Published in final edited form as:
J Neurol Phys Ther. 2012 March ; 36(1): 8–16. doi:10.1097/NPT.0b013e3182462ea6.

Evidence of Altered Corticomotor System Connectivity in Early-Stage Alzheimer's Disease

Eric D. Vidoni[1], **George P. Thomas**[2], **Robyn A. Honea**[1], **Natalia Loskutova**[3], and **Jeffrey M. Burns**[1]

[1]Department of Neurology, University of Kansas Medical Center

[2]Dartmouth-Hitchcock Medical Center

[3]American Academy of Family Physicians

Abstract

Background and Purpose—There is increasing evidence for subtle motor dysfunction early in Alzheimer's Disease (AD), including common motor behaviors that were once considered unaffected early in the disease process. Our objective was to assess if functional neural networks underlying motor behavior are altered by AD.

Methods—We investigated AD-related differences in regional brain activation during motor performance. Nine older adults with early-stage AD and 10 without dementia underwent fMRI while performing a visually-directed simple motor task (hand squeeze).

Results—Despite some similarity in brain activation during motor performance, we found that individuals without dementia exhibited greater activation in accessory motor regions supplementary motor area and cerebellum compared to those with AD. We also assessed disease-related differences in regions where activity was functionally integrated with primary motor cortex. Using a psycho-physiological interaction analysis, we found that those with AD displayed increased co-activation with primary motor cortex of bilateral motor and visual regions.

Discussion and Conclusions—These AD-related changes in regional co-activation during motor execution in may represent inefficiency in the motor network as a consequence of the disease process. Alternatively, they may represent compensatory activation. These findings provide further evidence that in early-stages of AD, neuromotor function is altered in AD even during simple motor behaviors. The results may have implications for performance of more complex tasks, and may be associated with the well-characterized decline in dual task performance in those with AD.

Keywords

Functional connectivity; dementia; motor control; visuomotor response; dual task performance

INTRODUCTION

Alzheimer's disease (AD) is commonly associated with failure of episodic memory as opposed to motor or physical changes[1]. Brain regions associated with formation of memories (i.e. medial temporal lobe) are among the first to experience disease-related atrophy[2]. In fact, primary motor cortex appears to be relatively spared of pathological

CORRESPONDENCE: Eric D. Vidoni, PT, PhD, Department of Neurology, KU Alzheimer's Disease Center, University of Kansas Medical Center, MS 1063, 3901 Rainbow Blvd. Kansas City, KS 66160, (P) 913-588-5312 (F) 913-945-5035 evidoni@kumc.edu.

change early in the disease[2, 3]. Yet, evidence continues to mount that motor behaviors are disturbed even in early AD. For example, Kluger et al.[4] reported that fine motor skill performance was disrupted in those with mild cognitive impairment and AD compared to non-demented controls. Similarly, Ghilardi et al[5] reported changes in basic characteristics of reaching movements in those with AD, including discontinuous movement, lower peak velocity, and heavy reliance on immediate visual feedback. Related deficits appear in classic experimental motor tasks such as serial response, Fitts' targeting task, and continuous pursuit-rotor tracking[4, 6]. These findings extend to behaviors more typically associated with daily function including greater variability in ambulation[7–9] and rising from a chair[10]. Demonstrating a possible neural basis for these reported motor disruptions changes, Agosta et al.[11] recently reported AD-related alterations in motor cortical activation measured by functional magnetic resonance imaging (fMRI).

Changes in movement execution early in the disease may result from pathological degeneration of connections mediating and enriching purposeful behavior[12–14]. Some studies have suggested that cognitive components of motor activity such as attention[15] and motor plan development[16–18] are disrupted in AD. This raises the possibility that functional networks typically supporting goal-oriented movement are altered by disease. Supporting this contention, we recently demonstrated that AD-related atrophy in medial frontal cortex is associated with poor cognitive and physical function associated with behaviors of everyday living[19]. Further evidence of the influence of cognitive decline on motor performance is worsened dual-task or high-load performance in AD individuals compared to age-matched controls[15, 20].

MRI is rapidly becoming an accepted tool for identifying early disease-related changes in both brain structure and function[21–23]. Functional connectivity analysis, a collection of methods for assessing temporal coherence in activation between regions, has been posited as a potential, non-invasive, imaging biomarker of early disease-related brain change[24–27]. To date, fMRI connectivity assessments in AD have primarily focused on "resting-state" pattern analysis with the general finding of decreased connectivity in a network of regions including precuneus, posterior cingulate cortex, medial frontal cortex, and lateral temporal lobes[25, 27–30]; the so-called "default-mode network". Of the few studies that have specifically addressed motor function with a connectivity analysis, specific regions of interest in the motor network were defined *a priori*, and therefore could not assess connectivity of regions outside the model[11].

The aim of the present study was to build on the evidence that connectivity is altered in AD. Specifically, we sought to identify any areas throughout the AD brain participating with motor cortex in a task-dependent manner during performance of a simple motor behavior. We hypothesized that regional differences in connectivity would be detected between those with and without dementia. However, we made no explicit hypothesis regarding the expected presentation of these differences given their variable nature[31]. We employed a simple visuomotor response paradigm to minimize problems with task comprehension. Primary motor cortex (M1) was chosen as a region of interest both because of its direct relationship to the task and its purported sparing in early AD pathology[2]. Psycho-physiological interaction (PPI) analysis was employed to assess regional co-activation modulated by the experimental condition and specifically associated with source region activity (M1). In a PPI analysis, the interaction of task and source region activation is regressed across the brain to assess task-specific correlation with the source region. In interpreting results of the PPI as applied here we, like others[32], have elected to use the terms functional integration or functional interaction as the present data inform our understanding of functionally connected regions rather than our knowledge of direct influence of one region on another.

METHODS

Participant recruitment and enrollment

Participants were recruited as part of a larger effort to establish a well-characterized cohort of community-dwelling adults aged over 60 years with and without dementia. Recruitment was performed through media appeals, word of mouth and through a referral-based memory clinic. Exclusion criteria included diabetes, disorders other than AD with the potential to impair cognition (e.g. Parkinson's disease), stroke, clinically significant depressive symptoms, abnormalities in vitamin B12 levels, abnormal thyroid function, or concurrent use of psychoactive or investigational medications[33]. A thorough exam by a board certified neurologist, including an interview with an informant familiar with the subject, was performed to characterize the severity of dementia, if present, with the Clinical Dementia Rating (CDR) scale[34]. Diagnostic criteria for AD included gradual and progressive memory impairment and deficit in at least one other cognitive domain[35]. The Functional Activities Questionnaire (FAQ) was also administered to an informant, knowledgeable about the participant's activity, to assess dependence on a caregiver to complete daily activities[36]. The FAQ consists of 10 instrumental activities of daily living, including shopping, preparing a meal or beverage, community navigation and managing finances among other activities, with a total score range of 0–30. Higher scores indicate greater dependence. Exams also included a description of apparent motor disturbance.

From this well-characterized cohort, a sample of convenience self-identifying as right-handed, willing to undergo fMRI, and having a Hachinski Ischemic score< 2[37] (Range 0–12, higher values indicative of cardiovascular contribution to dementia) was invited to participate in the present study. Twenty-seven individuals provided written informed consent in accordance with the University of Kansas Medical Center Human Subjects Committee. In the analysis phase, 1 data set was removed due to excessive head movement and 2 sets were removed due loss of dorsal signal. Additionally, based on recent accounts that individuals with mild cognitive impairment may exhibit differing activation patterns than those with frank AD[31], 5 datasets were removed from further analysis. Individuals were considered to have mild cognitive impairment with CDR = 0.5 (very mild dementia) and MMSE > 25. Thus, the final dataset included 9 individuals with AD and 10 individuals without cognitive impairment. Demographic differences between the group of individuals with AD and the group without dementia were tested using parametric and nonparametric tests as appropriate (e.g. Chi-square analysis, Student's t). An α of 0.05 was set for these tests.

Functional MRI Motor Task

Stimuli were presented with commercial software (Presentation, NeuroBehavioral Systems, Albany, CA) using an LCD back projection system with MRI-compatible vision correction when necessary. A simple visuomotor task, a right hand squeeze of a rubber bulb, was employed. Experimental conditions alternated between Move and Observe blocks during the run. Each of 5 active "Move" blocks consisted of a green circle on a black background presented 5 times for a duration of 2 seconds at each presentation, with a 2 second inter-stimulus interval. A red circle replaced the green circle for "Observe" blocks, which were otherwise identical to the active blocks in timing and duration. Text clues ("Move" and "Rest") were superimposed on each circle stimulus to serve as a reminder of the task. Participants were instructed to firmly squeeze the bulb with their right hand using a power grip when the green circle was presented and to not squeeze when the red circle was displayed. All participants were able to perform the task without verbal cues in a practice session prior to scanning. Participants were observed during the session for mirror movements and to ensure compliance with the instructions.

All imaging was performed with a Siemens 3T Allegra scanner using a quadrature head coil. For co-registration, a T1-weighed (Magnetization-Prepared Rapid Gradient Echo [MPRAGE]; TR=2300 ms, TE=3.05 ms, TI=1100ms, flip angle=8 deg, FOV= 240mm, matrix 256×192, slice thickness/gap/number =1mm, 0mm, 208) anatomic image was acquired. Functional images were collected using a sagittal, single-shot, echo-planar pulse sequence (TR=2000 ms, TE=50 ms, flip angle=90 deg, FOV= 240mm, 64x 100 matrix, slice thickness/gap/number=5.0mm/0mm/25, 102 analyzed volumes). Data were acquired parallel to the AC-PC line during performance of the motor task. Foam padding was placed around the head to minimize movement.

Identification of movement-related Activation

Images were processed using SPM8 (Wellcome Institute of Cognitive Neurology, London, UK). The first two volumes of the session were excluded to allow for stabilization of T1. Functional images were realigned to the first image of the run to account for subject motion and slice timing corrected to the first slice. Both anatomical and functional sets were spatially normalized to a standard MNI template using parameters generated under the unified segmentation procedure. Functional images were then smoothed using an 8mm FWHM Gaussian filter. The experiment was modeled using a boxcar function of Move and Observe conditions convolved with a canonical hemodynamic response function. Individual estimated movement parameters were entered into the model as regressors of no interest. Both conditions required sustained vigilance to the stimuli and thus the contrast of condition effects was designed to capture movement-related activity. Contrasts of active response condition effects (Move > Observe) were then applied in a second level mixed-effects analysis using a full factorial model including diagnosis group as a between subjects level and age and gender as covariates of no interest, with participant treated as a random effect. Condition and group effects were characterized using independent t-contrasts. Because structural variability can be increased by disease, we limited our analyses to voxels for which we were confident the probability of representing gray matter in individuals with AD was at least 25% (lower bound, 95% confidence interval=0.25 on gray matter probability map). We did this by calculating a gray matter probability map of those with AD[38], making a binary image of that map and using the resulting image as an inclusive mask for analysis. Because of the exploratory nature of the study and to inform future investigation, results are reported at $p \leq 0.005$, minimum voxel extent $(k) \geq 4$. Anatomic localization was determined using the computerized Talairach Daemon[39] within the WFU Pickatlas[40], and confirmed by visual inspection.

Movement-related Regional Integration

In the present study, PPI provides a measure of experimental, condition-specific, moment-to-moment co-activation, or functional integration of a source region and the rest of the brain[41]. The M1 region of interest from which the source physiological signal was extracted was defined for each individual according to the first level contrast in the prior analysis. In each single-subject contrast map the local maxima nearest M1 was selected. The BOLD signal in a sphere of 8mm radius centered at the peak activation nearest M1 was extracted as the source signal of interest. Regressor terms for the PPI analysis were then produced: a physiological regressor (the BOLD signal in the M1 ROI), a psychological regressor (Move vs. Observe periods, [1 –1]), and a PPI term, calculated as the cross-product of the physiological and the psychological regressors. These regressors were then convolved with the hemodynamic response function, high-pass filtered and entered into a first-level analysis that tested each voxel for positive association with the PPI regressor, adjusted for main effects. These one-tailed contrast maps, reflecting individual regions with a positive, condition-specific functional interaction with M1, were then entered into a second-level random effects analysis with age and gender used as covariates of no interest. Statistical

evaluation was performed in a manner similar to the conventional fMRI analysis described in the previous section.

RESULTS

Groups differed in gender distribution, with the group with AD having significantly fewer females (22%) than the group without dementia (70%). As expected the groups also differed on cognitive state, with lower MMSE scores on average in the group with AD (ND=29.8 versus AD=21.4). The groups did not differ in age or years of formal education ($p>0.3$). The mean (SD) FAQ score for the group with AD was 14.9 (7.9), indicating that most individuals required some assistance on IADLs. The individuals without dementia had a mean (SD) FAQ score of 0.4 (0.8). Group demographic values are given in Table 1. Two individuals with AD and 1 individual without dementia had bilateral essential tremor of the hands that did not impact function. No other motor impairments were noted in the clinical evaluation.

Task-related fMRI Activation

Within-group analysis of active movement compared to passive visualization of the stimuli indicated typical motor activity patterns in both the group with AD and the group without dementia (Move > Observe contrast). Figure 1 shows activation in those with AD (red), those without dementia (yellow) and regions where the two overlap (orange). Clusters of activation ($p<0.005$, $k\geq4$) are listed separately for analyses of each group in Table 2A and 2B. Both groups demonstrated activation in several regions when performing a motor response to the visual stimuli: left primary sensorimotor cortex, right cerebellum, left middle cingulate, left precentral gyrus and insula, right postcentral, and supramarginal gyri. The result confirms that both groups engaged expected motor areas during the Move condition compared to the Observe condition. Individually, the peak activations in this contrast served as the common source region (M1) for subsequent PPI analysis. The average location of this peak activation is indicated by the light blue circle in Figure 1.

Assessment of between-groups differences indicated that the participants without dementia displayed increased activation during active response (Move > Observe contrast; $p\leq0.005$ uncorrected, $k\geq4$) in the left supplementary motor area (BA 6), left middle frontal gyrus (Table 3, Figure 1 regions in purple) compared to those with AD. The group with AD did not exhibit greater activation in any area compared to those without AD ($p>0.005$).

PPI Analysis

PPI analysis revealed several regions that were functionally integrated with M1 activity in a task-specific manner. Importantly, these regions were exclusively observed to be greater in the group with AD compared to the group without dementia; no brain regions were greater in the group without dementia compared with those in the group with AD. The group with AD showed the largest clusters of functionally integrated activity with M1 in the right middle cingulate (BA 31), left sensorimotor cortex (BA 3 & 4) and bilateral anterior cerebellum. Visual association and processing regions also showed integration with M1 in the group with AD, including the left fusiform gyrus (BA 19) and left cuneus. (Table 4, Figure 2).

DISCUSSION

Using fMRI to assess patterns of brain activity associated with a simple visuomotor response behavior, i.e. power-grip hand squeeze, we were able to compare patterns of activation related to movements between those with and without AD. Although both groups activated

some brain regions in common, conventional and PPI analyses were able to detect differences between groups in connectivity with motor cortex, most notably in visual and motor association pathways. Specifically, using PPI we were able to capture a broader map of regions in AD that were correlated with the moment-to-moment activation of M1 as a function of the experimental task, rather than the generally increased activation of the conventional block design analysis. Although the absence of behavioral data limits interpretation of the results, these findings fit the growing literature that neuromotor activity supporting movement is altered in early-stage AD. These differences may not have been detected if we had employed a resting-state analysis or *a priori* model of motor cortex connectivity.

Motor-task Related Activation

We found that while the groups shared some motor-related activation in left primary motor cortex, right cerebellum, left middle cingulate, left precentral gyrus and insula, right postcentral and supramarginal gyri when assessed separately, the groups exhibit differences in activation when directly compared. Specifically, participants without dementia demonstrated greater activation in supplementary motor area and premotor cortex, commonly associated with motor preparation and planning[42], though this may also have been a result of variability in grip force[43] or perhaps attentional differences[44]. The reduced activity in these regions by the group with AD relative to their peers without dementia suggests either a failing motor planning system or alternative strategy for informing motor response. Though it remains unclear what functional ramification this might have, the failure to sufficiently recruit motor planning regions during a motor task could be a neural substrate for loss of independence with activities ranging from self-care to driving.

Disease-specific Functional Interaction with M1

In contrast to the conventional fMRI analysis, PPI identified a generally broader pattern of brain activation in the group with AD associated with M1 activity. In effect, individuals with AD showed more regions functionally integrated with M1 during visuomotor response. Importantly, these regions were not primarily associated with the task alone, but more specifically with M1 activation. This distinction is important because it allows for an assessment of co-activation with M1 specific to the changing task, in effect providing a picture of the moment-to-moment network of regions functionally integrated with M1. Further, unlike the motor region-restricted connectivity model of Agosta et al[11], our whole brain analysis identified not only similarities with that work, including increased integration of middle cingulate activation, but also revealed an extended network of higher-order processing and association regions in the AD participants.

Specifically, our results suggest that individuals with early AD exhibit integrated activity of M1 and visual association areas that subserve object recognition and visual memory[45]. Greater activation of certain visually-related cortices, such as left fusiform gyrus and cuneus was observed in those with AD compared to those without dementia and specifically in relation to recruitment of M1. Our data are consistent with previous reports of increased engagement of fusiform cortex by those with cognitive impairment during a visual encoding task[46]. In addition, multiple motor association and execution areas including broader activation of left sensorimotor cortex, beyond the hand region, and bilateral anterior cerebellum exhibited functional integration with M1 in the group with AD.

Disease-related Functional Change and Possible Effects on Motor-Cognitive Control

These results support and extend prior studies that show a widespread and perhaps nonspecific network of activation supplements cognitive control of motor action[11, 47]. Given that both groups exhibit typical activation of the primary motor execution network

(contralateral M1, ipsilateral cerebellum) the pattern of both visual association and motor control region recruitment in association with M1 suggests that these regions are inefficiently activated during a simple motor task. In the present study, individuals with AD activated multiple visual and motor accessory pathways in closely connected manner with M1 in a simple motor task compared to individuals without dementia. That these regions were functionally connected in a task-specific manner suggests inefficiency and absence of selectivity in recruited networks in early AD, perhaps as a consequence of disease. Neurofibrillary pathology and Aβ deposition are abundant in visual association cortices (BA 19)[48]. Recruitment of these pathologically burdened regions during simple visuomotor tasks may explain visuospatial and visual memory abnormalities frequently reported in the literature and underlie the deficits in performance of more complex activities in AD[15, 20, 49, 50].

Alternatively, the findings may reflect an emergent part of a compensatory visuo-motor network in AD to maintain performance despite disease-related dysfunction. Indeed, individuals without dementia showed increased activation in motor preparation and planning regions, premotor cortex and supplementary motor area. Individuals without dementia may generate and rely on a preplanned response set requiring lower vigilance to complete successfully, whereas each stimulus is evaluated and executed separately in the group with AD. This is not to suggest that visual pathways regions are unnecessary for individuals without dementia to perform the task, but that a fundamental change occurs as a consequence of the disease process that results in altered brain activity during performance of the task.

Whatever the cause, the apparently altered neural activity may underlie the well-characterized decline in dual task performance for those with AD. Studies on dual task performance in AD demonstrate significant impairments to both tasks when two cognitive tasks[51], or a cognitive and a motor task[49, 50], are performed simultaneously. Expanded recruitment of visual and motor pathways during a single task would limit available cognitive resources for a concomitant cognitive or motor task. Although the precise mechanisms of dual task deficits are still unclear, dementia often results in a failure of executive mechanisms, including set maintenance and switching, working memory, and attention, that underlie the ability to perform multiple simultaneous tasks. Deficits in cognitive coordination mechanisms have been postulated to explain poor dual task performance in AD[52]. As an example, if a simple visuomotor task such as picking out a specific item from a grocery shelf requires close co-activation of M1 and visual processing pathways, the multitude of other visual stimuli on the shelf, or a passing shopper, could interfere with appropriate selection of a motor plan.

Considerations

Some differences in regional activation between this and previous reports[11] of motor tasks may be attributed to different experimental conditions. The use of visual stimuli in the present study likely resulted in the activation of occipital structures. The use of PPI allowed us to globally assess regions functionally associated with M1, addressing the limitation of model-based connectivity analysis[11]. However, unlike Agosta et al[53] we cannot infer direct connectivity between regions. Further, 6 participants with AD were on an established regimen of an acetylcholinesterase inhibitor, a known modifier of cortical activation. Exploratory assessment revealed slight increases in bilateral middle temporal gyrus activation associated with use of an acetylcholinesterase inhibitor (data not shown), but no overlap with the reported regions of activation or motor cortex in our analyses. Gender differences have also been demonstrated in visuomotor-related BOLD signal[54];although we cannot rule out the influence of gender on our results, we note that it was used as a covariate in the mixed model. Finally and perhaps most importantly, the lack of motor response

information related to parameters such as timing and force limits more precise interpretation of these data. These limitations notwithstanding, our findings support and extend previous work identifying dementia-related differences in the neuromotor network of those with AD.

Limitations

The focus of this investigation was on characterizing differences in the cortical co-activation patterns during performance of a simple motor task. We did not assess how identified differences in cortical activation might influence performance of simple or complex motor tasks.

CONCLUSION

Our study suggests that, both in persons with early-stage AD, performance of a simple visuomotor task activates an extended network of motor and visual processing cortices. Altered connectivity with M1 in early AD may be explained by functional and pathological changes in the motor network as a result of disease. This hypothesis is in line with previous reports of global network dysfunction during movement in AD[55]. The present results support previous work identifying functional change in brain networks traditionally considered to be spared in early AD[11]. It is possible that even simple motor tasks activate an extended network of regions in interaction with M1, including visual and motor pathways that are not engaged to the same degree or in the same closely integrated manner in individuals without dementia.

The reliance on an extended and integrated network of cortical areas for the performance of motor behaviors in persons with early-state AD has implications for the rehabilitation professionals who work with them to improve motor function. Performance during functional activities that require set-switching or parallel information processing such as meal preparation, grocery shopping or driving, could be impaired as cognitive resources would already be engaged for more simple tasks. If further study determines that broad networks of activation are detrimental to performance, then clinicians could chose to focus on challenging the motor and attentional systems of individuals with early-stage AD to help train patients to handle multiple parallel tasks. Alternatively, the clinician could choose to educate caregivers on simplifying the environment to minimize allocation of limited cognitive resources and thereby promote successful performance of functional tasks. Future work should explore the inefficiency in the cognitive aspects of motor performance that may underlie reported motor control change occurring in AD before clinically relevant symptoms manifest[4, 56, 57].

Acknowledgments

We gratefully acknowledge the assistance of Phyllis Switzer, Pat Laubinger, JoAnn Lierman and the participants who so willingly give of their time and trust.

This study was supported by grants from the DANA Foundation, and the National Institute of Aging from the National Institute on Neurological Disorders and Stroke to JMB (AG026374 and AG029615 and K23NS058252). NL was supported by a training grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (T32HD057850). EDV was supported in part by a fellowship from the Foundation for Physical Therapy, the Heartland Institute for Clinical &Translational Research, University of Kansas Medical Center CTSA (KL2 RR033177 & UL1 RR033179). JMB and EDV were supported by the University of Kansas Alzheimer's Disease Center (P30AG035982). The Hoglund Brain Imaging Center provided imaging and clinical support (C76HF00201).

References

1. Alzheimer's Association. Alzheimer's Disease Facts and Figures. Alzheimers Dement. 2008; 4:110–33. [PubMed: 18631956]
2. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl). 1991; 82:239–259. [PubMed: 1759558]
3. Suva D, Favre I, Kraftsik R, Esteban M, Lobrinus A, Miklossy J. Primary motor cortex involvement in Alzheimer disease. J Neuropathol Exp Neurol. 1999; 58:1125–1134. [PubMed: 10560655]
4. Kluger A, Gianutsos JG, Golomb J, et al. Patterns of motor impairement in normal aging, mild cognitive decline, and early Alzheimer's disease. J Gerontol B Psychol Sci Soc Sci. 1997; 52:P28–39. [PubMed: 9008673]
5. Ghilardi MF, Alberoni M, Rossi M, Franceschi M, Mariani C, Fazio F. Visual feedback has differential effects on reaching movements in Parkinson's and Alzheimer's disease. Brain Res. 2000; 876:112–123. [PubMed: 10973599]
6. Willingham DB, Peterson EW, Manning C, Brashear HR. Patients with Alzheimer's disease who cannot perform some motor skills show normal learning of other motor skills. Neuropsychology. 1997; 11:261–271. [PubMed: 9110332]
7. Della Sala S, Spinnler H, Venneri A. Walking difficulties in patients with Alzheimer's disease might originate from gait apraxia. J Neurol Neurosurg Psychiatry. 2004; 75:196–201. [PubMed: 14742586]
8. Thomas VS, Vandenberg EV, Potter JF. Non-neurological factors are implicated in impairments in gait and mobility among patients in a clinical dementia referral population. Int J Geriatr Psychiatry. 2002; 17:128–133. [PubMed: 11813274]
9. Alexander NB, Mollo JM, Giordani B, et al. Maintenance of balance, gait patterns, and obstacle clearance in Alzheimer's disease. Neurology. 1995; 45:908–914. [PubMed: 7746405]
10. Manckoundia P, Mourey F, Pfitzenmeyer P, Papaxanthis C. Comparison of motor strategies in sit-to-stand and back-to-sit motions between healthy and Alzheimer's disease elderly subjects. Neuroscience. 2006; 137:385–392. [PubMed: 16289889]
11. Agosta F, Rocca MA, Pagani E, et al. Sensorimotor network rewiring in mild cognitive impairment and Alzheimer's disease. Hum Brain Mapp. 2010; 31:515–525. [PubMed: 19777557]
12. Camarda R, Camarda C, Monastero R, et al. Movements execution in amnestic mild cognitive impairment and Alzheimer's disease. Behav Neurol. 2007; 18:135–142. [PubMed: 17726241]
13. Babiloni C, Miniussi C, Moretti DV, et al. Cortical networks generating movement-related EEG rhythms in Alzheimer's disease: an EEG coherence study. Behav Neurosci. 2004; 118:698–706. [PubMed: 15301597]
14. Babiloni C, Ferri R, Binetti G, et al. Fronto-parietal coupling of brain rhythms in mild cognitive impairment: a multicentric EEG study. Brain Res Bull. 2006; 69:63–73. [PubMed: 16464686]
15. Rosano C, Aizenstein HJ, Cochran JL, et al. Event-related functional magnetic resonance imaging investigation of executive control in very old individuals with mild cognitive impairment. Biol Psychiatry. 2005; 57:761–767. [PubMed: 15820233]
16. Dick MB, Shankle RW, Beth RE, Dick-Muehlke C, Cotman CW, Kean ML. Acquisition and long-term retention of a gross motor skill in Alzheimer's disease patients under constant and varied practice conditions. J Gerontol B Psychol Sci Soc Sci. 1996; 51:P103–111. [PubMed: 8785686]
17. Dick MB, Hsieh S, Dick-Muehlke C, Davis DS, Cotman CW. The variability of practice hypothesis in motor learning: does it apply to Alzheimer's disease? Brain Cogn. 2000; 44:470–489. [PubMed: 11104538]
18. Bellgrove MA, Phillips JG, Bradshaw JL, Hall KA, Presnell I, Hecht H. Response programming in dementia of the Alzheimer type: a kinematic analysis. Neuropsychologia. 1997; 35:229–240. [PubMed: 9051672]
19. Vidoni ED, Honea RA, Burns JM. Neural correlates of impaired functional independence in early Alzheimer's disease. J Alzheimers Dis. 2010; 19:517–527. [PubMed: 20110598]
20. Howieson DB, Dame A, Camicioli R, Sexton G, Payami H, Kaye JA. Cognitive markers preceding Alzheimer's dementia in the healthy oldest old. J Am Geriatr Soc. 1997; 45:584–589. [PubMed: 9158579]

21. Fennema-Notestine C, Hagler DJ Jr, McEvoy LK, et al. Structural MRI biomarkers for preclinical and mild Alzheimer's disease. Hum Brain Mapp. 2009; 30:3238–3253. [PubMed: 19277975]
22. Toepper M, Beblo T, Thomas C, Driessen M. Early detection of Alzheimer's disease: a new working memory paradigm. Int J Geriatr Psychiatry. 2008; 23:272–278. [PubMed: 17621381]
23. Diamond EL, Miller S, Dickerson BC, et al. Relationship of fMRI activation to clinical trial memory measures in Alzheimer disease. Neurology. 2007; 69:1331–1341. [PubMed: 17893294]
24. Sorg C, Riedl V, Perneczky R, Kurz A, Wohlschlager AM. Impact of Alzheimer's disease on the functional connectivity of spontaneous brain activity. Curr Alzheimer Res. 2009; 6:541–553. [PubMed: 19747154]
25. Zhang HY, Wang SJ, Xing J, et al. Detection of PCC functional connectivity characteristics in resting-state fMRI in mild Alzheimer's disease. Behav Brain Res J. 2009; 197:103–108.
26. Zhou Y, Dougherty JH Jr, Hubner KF, Bai B, Cannon RL, Hutson RK. Abnormal connectivity in the posterior cingulate and hippocampus in early Alzheimer's disease and mild cognitive impairment. Alzheimers Dement. 2008; 4:265–270. [PubMed: 18631977]
27. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci U S A. 2004; 101:4637–4642. [PubMed: 15070770]
28. Wang L, Zang Y, He Y, et al. Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. Neuroimage. 2006; 31:496–504. [PubMed: 16473024]
29. Sorg C, Riedl V, Muhlau M, et al. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proc Natl Acad Sci U S A. 2007; 104:18760–18765. [PubMed: 18003904]
30. Petrella JR, Sheldon FC, Prince SE, Calhoun VD, Doraiswamy PM. Default mode network connectivity in stable vs progressive mild cognitive impairment. Neurology. 2011; 76:511–517. [PubMed: 21228297]
31. Dickerson BC, Sperling RA. Large-scale functional brain network abnormalities in Alzheimer's disease: insights from functional neuroimaging. Behav Neurol. 2009; 21:63–75. [PubMed: 19847046]
32. Egner T, Hirsch J. The neural correlates and functional integration of cognitive control in a Stroop task. Neuroimage. 2005; 24:539–547. [PubMed: 15627596]
33. Burns JM, Cronk BB, Anderson HS, et al. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. Neurology. 2008; 71:210–216. [PubMed: 18625967]
34. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993; 43:2412b–2414. [PubMed: 8232972]
35. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]
36. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. J Gerontol. 1982; 37:323–329. [PubMed: 7069156]
37. Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementias. Ann Neurol. 1980; 7:486–488. [PubMed: 7396427]
38. Momenan R, Rawlings R, Fong G, Knutson B, Hommer D. Voxel-based homogeneity probability maps of gray matter in groups: assessing the reliability of functional effects. Neuroimage. 2004; 21:965–972. [PubMed: 15006663]
39. Lancaster JL, Rainey LH, Summerlin JL, et al. Automated labeling of the human brain: A preliminary report on the development and evaluation of a forward-transform method. Hum Brain Mapp. 1997; 5:238–242. [PubMed: 20408222]
40. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage. 2003; 19:1233–1239. [PubMed: 12880848]
41. Price CJ, Friston KJ. Cognitive conjunction: a new approach to brain activation experiments. Neuroimage. 1997; 5:261–270. [PubMed: 9345555]

42. Krakauer, J.; Ghez, C. Voluntary Movement. In: Kandel, ER.; Schwartz, JH.; Jessell, TM., editors. Principles of Neural Science. 4. New York: McGraw-Hill; 2000.
43. Cramer SC, Weisskoff RM, Schaechter JD, et al. Motor cortex activation is related to force of squeezing. Hum Brain Mapp. 2002; 16:197–205. [PubMed: 12112762]
44. Keisker B, Hepp-Reymond MC, Blickenstorfer A, Meyer M, Kollias SS. Differential force scaling of fine-graded power grip force in the sensorimotor network. Hum Brain Mapp. 2009; 30:2453–2465. [PubMed: 19172654]
45. Vaidya CJ, Zhao M, Desmond JE, Gabrieli JD. Evidence for cortical encoding specificity in episodic memory: memory-induced re-activation of picture processing areas. Neuropsychologia. 2002; 40:2136–2143. [PubMed: 12208009]
46. Hamalainen A, Pihlajamaki M, Tanila H, et al. Increased fMRI responses during encoding in mild cognitive impairment. Neurobiol Aging. 2007; 28:1889–1903. [PubMed: 16997428]
47. Ferreri F, Pauri F, Pasqualetti P, Fini R, Dal Forno G, Rossini PM. Motor cortex excitability in Alzheimer's disease: a transcranial magnetic stimulation study. Ann Neurol. 2003; 53:102–108. [PubMed: 12509853]
48. McKee AC, Au R, Cabral HJ, et al. Visual association pathology in preclinical Alzheimer disease. J Neuropathol Exp Neurol. 2006; 65:621–630. [PubMed: 16783172]
49. Cocchini G, Della Sala S, Logie RH, Pagani R, Sacco L, Spinnler H. Dual task effects of walking when talking in Alzheimer's disease. Rev Neurol (Paris). 2004; 160:74–80. [PubMed: 14978396]
50. Della Sala S, Cocchini G, Logie RH, Allerhand M, Macpherson SE. Dual Task During Encoding, Maintenance, and Retrieval in Alzheimer's Disease. J Alzheimers Dis. 2010:503–515. [PubMed: 20110597]
51. MacPherson SE, Della Sala S, Logie RH, Wilcock GK. Specific AD impairment in concurrent performance of two memory tasks. Cortex. 2007; 43:858–865. [PubMed: 17941344]
52. Kaschel R, Logie RH, Kazen M, Della Sala S. Alzheimer's disease, but not ageing or depression, affects dual-tasking. J Neurol. 2009; 256:1860–1868. [PubMed: 19543789]
53. Thiyagesh SN, Farrow TF, Parks RW, et al. Treatment effects of therapeutic cholinesterase inhibitors on visuospatial processing in Alzheimer's disease: a longitudinal functional MRI study. Dement Geriatr Cogn Disord. 2010; 29:176–188. [PubMed: 20215749]
54. Gorbet DJ, Sergio LE. Preliminary sex differences in human cortical BOLD fMRI activity during the preparation of increasingly complex visually guided movements. Eur J Neurosci. 2007; 25:1228–1239. [PubMed: 17331218]
55. Babiloni C, Babiloni F, Carducci F, et al. Movement-related electroencephalographic reactivity in Alzheimer disease. Neuroimage. 2000; 12:139–146. [PubMed: 10913320]
56. Gillain S, Warzee E, Lekeu F, et al. The value of instrumental gait analysis in elderly healthy, MCI or Alzheimer's disease subjects and a comparison with other clinical tests used in single and dual-task conditions. Ann Phys Rehabil Med. 2009; 52:453–474. [PubMed: 19525161]
57. O'Bryant SE, Waring SC, Cullum CM, et al. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. Arch Neurol. 2008; 65:1091–1095. [PubMed: 18695059]

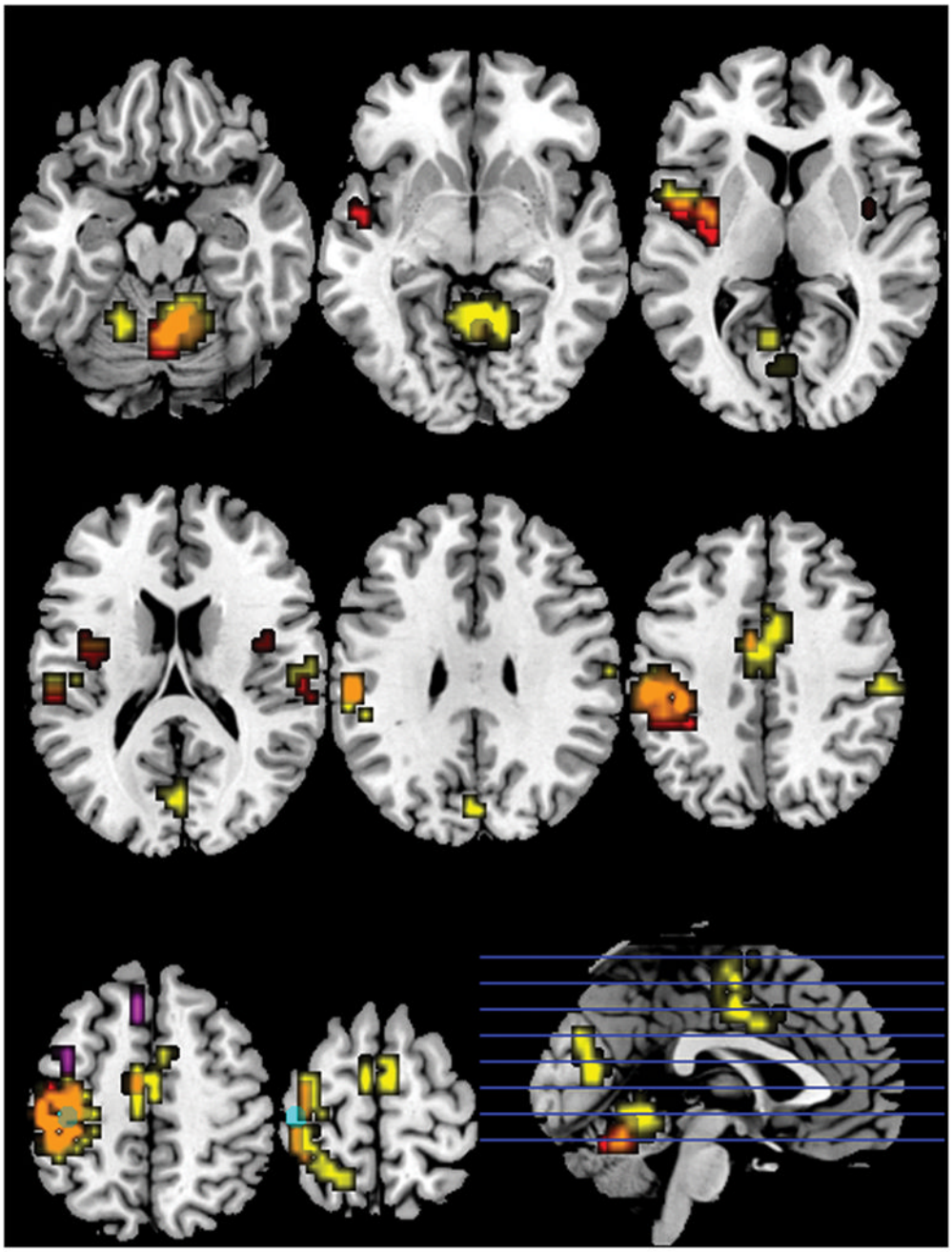

Figure 1.

Within-groups map illustrates greater activation during movement than during observation. . Colors are thresholded to the minimum significant t-statistic (Table 2). Red = AD, yellow = group without dementia, orange = overlapping active regions, purple = regions wherein movement-related activity was greater in the group without dementia than those with AD (see Table 3). The light blue circle is the average location of peak activation used for extracting the M1 seed signal for PPI analysis.

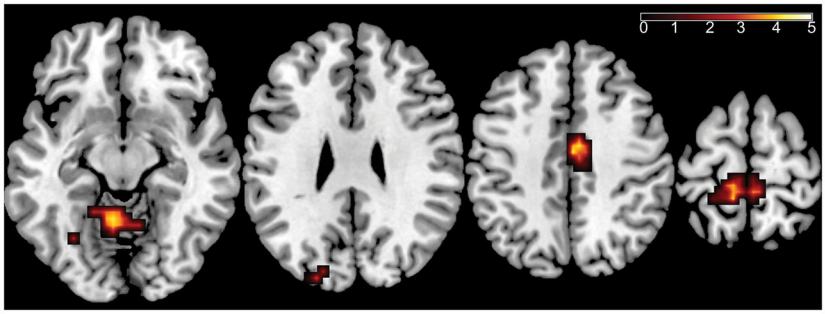

Figure 2.

Regions functionally integrated (PPI analysis) with M1 in the group with AD compared to the ND group (warm colors). The statistical map is overlaid on a template structural image. T-statistics are displayed according to the color chart and statistical maps are displayed at $p \leq 0.005$, $k \geq 4$. The activation pattern suggests expanded recruitment of both visual and motor networks by the group with AD during a simple visuomotor task. The blue circle is centered at the average peak activation of all participants during the Move condition.

Table 1

Demographic characteristics of participants

	ND (n=10)	AD (n=9)	Sig.
Females (n, %)	7 (70%)	2 (22%)	0.035
Age (SD)	73.6 (6.3)	69.0 (7.2)	0.337
Mini-Mental State Exam	29.8 (0.4)	21.7 (3.4)	0.006
Years of Formal Education	16.1 (2.8)	14.8 (3.9)	0.301
Functional Activities Questionnaire	0.4 (0.8)	14.9 (7.9)	<0.001

J Neurol Phys Ther. Author manuscript; available in PMC 2013 March 1.

Table 2

Summary of regions where individuals with AD (A) and those without dementia (B) exhibited movement related activation (Move condition as compared to Observe condition).

					Peak MNI Coordinates		
Regions	**voxels**	**T**	**Z**	**p**	**x**	**y**	**z**
A) Individuals with AD							
Left Sensorimotor Cortex	138	11.06	5.68	<0.001	−46	−28	50
		8.08	4.95	<0.001	−38	32	45
		4.59	3.57	<0.001	−54	−24	30
Right Anterior Cerebellum	41	6.87	4.55	<0.001	10	−52	−20
		5.71	4.10	<0.001	2	−64	−20
Left Precentral Gyrus (BA 44) /Insula (BA 13)	60	5.31	3.92	<0.001	−34	−8	5
		4.47	3.51	<0.001	−42	−8	15
		4.22	3.37	<0.001	−50	0	10
Left Middle Cingulate / Superior Frontal Gyrus (BA 6)	13	3.99	3.25	0.001	−6	0	35
		3.69	3.06	0.001	−6	12	55
Right Postcentral (BA 40) / Supramarginal Gyrus	7	3.69	3.06	0.001	58	−24	20
Right Inferior Frontal Gyrus (BA 47)	4	3.65	3.04	0.001	50	16	0
R Insula	5	3.35	2.85	0.001	38	0	10
B) Individuals without dementia							
Left Sensorimotor Cortex	194	8.21	4.98	<0.001	−46	−28	45
		5.66	4.08	<0.001	−54	−24	30
		5.30	3.92	<0.001	−42	−40	60
Bilateral Anterior Cerebellum	102	7.52	4.77	<0.001	14	−56	15
		5.99	4.22	<0.001	6	−48	−5
		3.66	3.04	0.001	−6	−64	0
Bilateral Middle Cingulate / Middle Frontal Gyrus	90	5.53	4.02	<0.001	−6	12	50
		5.30	3.92	<0.001	2	0	40
		5.13	3.84	<0.001	−6	−8	65
Bilateral Cuneus / Precuneus (BA 31)	21	4.47	3.51	<0.001	−2	72	15

					Peak MNI Coordinates		
Regions	**voxels**	**T**	**Z**	**p**	**x**	**y**	**z**
		4.36	3.45	<0.001	2	−80	30
Left Precentral Gyrus (BA 6 &44) / Insula	31	4.30	3.42	<0.001	−50	0	10
		4.22	3.37	<0.001	−58	4	10
		3.81	3.14	0.001	−34	−4	5
Left Cerebellum	12	3.91	3.20	0.001	−18	−52	−20
Right Postcentral (BA 40) /Supramaginal Gyrus	9	3.74	3.09	0.001	62	−16	25
Right Postcentral Gyrus (BA3)	16	3.59	3.00	0.001	54	−20	40

Results are presented at a threshold of p=0.005, k≥4. Region labels are derived from the Talairach atlas within the Wake Forest PickAtlas and confirmed with visual inspection on average structural image. Nearest Brodmann's Area designation within 3mm.

Table 3

Summary of regions where individuals without dementia exhibited greater activation than those with AD when squeezing (Move condition as compared to Observe condition).

Region					Peak MNI Coordinate		
	voxels	T	Z	p	x	y	z
Left Supplementary Motor Area / Superior Frontal Gyrus (BA 6)	7	4.44	3.49	<0.001	−6	24	55
Left Premotor Cortex / Middle Frontal Gyrus (BA6)	6	3.8	3.13	0.001	−38	0	50

Results are presented at a threshold of p=0.005, k≥4. Region labels are derived from the Talairach atlas within the Wake Forest PickAtlas and confirmed with visual inspection on average structural image. Nearest Brodmann's Area designation within 3mm.

Table 4

Summary of regions functionally interacting (PPI) with M1 in a task-specific manner. All regions are AD > nondemented.

Region					Peak MNI Coordinate		
	voxels	T	Z	p	x	y	z
Fusiform Gyrus (BA 19)	5	4.83	3.69	<0.001	−34	−64	−5
Middle Cingulate (BA 24 & 31)	24	4.63	3.59	<0.001	2	−12	45
		3.77	3.11	0.001	10	−16	40
Sensorimotor Cortex (BA 3 & 4)	31	4.42	3.48	<0.001	−10	−40	70
		4.35	3.44	<0.001	−6	−32	65
Anterior Cerebellum	35	4.26	3.39	<0.001	−6	−52	−10
		3.97	3.23	0.001	2	−56	−5
		3.27	2.79	0.003	−18	−48	−10
Cuneus (BA 19)	4	3.57	2.99	0.001	−26	−88	25

Results are presented at a threshold of p=0.005, k≥4. Region labels are derived from the Talairach atlas within the Wake Forest PickAtlas utility and confirmed with visual inspection on average structural image. BA = Nearest Brodmann's Area designation within 3mm.