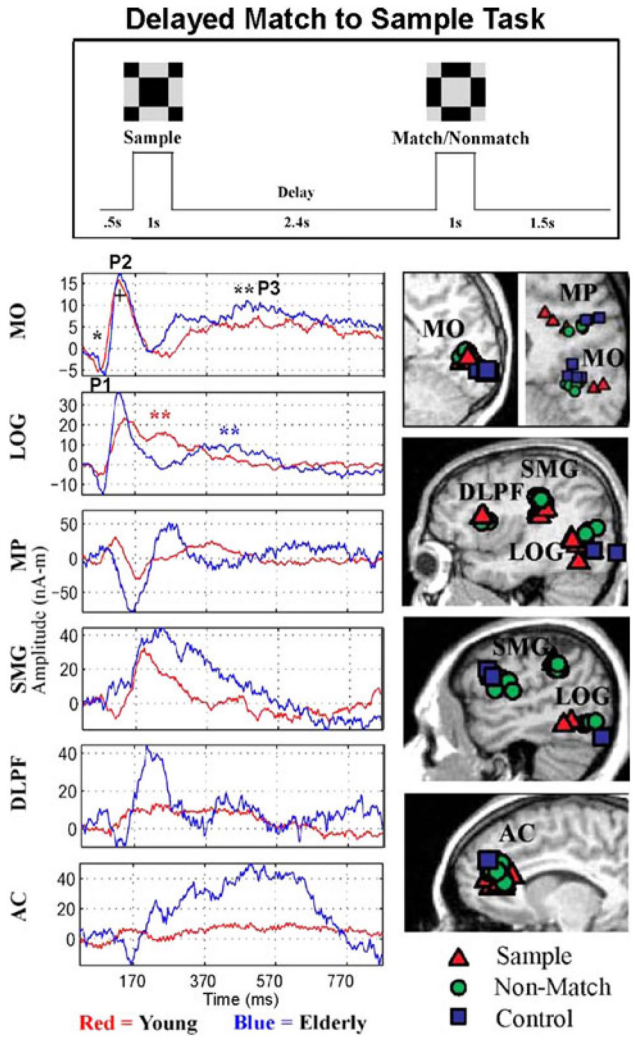


Fig. 4.

Age-related effects in a DMS task. *Top*: DMS design. *Lower left*: Averaged time-courses for six cortical regions. Young (*red tracings*) and elderly (*blue tracings*) are shown for the delayed recognition task. *Asterisks* and *plus* represent peaks of statistical significance. *Lower right*: Sample source locations shown for the three conditions of the task (*1* sample pattern was shown to participants; *2* participants indicated the probe stimulus did not match the sample; *3* passive control condition where no behavioral responses were required). Note the criterion for a source to be labeled as the same source for each cortical location was determined by examining source locations across subjects and choosing those within 1 cm radius of the average location. *MO* Medial occipital, *LOG* lateral occipital gyrus, *MP* medial parietal, *SMG* supramarginal gyrus; *DLPF* dorsolateral prefrontal cortex; *AC* anterior cingulate. Adapted from Aine et al. (2006)

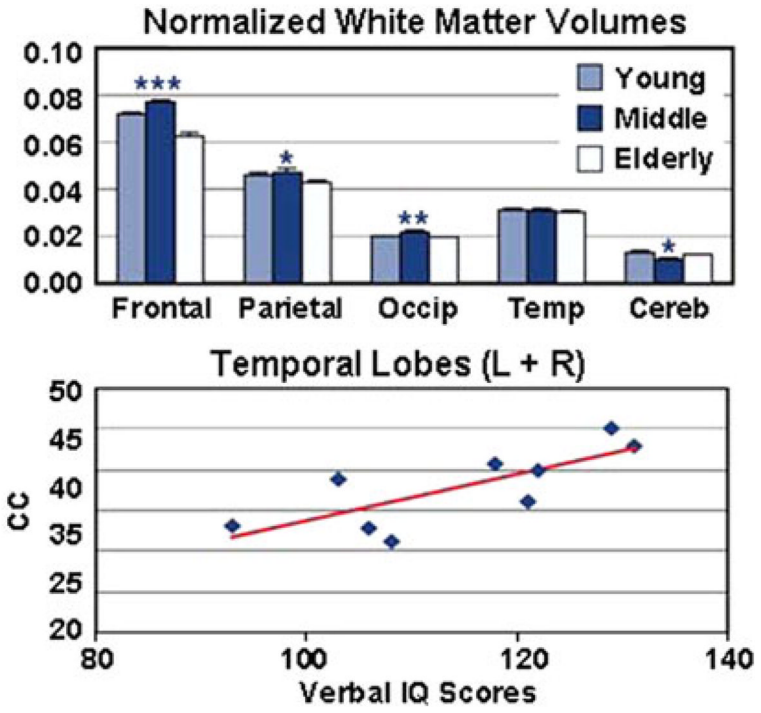


Fig. 5.

Top: GM and WM volumes were calculated and normalized to the whole brain in 11 young, 9 middle-aged and 9 elderly subjects. *Asterisks* indicate significant differences. The three groups were significantly different in frontal WM volumes: Young versus elderly ($P < 0.0001$); middle age versus elderly ($P < 0.00005$) and middle age versus young ($P < 0.02$). *Bottom*: WM volumes in the temporal lobe correlated positively with verbal IQ for elderly participants. Adapted from Aine et al. (2006)

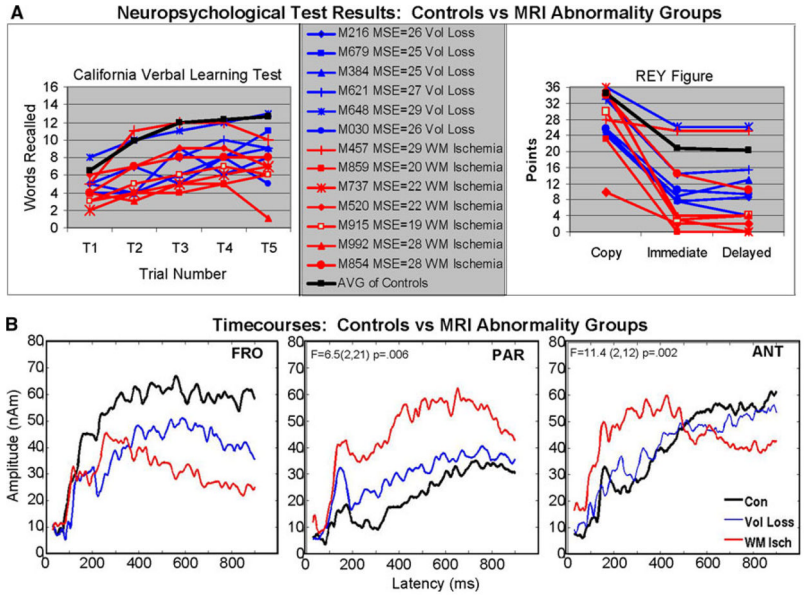
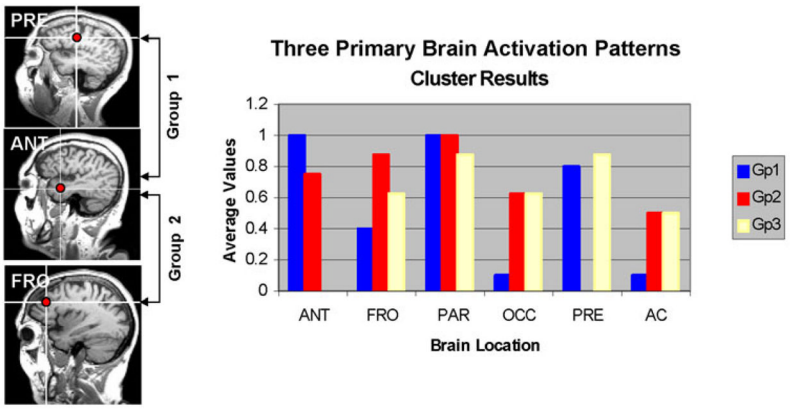


Fig. 6.

a Performance measures are shown for individuals with moderate to severe abnormalities rated from their MRIs. The *solid black line* shows the average response of all the elderly control participants (i.e., no or only mild abnormalities on their MRIs). MSE refers to their scores on the mini-mental status exam. In the California Verbal Learning Test, a list of 16 words is presented five times and participants are explicitly instructed to learn these words. Trials *T1–T5* records the number of words recalled. The REY complex figure tests for implicit spatial memory; i.e., they are not told in advance to remember the details of the figure they are instructed to copy. After they finish copying the figure the original is taken away and they are asked to draw it from memory (immediate). After 20 min of additional tests they are asked to draw the figure once more (delayed). **b** Time-courses localized to each cortical region were averaged together for individuals within MRI groups. Parietal (PAR) and anterior temporal lobe (ANT) regions show significantly higher amplitudes compared to the control group and the group with moderate to severe volume loss. The frontal (FRO) region showed a trend in the opposite direction



Cluster Group	"Yes" Correct	"Yes" RT	Full IQ	MSE	EDU	AGE	CVLT	REYD
1=ANT+PAR+PRE (n=11)	84.9* (6.4)	1209 (147.4)	134*	29.8	17	72.1	13	22.7*
2=PAR+FRO+ANT (n=8)	62.2* (25.5)	1258 (196.2)	117*	27.8	16	74.8	10.4	13.6*
3=PRE+PAR+FRO (n=9)	78.2 (9.7)	1200 (187.2)	108*	25.9	15	76.8	9	8.4*

Fig. 7.

Upper left: MRIs show three cortical regions found during source localization that helped to differentiate between the three groups identified in a cluster analysis. *Upper right*: A cluster analysis performed on the MEG data shows three different activation patterns. The *bar graphs* show the relative weightings for each area (i.e., the percentage of participants showing activity in these regions by group; 1 = 100%). *Bottom*: The table shows average group characteristics. *Full IQ* Full scale IQ on WAIS-R, *MSE* mini mental status exam score, *EDU* education level, *CVLT* California Verbal Learning Test, *REYD* delayed recall of the REY complex figure test, *ANT* anterior temporal lobe, *FRO* frontal, *PAR* parietal, *OCC* occipital, *PRE* premotor, *AC* anterior cingulate. *Asterisks* represent statistical significance. Adapted from Aine et al. (2010)

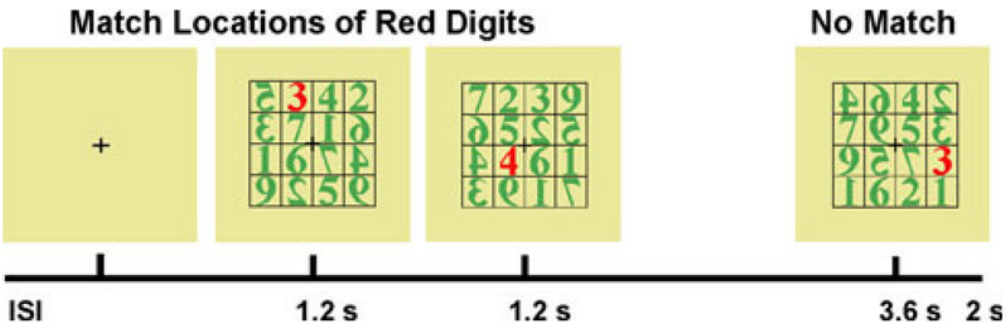


Fig. 8.

Working memory task used in our ongoing studies. Spatial and verbal working memory is examined using a variant of the Sternberg task. The stimulus arrays are identical for each condition, only the task instruction differs (i.e., attend to the location of the *red digit* or the *red digit* itself). Two other conditions present enhancers or distracters during the delay interval. Spatial enhancers/distracters consist of *red highlighted cells* of the 16 cell-array that either are the same as the to-be-remembered locations (enhancers) or are different (distracters). Verbal enhancers/distracters consist of single digits presented during the delay interval that are either the same as the to-be-remembered digits (enhancers) or are different (distracters)

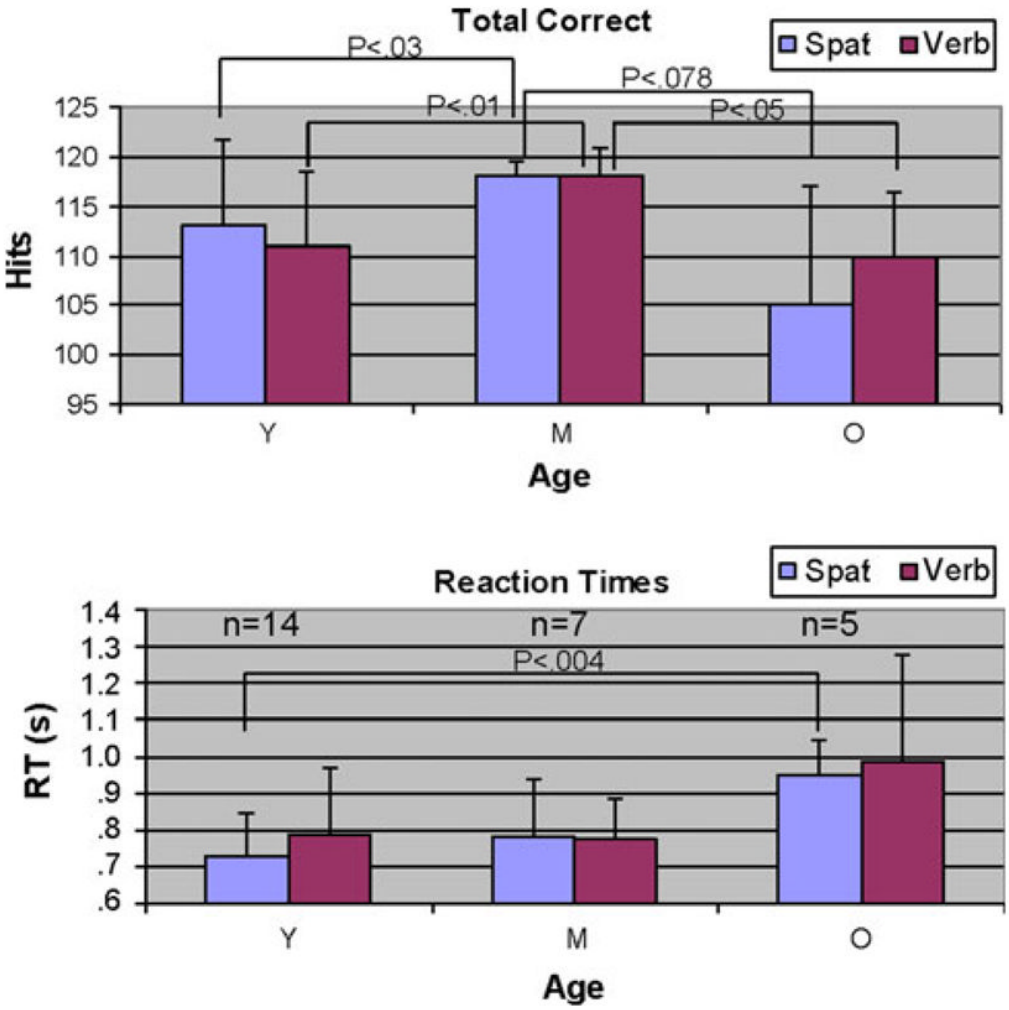


Fig. 9.

Preliminary behavioral results for 26 participants (young, middle age, elderly) during the spatial and verbal Sternberg tasks. Statistical significance is shown for total correct and reaction times (RTs) for three age groups and two tasks

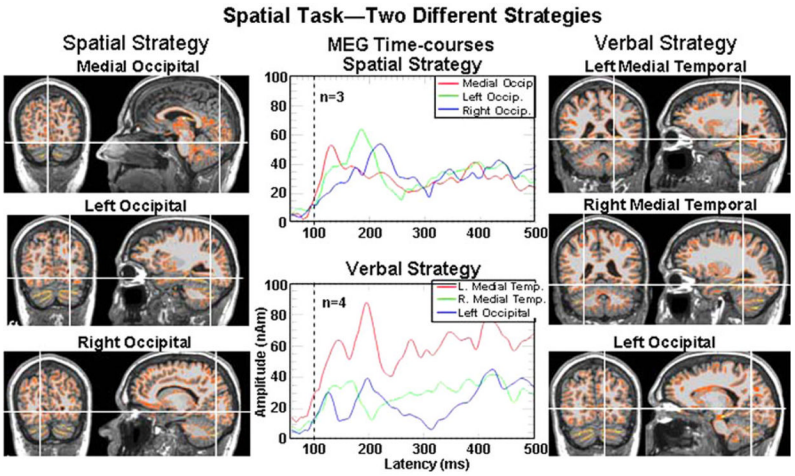


Fig. 10.

Left column and *upper middle panel*: MEG source locations and time-courses, respectively, were localized for three participants who reported using a spatial strategy during the spatial task (i.e., remember the locations of the *red digits*). Time-courses for individuals who reported using a spatial strategy were averaged together. Primary/secondary visual cortex is denoted as medial occipital regions (*red tracing*). *Right column* and *lower middle panel* shows source locations and time-courses for four individuals reporting that they used a verbal strategy during the spatial task. *White cross-hairs* reflect locations of sources. *Red–orange color* reflects cortex that was segmented during preprocessing to help define the head volume (i.e., search space) for each participant. Time scales do not begin at "0" since visual responses are not evident until after 50 ms (50–500 ms intervals were modeled for each participant)

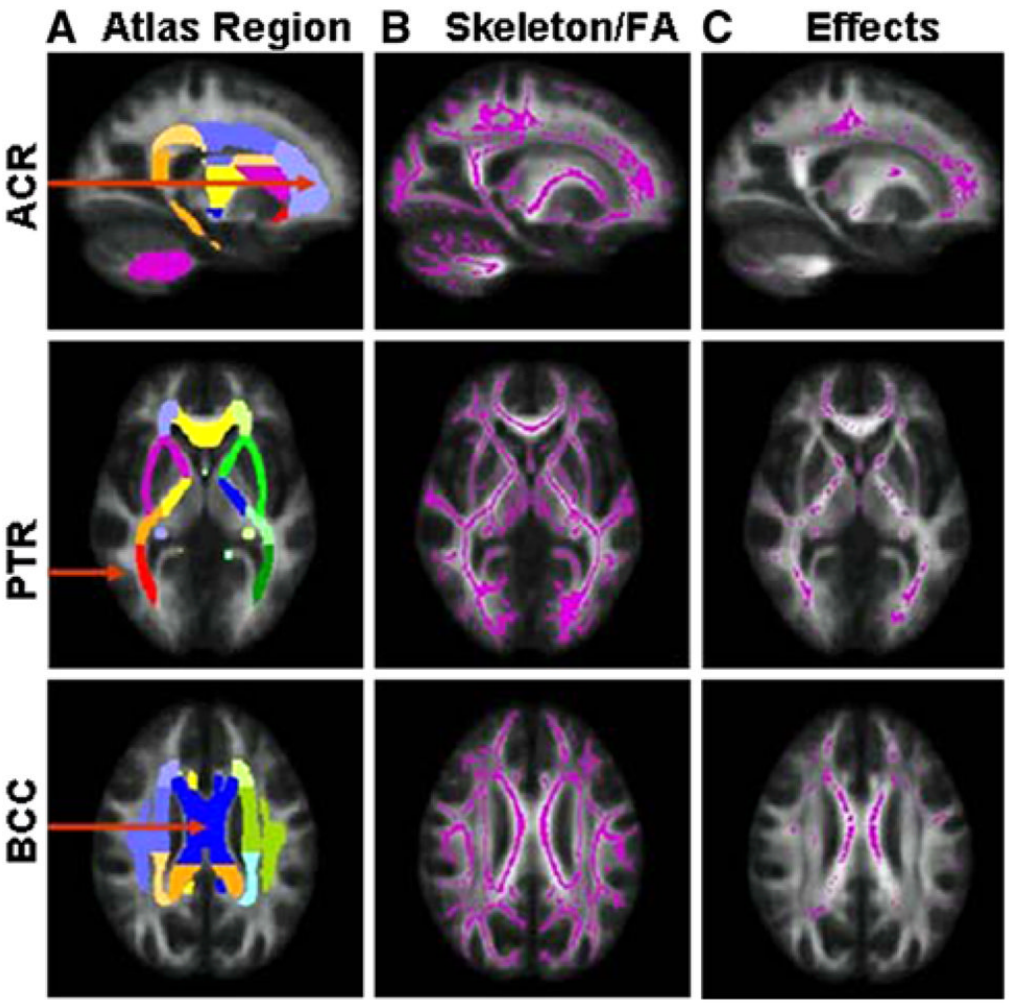


Fig. 11.

a Atlas regions, **b** the corresponding skeleton and mean FA for that slice, **c** the part of the skeleton showing a significant negative FA correlation with age. The skeleton corresponding to the body of corpus callosum (*BCC*), anterior corona radiata (*ACR*), and the posterior thalamic radiation (*PTR*) had more than 40% significant voxels

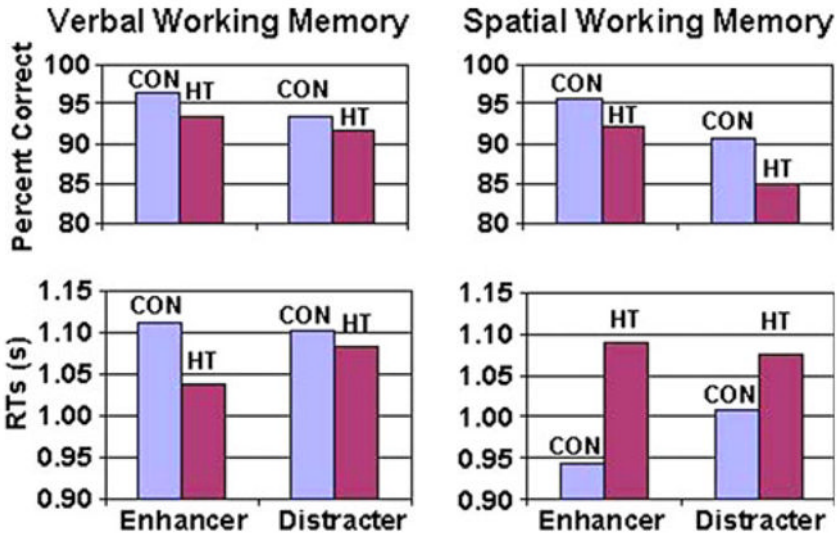


Fig. 12.

Preliminary behavioral data for individuals with at least a 5 year history of hypertension during verbal (*left column*) and spatial (*right column*) working memory tasks acquired during the MEG exam. Four normal controls (CON) and four hypertensive (HT) subjects are shown