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Volumetric correlates of memory and executive function in normal elderly, mild cognitive impairment and Alzheimer's disease

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Abstract

In Alzheimer's disease (AD), atrophy negatively impacts cognition while in healthy adults, inverse relationships between brain volume and cognition may occur. We investigated correlations between gray matter volume and cognition in elderly controls, AD and mild cognitive impairment (MCI) patients with memory and executive deficits. AD demonstrated substantial loss in temporal, parietal and frontal regions while MCI exhibited moderate volume loss in temporal and frontal regions. In controls, memory and executive function were negatively correlated with frontal regions, while in AD, memory was positively correlated with temporal and frontal gyri, and executive function with frontal regions. The combination of the two patterns may explain the lack of correlations in MCI. Developmental versus pathological contributions to these relationships are discussed.

Keywords: Mild cognitive impairment; Alzheimer's; Correlation; Volumetry; Memory; Executive

In vivo neuroimaging studies suggest that normal aging [4] as well as Alzheimer's disease (AD) [12] are associated with gray matter loss. Normal aging is associated with atrophy primarily in frontal [20] and to a lesser degree in parietal [11,20] and temporal cortices [25] while AD patients have substantial losses in the temporal (see [15] for review) and parietal [12,17] cortices with less atrophy in frontal regions [14]. Most previous studies have used the region of interest (ROI) approach but more recently studies have applied whole brain morphometric techniques, such as voxel-based morphometry (VBM), and have identified atrophy in these same regions [1,11,12]. Whole brain techniques allow for exploration of brain areas that are not easily assessed with ROI approaches [11].

Normal aging is associated with impairments in high level cognitive operations or "executive functions" as well as episodic memory for events (see [16] for review). In contrast, AD patients have predominant impairments in episodic memory, in addition to deficits in executive function (see [2] for review). Based on lesion studies showing that damage to the medial temporal lobe (MTL) impairs memory [27] while frontal damage affects both memory and executive function [24], it seems likely that these cognitive changes may be related to the atrophy described above. For example, studies have shown that in AD, volumes of the hippocampi and entorhinal cortex (ERC) are directly correlated with memory [8,18] while frontal volumes are related to executive function [14]. In contrast, similar correlations in healthy elderly have reported mixed results ([26] for review). Interestingly, similar correlations in young adults are almost exclusively in the negative direction [3,10,22]. One proposed explanation for this seemingly counterintuitive finding is that pruning of ineffective synapses that occurs during early development results in smaller volumes and improved cognition in young subjects [10]. In cognitively intact normal elderly adults with minimal volume loss, these negative relationships may remain whereas adults with more advanced age-associated or pathological atrophy may demonstrate positive associations.

Patients with mild cognitive impairment (MCI) are at a higher risk than the general population of developing dementia and as such, MCI is sometimes referred to as a "transitional state" [19]. Thus, these patients, with an intermediate level of atrophy between healthy aging and AD, might exhibit relationships

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between cerebral volume and cognition reflective of their transitional state. In the present study, we wanted to determine whether regional atrophy could explain the specific cognitive deficits associated with AD and MCI and to compare these structure/function relationships to those found in healthy older controls. To this end, we examined correlations between gray matter volumes, using VBM, and both episodic memory and executive functioning in controls, MCI, and AD. We hypothesized that in AD, frontal volumes would be positively correlated with executive functioning and frontal and temporal volumes with episodic memory, while similar relationships would be in the negative direction for a group of cognitively superior older adults. Finally, to assess transitional effects from normal aging to AD, we examined these same relationships in MCI subjects.

Fourteen healthy controls (CN), 32 MCI and 14 probable AD patients participated. Subjects were paid for participation and signed consent statements approved by the Institutional Review Board of the San Francisco VA Medical Center. All subjects were administered neurological examinations and an extensive battery of neuropsychological tests (see Supplementary Methods). Exclusion criteria were presence and/or history of neurological (e.g. stroke) or psychiatric (e.g. major depression) disorder or any medical condition that might produce cognitive impairment (e.g. uncontrolled diabetes, moderate cerebrovascular disease (including the presence of white matter lesions)). All MCI patients presented to our memory clinic with self-reported complaints of cognitive deterioration that were corroborated by an informant, and objective impairments that were limited to episodic memory and/or executive functioning at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests assessing these cognitive domains.[1] Additionally, MCI diagnoses were made only if patients were not demented and if activities of daily living were preserved. Final diagnoses of subjects were made at the time of initial presentation to the clinic and were based on the above factors and consensus of a team of clinicians. Importantly, subjective complaints and neurological examination of all patients suggested that their cognitive impairments were progressive. A diagnosis of probable AD was made using National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorder's Association criteria [6]. Group characteristics are shown in Table 1.

All subjects were administered a large battery of neuropsychological tests assessing multiple cognitive domains (see Supplementary Methods). As noted above, MCI patients exhibited impairments in episodic memory and/or executive function only. These domains were also affected in AD patients, although some of these patients exhibited other impairments (e.g. visuospatial). Thus, in order to draw comparisons between the groups, we limited our volumetric correlations to memory and executive domains for all subjects.

In order to limit the number of statistical tests, two composite scores was created based on tests that we felt best represented the memory and executive domains. These composites were based on the published age-standardized *z*-scores (standard deviations from the mean) for each test. For the episodic Memory Score, referred to hereafter as the Memory Score, the *z*-scores for the Long Delay Free Recall Discriminability and Recognition Discriminability indices from the standard form of the California Verbal Learning Test (CVLT-II) were averaged together. The composite score for executive function, or the Executive Score, was based on the average of the *z*-scores for the number of seconds for Number–Letter Switching on the Delis Kaplan Executive Function System (D-KEFS) Trail Making test and the number correct from the Digit Symbol substitution test of the (Wechsler Adult Intelligence Scale, WAIS-III). For AD, the Executive Score was based on the *z*-score of the WAIS-III Digit Span test. The means and ranges for these scores and subtests are shown in Table 1.

All subjects were scanned on a Siemens 1.5T MR scanner within no more than 2 months after their neuropsychological assessments. T1-weighted structural images were acquired with a magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence (TR 9.7 ms, TE 4 ms, FOV 256 mm, matrix 256 mm × 256 mm, 154 contiguous slices, slice thickness 1.5 mm, 15° flip angle). A study-specific T1 template for all subjects was created for use in all processing procedures using SPM2 (Wellcome Department of Imaging Neuroscience; London, UK). Individual T1 images were segmented, normalized and modulated according to the optimized VBM protocol [11]. The modulated gray matter (GM) images were smoothed with a 10 mm Gaussian kernel.

GM contrasts were corrected for age and total intracranial volume (TIV). Results were assessed under an $\alpha = .05$, Bonferroni corrected for the number of resels. Results of group comparisons are displayed on a rendered 3D brain of one of the MCI patients chosen at random (see Supplementary Fig. 1). Corrected voxel-level statistics are reported in all cases.

Voxel-by-voxel correlations between Memory and Executive Scores and GM volume were performed separately for each group. For the Memory Score–GM correlations, age, TIV and the Executive Score were entered as nuisance variables, while for the Executive Score–GM correlations, age, TIV and the Memory Score were entered as nuisance variables. Results were assessed under an $\alpha = .05$, Bonferroni corrected for the number of resels. Results from all significant correlations are displayed on the average T1 image of all participants and on the 3D views. Corrected voxel-level statistics are reported in all cases.

Group demographics and neuropsychological test scores are shown in Table 1. No significant differences were found between the groups for age, gender and education (all $F(2, 59)$'s < 1.98, p's > .15) while the groups differed in Mini Mental State Exam (MMSE) scores ($F(2, 59) = 91.0$, $p < .000001$), memory ($F(2, 59) = 19.6$, $p < .000001$) and executive function ($F(2, 59) = 18.9$, $p < .000001$). Follow up *t*-tests confirmed that MCI were slightly older than CN ($t(44) = 2.23$, $p = .03$) but there were no age differences between CN and AD or AD and MCI (all p's > .1). MMSE, memory and executive composite scores were higher

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[1] Although MCI patients may be diagnosed on the basis of impairments in other domains (i.e. single non-memory domain), the majority of the patients in our clinic exhibit memory and/or executive functioning deficits.

Table 1
Group characteristics

Characteristic	Controls (CN) ($n = 14$)		Mild cognitive impairment (MCI) ($n = 32$)		Alzheimer’s disease (AD) ($n = 14$)	
	Mean (S.D.)	Range	Mean (S.D.)	Range	Mean (S.D.)	Range
Age	69.5 (7.4)	61–87	74.1 (6.0)	63–86	74.6 (11.4)	55–94
Gender	8/14 F	–	11/32 F	–	5/14 F	–
Education	16.4 (2.0)	12–20	15.3 (3.5)	8–20	14.9 (4.7)	5–22
MMSE	29.5 (0.69)	28–30	28.0 (1.8)	24–30	21.3 (2.3)	18–26
Memory Score	0.80 (0.94)	−0.5 to 2.5	−0.42 (1.1)	−2.75 to 1.50	−1.55 (0.73)	−3.25 to −0.25
CVLT-II Long Delay Free Recall Discriminability	1.0 (1.1)	−0.66 to 3	−0.25 (1.23)	−2.50 to 2	−2.1 (1.2)	−4.5 to 0
CVLT-II Recognition Discriminability	0.57 (0.93)	−0.66 to 2	−0.59 (1.13)	−3 to 1	−1 (0.73)	−2 to 0
Executive Score[a]	0.82 (0.60)	0–1.67	−0.27 (1.04)	−2.33 to 2.16	−1.16 (0.50)	−1.66 to −0.33
WAIS-III Digit Symbol Correct	0.90 (0.79)	−0.33 to 2.0	−0.042 (0.94)	−1.66 to 2	–	–
D-KEFS Number–Letter Switching (s)	0.79 (0.66)	−0.33 to 1.66	−0.44 (1.46)	−3 to 1.66	–	–

MMSE: Mini Mental State Exam; CVLT: California Verbal Learning Test; WAIS: Wechsler Adult Intelligence Scale; DKEFS: Delis Kaplan Executive Function System.

[a] Executive Score in AD patients based on z-score of WAIS Digit Span.

in CN than MCI or AD (all p’s < .005) and in MCI relative to AD (all p’s < .001). Memory subtests were greater in CN than in either patient group (all p’s < .002) while recall ($t(44) = 4.7$, $p = .0001$) but not recognition ($t(44) = 1.2$, $p = .2$) discriminability was greater in MCI than AD. Executive subtests were greater in CN than MCI (all $t(44)$’s > 2.9, p’s < .006).

The results of the group contrasts are shown in Supplementary Table 1 and displayed in Supplementary Fig. 1. A few regions of GM atrophy were found in MCI patients relative to controls including the inferior frontal gyrus, entorhinal cortex (ERC) region of the parahippocampal gyrus, temporal and fusiform gyri. Relative to controls, AD patients demonstrated the most significant volume loss in bilateral medial and lateral temporal regions, extending into medial and lateral parietal cortex. AD patients also demonstrated more atrophy than MCI patients in these regions.

The results of the within group voxel-by-voxel correlations are shown in Table 2 and displayed on the group average brain and on a 3D rendered brain of one participant in Fig. 1. In controls, all correlations between GM volume and the executive

Table 2
Locations of significant voxel-by-voxel correlations for gray matter volume

Group	Score	Direction of correlation	Anatomical location	Peak voxel coordinates	Peak T value	Cluster size	p-Value
CN	Memory	Negative	L inferior frontal gyrus	−55, 24, 18	8.91	311	<.00001
	Memory	Negative	L middle frontal gyrus	−25, 19, 61	8.32	117	<.00001
	Memory	Negative	L superior frontal gyrus	−12, −8, 73	6.39	155	.00006
	Memory	Negative	L inferior parietal lobe	−36, −56, 56	6.03	28	.0001
	Memory	Negative	L inferior frontal gyrus	−39, 20, 30	5.39	80	.0002
	Executive	Negative	L middle frontal gyrus	−34, 18, 48	5.55	84	.0001
AD	Executive	Positive	L inferior orbital frontal gyrus	−25, 15, −28	9.71	453	<.00001
	Memory	Positive	L inferior orbital frontal gyrus	−26, 16, −29	7.07	118	.00002
	Executive	Positive	L medial frontal gyrus	−3, 50, 23	7.06	95	.00003
	Memory	Positive	R superior temporal pole/inferior frontal gyrus	58, 12, −6	6.85	87	.00003
	Executive	Positive	L middle frontal gyrus	−34, 51, 26	5.84	99	.0001
	Memory	Positive	R anterior cingulate	12, 39, 5	5.56	68	.0001

Voxel-level statistics (Bonferroni, $\alpha = .05$ resels) are reported. L: left; R: right. Coordinates in Montreal Neurological Institute (MNI) average brain space.

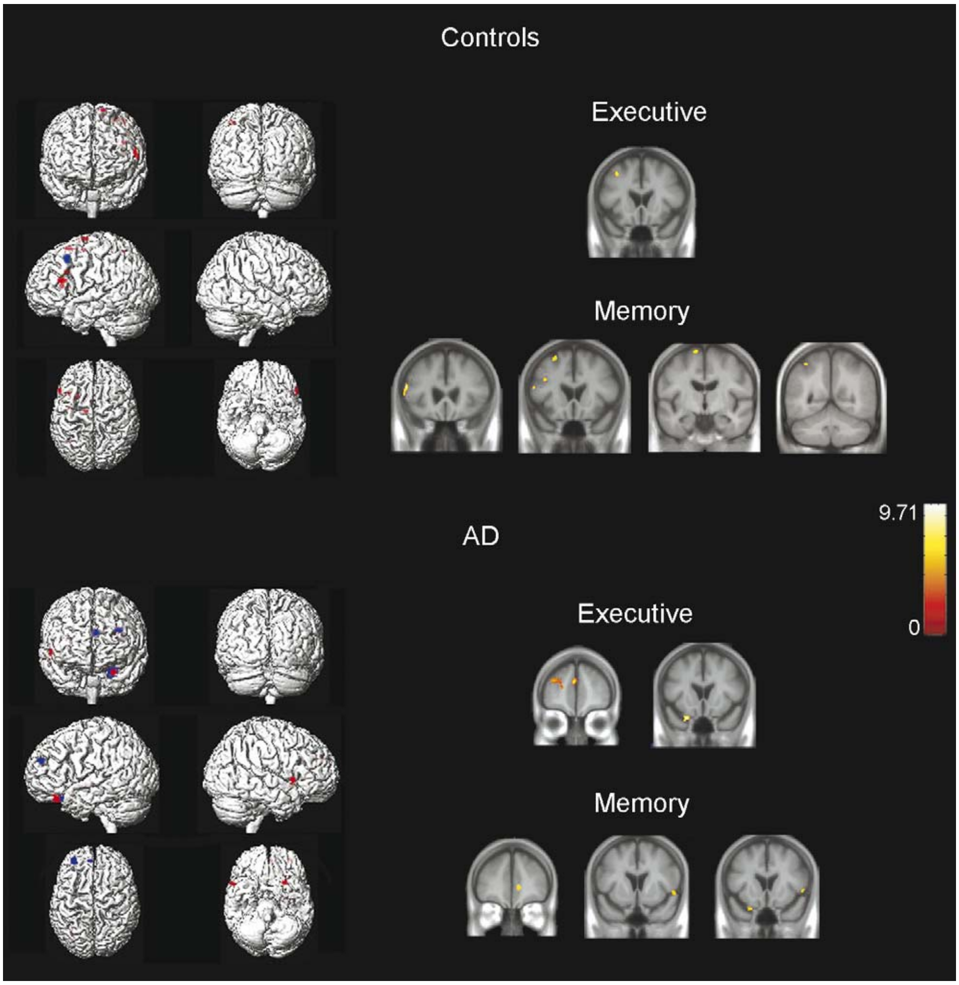

Fig. 1. Regions identified in the correlations between gray matter volumes and memory and executive function in CN and AD groups. Areas shown correspond to the locations described in Table 2. On the 3D views, red clusters represent memory correlations and blue clusters represent executive correlations. On the coronal views, in the CN group, for executive—middle frontal, and for memory (from left to right)—inferior, middle, superior frontal and inferior parietal gyri are shown. In the AD group, for executive (from left to right)—middle, medial and orbital frontal gyri, and for memory (from left to right)—anterior cingulate, inferior and orbital frontal gyri are shown.

and memory composite scores were in the negative direction. Specifically, memory was negatively correlated with GM volumes of several frontal gyri and the inferior parietal lobe while executive function was negatively correlated with the left middle frontal gyrus. In AD patients, all correlations were positive. Memory was positively correlated with temporal polar, orbital and inferior frontal gyri while executive function was positively correlated with left frontal gyri. As can be seen in the figure, the regions correlated with executive and memory functioning did not overlap substantially in either group. No significant correlations were observed between GM volume and cognition in MCI patients at the corrected statistical threshold. At a reduced threshold of $p < .001$ uncorrected, only one significant positive correlation between executive function and the left middle frontal gyrus was identified (peak Montreal Neurological Institute (MNI) coordinates: −29, 31, 31; cluster size: 132 voxels; peak T value: 4.02). No other correlations were identified at this reduced threshold.

In the current study, MCI and AD patients demonstrated cognitive impairments and we aimed to investigate the volumetric substrates of these impairments. As predicted, MCI patients had brain volumes intermediate between normal aging and AD, with moderate loss in temporal, frontal and parietal regions while AD exhibited substantial losses in these areas. Distinct relationships were identified between memory and specific frontal and temporal regions in AD patients, suggesting that atrophy in these specific brain regions contributed to this group's memory deficits. These positive correlations were in direct contrast to the negative correlations between volumes of similar frontal regions and memory in healthy controls. Similarly, positive and negative correlations in AD patients and controls, respectively, were found between specific frontal regions and executive function, although different measures of executive performance were assessed in these groups. Despite the regional atrophy and cognitive impairments in the MCI patients, no significant correlations between brain volumes and memory or executive function were identified in this group. These findings and their implications are discussed in further detail below.

We hypothesized that temporal and/or frontal regions would be associated with episodic memory while frontal regions would be associated with executive function. Consistent with this, in AD patients, orbital and inferior frontal gyri and a temporal polar region were positively correlated with memory while middle, medial and orbital frontal regions were positively correlated with executive functioning. Similarly, in healthy elderly, superior, middle and inferior frontal regions were negatively correlated with memory and the middle frontal gyrus was negatively correlated with executive functioning. Lesion studies suggest that the these frontal regions may be involved in episodic memory [9], while the temporal poles have been implicated in language processing [5], which likely contributed to memory performance for the verbal materials in the present study. In addition, superior, middle and inferior frontal regions have been implicated in executive control processes, including initiation, attention switching, monitoring of information and inhibition of irrelevant stimuli [24]. Although, as predicted, frontal regions were correlated with executive function in both AD and control groups, it must be noted that different neuropsychological tests were used to assess this cognitive domain in these groups, as described previously. This may, in part, account for the fact that the frontal regions involved were not entirely overlapping between the groups, as these tests may have tapped into slightly different aspects of executive functioning and as such, caution must be taken when comparing these correlations between the groups. Importantly, although atrophy in AD patients was pronounced and widespread, the positive correlations between these cognitive domains and frontal and temporal volumes were highly specific, supporting the idea that atrophy in these particular brain regions, rather than global atrophy, contributed to the memory and executive deficits in this group.

As noted above, while the correlations between cognition and gray matter volume were positive in AD patients, consistent with previous studies (e.g. [7]), all correlations were in the negative direction in controls, meaning that smaller volumes reflected better cognition. Although these negative relationships may at first seem counterintuitive, they are not inconsistent with previous findings of negative correlations in young adults [10,22]. One hypothesis suggests that insufficient synaptic pruning during brain development in adolescence may lead to reduced cognition in young adults, hence the inverse relationships [10]. More specifically, in early childhood, total gray matter volumes initially increase between 2 and 9 years of age and then begin to slowly decline into advanced aging [4]. These initial increases are concurrent with increases in the size of neurons and number of neurons and synapses and followed by elimination of ineffective or redundant synapses (see [23] for review). One possibility is that some older adults, within or above the age-adjusted level for gray matter volume and cognition, exhibit negative correlations like those of young adults [25]. The older controls in the current study were thoroughly screened for cognitive deficits/decline and they scored above the age-adjusted norms on all measures. The negative correlations we observed in this group are consistent with previous reports of negative correlations between frontal gray matter volumes and memory and executive function in healthy older adults scoring above the age-adjusted mean for various cognitive tests [13,21,25]. Thus, in cognitively superior older adults, cerebral volumes may be more dependent on developmental changes rather than age-associated atrophy. Indeed, it has been suggested that positive relationships between cognition and brain volumes may only be present in samples containing a large proportion of poor performing subjects [20]. Thus, previous studies which have identified positive relationships between similar cognitive domains and cerebral volumes in normal elderly may have included low performing subjects in their samples.

In AD patients with substantial atrophy in frontal and temporal regions and reduced memory and executive function, smaller volumes in a subset of these regions were associated with lower functioning in these cognitive domains. From this we conclude that while developmental synaptic pruning, as described above, dominates the relationship between gray matter volumes and cognition in healthy older adults, pathologically induced atrophy dominates this association in AD. In MCI patients with moderate loss in frontal and temporal regions relative to controls but substantially less atrophy than AD patients, no significant correlations between cognition and brain volume were found. Only at a greatly reduced uncorrected statistical threshold did we identify a positive correlation between executive function and the middle frontal gyrus, consistent with the frontal foci identified in the correlations with this domain in the other groups. We do not feel that reduced statistical power can account for the lack of correlations in this group because of all groups studied, the MCI group was the largest and statistical analysis confirmed that there was sufficient sensitivity to detect significant effects in this group at our corrected threshold (90% power). We instead suggest that the lack of correlations in MCI may be explained by the fact that this group likely represents a combination of early AD and normal aging and the combination of the two contrasting correlation patterns resulted in no observable correlations across this group. Another possibility is that the contrasting patterns are explained by a transitional stage from normal aging to MCI to AD. Specifically, if insufficient pruning during development results in a larger number of low functioning neurons, an inverse relationship between volume and cognition may occur. A transition from negative to positive correlations could evolve as progressive neuron loss reduces the overall number of neurons. That is, assuming that there are more high than low functioning neurons in the healthy brain, the progressive loss would result in a greater contribution of high functioning neurons to cognition, producing the positive correlations. One prediction from these data is that as some MCI patients progress toward dementia and exhibit further volume loss, they will exhibit more positive relationships between cognition and cerebral volumes, suggesting that the null correlations may be an early sign of impending cognitive decline/dementia.

In summary, this study suggests that examining relationships between brain volume and cognitive function may offer insight into the organization of cognitive functioning in the normal brain and also how neuropathology may affect these relationships. The fact that these brain–behavior correlations were positive in AD and in the negative direction for high performing elderly suggests that distinct processes may influence the regional brain volumes that support cognition in these groups. Gaining a complete understanding of these brain–behavior relationships may become especially important as new preventative treatments become available, to treat or delay AD pathology in at risk individuals, which may be able to target specific brain regions that are affected by AD pathology and also believed to support the cognitive functions that deteriorate in this group.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neulet.2006.07.029.

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