Relating anatomy to function in Alzheimer's disease

Neuropsychological profiles predict regional neuropathology 5 years later

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Article abstract—Neuropsychological profiles were assessed in a large group of nondemented control subjects (n = 261) and individuals with dementia of the Alzheimer type (DAT) (n = 407) by subjecting their psychometric test results to a factor analysis. Nondemented control subjects were functionally homogeneous with only one factor accounting for the results. The results of the factor analysis on the very mild DAT and mild DAT groups, however, yielded a mental control/frontal factor, a memory-verbal/temporal factor, and a visuospatial/parietal factor. Forty-one of the original set of participants came to autopsy an average of 5.1 years after psychometric testing and had neurofibrillary tangles, total senile plaques, and cored senile plaques estimated from frontal, temporal, and parietal regions. The results of correlations indicated that the relative burden of cored senile plaques was systematically related to the three psychometric factors. These results suggest a connection between the specific functions as defined by neuropsychological measures and specific neuropathology occurring in associated areas of cortex.

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The evidence relating Alzheimer's disease (AD) pathology to functional deterioration falls short in elucidating how pathology occurring in a specific region of cortex is related to a particular functional deficit. In the past, general cognitive deficits were related to a pathologic process without a clear connection between the location of the lesions and the functions impaired (e.g., cortical plaque counts and the Mini-Mental State Examination).[1] Our knowledge of AD requires better explanations for the role of specific lesions in producing specific cognitive deficits. The present research attempted to clarify whether specific neuropathology is related to specific functional deficits in a selected group of individuals with pathologically confirmed AD.

The first step in the investigation of the relationship between specific lesions and functional deficits requires the identification of differences in cognitive functioning in individuals with dementia of the Alzheimer type (DAT). We accomplished this through factor analytic procedures using a large database of psychometric test results collected over 16 years by the Alzheimer's Disease Research Center (ADRC) at Washington University. We then related the resulting functional factor scores to neuropathologic burden in various cortical areas in a subset of demented individuals who came to autopsy on average 5.1 years after psychometric testing.

Methods. The recruitment, descriptions, and assessment procedures for this sample have been presented in detail elsewhere.[2-5]

Participants. The 668 individuals included in the present study participated in longitudinal studies of the ADRC from 1979 through 1996. They ranged in age from 47.5 to 100.2 years (mean ± SD, 74.6 ± 9.3) and included both nondemented elderly control subjects (n = 261) and individuals with DAT (n = 407). All participants underwent assessment at regular intervals unless prevented by death, refusal, or relocation away from St. Louis. The present analyses consider only the first time of assessment to eliminate practice effects and because many DAT participants were unable to complete all tests at subsequent assessments. Numerous previous reports from the Center include data from these participants.

The 261 control subjects showed no evidence of dementia or any disorders suspected to contribute to dementia.[6] The 407 DAT participants were diagnosed according to validated clinical criteria[2,6] that are equivalent to those for probable AD as proposed by McKhann et al.[7] AD is confirmed neuropathologically in 97% of DAT subjects in our studies who come to autopsy.[3] We did not include participants with uncertain dementia, other diagnoses that might contribute to dementia (e.g., Parkinson's disease, cerebral infarction), active or questionably active depression, or advanced DAT.

Clinical assessment. An experienced clinician performed a semistructured interview with the participant and a collateral source (usually the spouse or an adult

Table 1 *Predicted psychometric test groupings by cortical areas with examples of supporting evidence*

Cortical area	Psychometric test	Examples of supporting evidence
Superior/ midtemporal	Information	Chase et al.[15]
	Boston Naming	Lezak[12]
Medial-temporal	Logical Memory	Milner,[18] Mishkin[19]
	Associate Learning	Milner,[18] Mishkin[19]
Parietal	Benton: Copy	Lezak[12]
	Block Design	Chase et al.[15]
	Digit Symbol	Chase et al.[15]
Frontal	Digit Span Forward	Chase et al.[15]
	Word Fluency	Parks et al.[20]
	Mental Control	Mann et al.[21]
	Trailmaking A	Haxby et al.,[22] Grady et al.[23]

child). The clinical protocol included several brief cognitive scales and general physical and neurologic examinations of the participant.[6] Clinicians determined the presence or absence of dementia using the participant and collateral source interviews. If dementia was present, its severity was assessed in accordance with the Washington University Clinical Dementia Rating (CDR),[8,9] where CDR 0 (n = 261) indicates no impairment, CDR 0.5 (n = 183) indicates very mild dementia, and CDR 1 (n = 224) indicates mild dementia. Assignment of the CDR score is made without reference to psychometric performance, which is assessed independently.

Psychometric assessment. The psychometric battery administered to all participants has also been described in detail elsewhere.[5] Although the battery has been modified over time (it was initiated in 1979), all participants in the present study received the tests described here.

For the present analyses, a subset of tests from the complete psychometric battery were a priori selected to sample various cognitive functions believed to be subserved by specific anatomic regions. The anatomic regions that guided the selection process were frontal, medial temporal, superior/midtemporal, and parietal cortical areas. Table 1 presents the predicted groupings of the psychometric tasks according to their associated cortical regions and reference to evidence supporting these selections. Tasks sampling temporal (verbal) performance included the Information subtest from the Wechsler Adult Intelligence Scale (WAIS)[10] and the Boston Naming Test.[11] Although there is little evidence that these tests are localized to a specific region, they are both verbal tests traditionally associated with the temporal cortical region in the left hemisphere.[12] The Logical Memory and Associate Learning subscales of the Wechsler Memory Scale (WMS)[13] measured secondary memory and presumably are mediated by medial temporal structures such as the hippocampus. Measures used to estimate parietal area functioning (visuospatial) were the copy-only administration of Benton's Visual Retention Test, Form D,[14] and the Block Design subtest of the WAIS. The Digit Symbol subtest of the WAIS was included as an estimate of general speed and

motor ability; however, it should be noted that evidence shows this test is subserved by the parietal lobe as well.[15] The measures used to test frontal lobe functioning (simple attention and mental control) were the Mental Control and Digit Span Forward subscales of the WMS, Trailmaking A (Trailmaking B was not included because many DAT participants could not perform the task),[16] and Word Fluency for S and P.[17]

All tests were administered by psychometricians who were unaware of the individual's diagnosis or CDR rating and were scored according to test manual instructions. The only exception was the Boston Naming Test in which all items were administered without phonemic cues.

Factor analyses. The factor analyses of the psychometric data for the nondemented, very mild DAT, and mild DAT groups were conducted separately to determine whether the patterns of correlations among the test results were different for the individual groups. Because of the large sample size, each group was randomly divided in half so that the results of the factor analyses could be cross-validated. A principal components analysis with varimax rotation was conducted separately on each of the six groups (two halves per each CDR 0, CDR 0.5, and CDR 1 groups).

The results of the factor analyses were interpreted using both the Kaiser-Guttman rule of retaining components with eigenvalues greater than 1.0 and examining the scree plots of eigenvalues versus their ordinal positions. The greatest weight, however, was placed on the cross-validation results across the randomly selected halves from the groups.

Postmortem assessment. Forty-one participants who died during the longitudinal studies were studied postmortem. The average period between initial psychometric testing and postmortem neuropathologic assessment was 5.1 years (median, 4.5; range, 0.2 to 11.9). As described in detail elsewhere,[24,25] whole or hemibrains were fixed for at least 2 weeks in neutral 10% formalin and sectioned at 1-cm intervals in the coronal plane. Tissue blocks were taken from the midfrontal (Brodmann 9/10), superior and middle temporal gyri (Brodmann 22), and inferior parietal neocortex (Brodmann 39) after fixation. In addition, tissue blocks were taken from the hippocampal formation at pes hippocampus and lateral geniculate gyrus levels to include entorhinal cortex (Brodmann 28) and the CA1 region of the hippocampus (Brodmann 27). These sections were routinely stained with hematoxylin and eosin, thioflavin S, modified Bielschowsky (mBT), and Hedreen-modified Bielschowsky (hmBP) methods.[26]

Six-micrometer-thick paraffin brain sections were stained with mBT and hmBP to assess intraneuronal and extracellular neurofibrillary tangles (NFTs), cored senile plaque subtypes (CSPs), and total senile plaques (TSPs), which are the sum of diffuse and cored plus non-cored neuritic plaques. Diffuse plaques varied in diameter from about 15 to 80 mm and lacked argyrophilic or thioflavin S-positive dystrophic neurites or compact central cores. Cored senile plaques were identified by the presence of argyrophilic dystrophic neurites and a compact central core that was evident in both silver methods and with thioflavin S viewed in a fluorescence microscope. Microscopic fields were assessed blindly (rater was aware only of the brain region and stain type but was unaware of any

clinical details) with a 10× objective using a 1-cm² ruled graticule with 100 subdivisions. NFT, TSP, and CSP density assessments represent the mean number of lesions/mm² (density) in 10 1-mm² representative microscopic fields that included five upper and five lower cortical fields for neocortical and entorhinal sites and 10 adjacent fields for area CA1 of the hippocampus. To assess the reliability of the neuropathologic assessments, a representative sample was chosen (25 cases from the total ADRC bank of 110 cases that had come to autopsy) and a single neuropathologist made repeat assessments while blind to all information except lesion site and type of stain. Reliability analyses were performed on the log transformed values from each area assessed and provided intraclass correlation coefficients of 0.95 for total senile plaques, 0.95 for neurofibrillary tangles, and 0.56 for cored senile plaques.

AD was diagnosed in accordance with the criteria reported by Khachaturian.[27] These criteria use age-adjusted senile plaque scores; for example, a senile plaque density of 15 mm² in a person aged 75 years is considered necessary for a diagnosis of AD, although fewer senile plaques may be diagnostic if there is also a clinical history of DAT. All 41 individuals used in the analysis had pathologically confirmed AD.

Correlative analyses. Correlative analyses were performed using both raw scores and proportional scores. Factor scores for each DAT sample were calculated by combining the factor scores from both halves of each sample. Raw neuropathologic assessments were correlated with the raw factor scores for each group.

Proportional scores for each factor score and lesion type (CSP, TSP, and NFT) were computed to adjust for individual differences in overall psychometric performance and overall neuropathologic burden. Proportional scores were computed by dividing the raw factor score or regional neuropathologic value by the sum of the values for all factor scores or regions. Specifically, the parietal psychometric proportional score for each individual was the parietal factor score divided by the sum of the parietal, frontal, and temporal factor scores. The neuropathologic proportional scores were computed in an analogous fashion to the proportional psychometric scores. For example, if the mean parietal plaque burden was 5 mm², the frontal was 10 mm², the superior/midtemporal was 15 mm², the hippocampal CA1 was 5 mm², and the entorhinal cortex/perforant pathway was 5 mm², there would be a total mean plaque count of 40 mm² (5 + 10 + 15 + 5 + 5). Therefore, the proportional score for the parietal area would be 0.125 (5/40), whereas the frontal proportional score would be 0.25 (10/40).

Results. *Factor analyses of psychometric measures.* Descriptive statistics for the psychometric measures are presented in table 2.

Nondemented control subjects. The first factor for the control group accounted for 37% of the variance in one-half of the sample and 41% in the other half. To examine whether a multiple factor solution would replicate, three factors were rotated from each half of the sample. The results, shown in table 3, demonstrate that the psychometric tests did not group on the three factors similarly in the two samples and thus the solution did not replicate. For example, Logical Memory and Associate Learning, which loaded with Trailmaking A and Digit Symbol in one-half of

Table 2 *Psychometric means (± SD) and demographics for the nondemented control subjects, very mild DAT, and mild DAT groups*

	Control subjects	Very mild DAT	Mild DAT
Age (y)	75.7 ± 10.3	74.1 ± 8.5	73.8 ± 8.6
Education	14.0 ± 3.4	13.0 ± 3.4	12.2 ± 3.5
Gender (M/F)	98/163	92/91	86/138
Information	19.9 ± 4.6	15.1 ± 5.7	9.7 ± 5.2
Boston Naming	52.7 ± 7.0	44.4 ± 12.0	33.7 ± 14.3
Logical Memory	8.1 ± 2.8	4.3 ± 2.7	1.9 ± 1.7
Associate Learning	20.4 ± 4.1	15.9 ± 4.7	11.2 ± 5.0
Benton: Copy	9.4 ± 1.3	9.1 ± 1.6	7.3 ± 2.7
Trailmaking A	50.3 ± 26.0	70.2 ± 39.2	108.3 ± 50.5
Block Design	28.5 ± 8.1	22.2 ± 9.8	12.0 ± 9.6
Digit Symbol	42.5 ± 12.5	31.7 ± 13.6	17.0 ± 13.3
Digit Span Forward	6.7 ± 1.2	6.1 ± 1.2	5.8 ± 1.3
Word Fluency	28.3 ± 9.5	23.4 ± 9.7	14.7 ± 9.3
Mental Control	7.2 ± 1.9	5.9 ± 2.4	4.4 ± 2.7

Psychometric tests are scored such that greater scores indicate better performance with the exception of Trailmaking A, for which higher scores indicate slower performance.

DAT = dementia of the Alzheimer type.

the sample, did not load with tasks in the other sample half. Rotating two or four factors produced the same failure to replicate. Moreover, as shown in table 3, there was relatively little systematicity in the grouping of tasks with the predicted cognitive functions displayed in table 1. Therefore, the most appropriate choice for the control group was a single factor solution. All measures had loadings ranging from 0.43 to 0.75 on this single factor.

Very mild DAT. In contrast to the nondemented control subjects, three factors were identified for the very mild DAT group. These factors accounted for 64% of the variance in half of the sample and 67% of the variance in the other half. Moreover, as shown in table 4, the three factors were clearly grouped into the predicted pattern of tasks belonging to a temporal group (including Information, Boston Naming, Logical Memory, and Associate Learning), a parietal group (including Benton Copy, Trailmaking A, Block Design, and Digit Symbol), and a frontal group (including Digit Span Forward, Word Fluency, and Mental Control). Perhaps not so surprising in retrospect, the tasks that were thought to estimate verbal performance correlated with the tasks that were predicted to estimate memory performance. The heavy reliance on memory in the verbal tests used and the verbal skills needed to perform the memory tasks provide a plausible account of this grouping. Also, Trailmaking A, included as a measure of simple attention for the frontal region, loaded with the parietal group. The spatial skills needed to perform this task most likely caused it to be grouped with the other spatial tasks. Unlike Trailmaking B, Trailmaking A does not require the set switching that is thought to be mediated by pathways dependent on intact frontal lobe functioning. Digit Symbol grouped with the parietal measures as one would expect based on the results of past imaging

Table 3 *Results of principal components analysis for nondemented control subjects, Sample 1 (n = 131) and Sample 2 (n = 130), three factors rotated*

	Factor 1		Factor 2		Factor 3	
Measure	Sample 1	Sample 2	Sample 1	Sample 2	Sample 1	Sample 2
Information		0.85	0.69			
Boston Naming	0.50	0.70	0.62			
Logical Memory	0.76					0.76
Associate Learning	0.62					0.81
Benton: Copy			0.72	0.77		
Trailmaking A	0.64			0.70		
Block Design		0.60	0.67	0.40		
Digit Symbol	0.57	0.40		0.60	0.50	
Digit Span Forward		0.56			0.78	
Word Fluency		0.61			0.77	
Mental Control			0.43	0.49	0.51	
Explained variance (%)	37	41	12	10	9	9

Factor loadings beneath 0.40 are not shown.

work.[15] This task involves a considerable amount of spatial skill in identifying and copying the appropriate symbols. As is clear from table 4, the results replicated between the two sample halves, providing strong support for the reliability of the three factors.

Mild DAT. Three factors were also identified for the mild DAT group that accounted for 70% of the variance in one-half of the sample and 69% of the variance in the other half. Moreover, the factor structure was replicated for the two halves of the mild DAT group and was the same as the results of the very mild DAT group (see table 4). The pattern was again quite consistent with the predicted grouping of tasks. The only exception was Associate Learning, which was correlated with the frontal factor for one-half of the sample and the temporal factor for the other half of the sample. It is possible that the breakdown in source memory with disease progression[28] may account for a greater reliance on frontal memory systems rather than medial-temporal memory systems for at least some people with mild DAT.[29,30]

Neuropathology and correlation with factor scores. The total mean numbers of NFTs, TSPs, and CSPs for each area of cortex are summarized in table 5. The results are consistent with a recent study by Morris et al.,[4] who found

Table 4 *Factor loadings from the principal components analysis for the very mild DAT groups, Sample 1 (n = 92) and Sample 2 (n = 91), and for the mild DAT groups, Sample 1 (n = 112) and Sample 2 (n = 112)*

	Very mild DAT						Mild DAT					
	Temporal		Parietal		Frontal		Temporal		Parietal		Frontal S	
Measure	S1	S2	S1	S2	S1	S2	S1	S2	S1	S2	S1	S2
Information	**0.77**	**0.76**					**0.80**	**0.85**				
Boston Naming	**0.69**	**0.72**					**0.86**	**0.87**				
Logical Memory	**0.72**	**0.79**					**0.73**	**0.67**				
Associate Learning	**0.77**	**0.83**						**0.65**	0.43		0.64	
Benton: Copy			**0.77**	**0.80**					**0.84**	**0.75**		
Trailmaking A			**0.71**	**0.80**	0.41				**0.80**	**0.87**		
Block Design			**0.68**	**0.73**					**0.79**	**0.81**		
Digit Symbol		0.50	**0.66**	**0.69**	0.49				**0.83**	**0.86**		
Digit Span Forward					**0.83**	**0.86**					**0.75**	**0.87**
Word Fluency					**0.58**	**0.44**			0.40		**0.69**	**0.52**
Mental Control					**0.46**	**0.71**		0.48			**0.72**	**0.56**
Explained variance (%)	43	44	11	12	10	11	10	16	45	42	15	11

Primary factor loadings in bold. Factor loadings beneath 0.40 are not shown.

DAT = dementia of the Alzheimer type; S = sample.

Table 5 *Total mean number (± SD) of NFTs, TSPs, and CSPs for each area of cortex for 41 DAT patients*

Cortical area	NFT/mm^2	TSP/mm^2	CSP/mm^2
Temporal			
Superior/	9.9 ± 14.8	52.0 ± 33.2	7.0 ± 6.4
midtemporal gyrus	(0.0–57.4)*	(0.8–145.8)	(0.1–30.6)
Hippocampus	39.1 ± 38.3	12.1 ± 10.2	1.9 ± 2.0
	(0.0–164.3)	(0.0–48.1)	(0.0–8.3)
Entorhinal cortex	19.3 ± 14.8	27.6 ± 22.2	3.1 ± 4.0
	(0.0–61.6)	(0.0–110.5)	(0.0–17.8)
Parietal	6.3 ± 8.4	58.3 ± 40.3	8.6 ± 5.5
	(0.0–28.6)	(0.0–196.9)	(0.0–20.3)
Frontal	7.6 ± 9.6	82.4 ± 49.8	6.9 ± 4.8
	(0.0–33.3)	(0.0–230.1)	(0.0–17.2)

* Range for neuropathologic marker.

NFT = neurofibrillary tangle; TSP = total senile plaque; CSP = cored senile plaque; DAT = dementia of the Alzheimer type.

a high density of senile plaques (primarily diffuse) in the frontal regions of individuals who were at the threshold of detectable dementia. Here, the 41 DAT individuals also displayed the highest density of TSPs in the frontal region. Also consistent with other studies,[31] the highest density of NFTs was in the hippocampal regions of cortex.

The correlations between the raw neuropathologic assessments and the raw factor scores ranged from −0.25 to 0.29 for the cored senile plaques, from −0.19 to 0.28 for the total senile plaques, and from −0.25 to 0.26 for the neurofibrillary tangles. None of the correlations were statistically significant. More important, there was no meaningful pattern of correlations where every factor score correlated with its respective anatomic region within a specific type of neuropathology.

It is important to note, however, that *raw* neuropathologic scores and the *raw* factor scores may be misleading because they do not take into account an individual's overall cognitive status or an individual's overall neuropathologic burden. There is considerable variability in both measures across individuals who are within the same DAT group. It is quite possible that such between-individual variability may mask any underlying relation between function and region. Consider, for example, an individual who had a relatively high level of premorbid intellectual functioning but initially showed cognitive decline due to AD-type neuropathology primarily in the frontal regions. Instead of being relatively low on the frontal measures, this individual might produce relatively modal performance on this measure compared with other individuals within the same DAT group because of the high premorbid level of functioning. In fact, because of the high premorbid level of functioning, it is likely that this individual will perform considerably higher than the modal performance on both the temporal and parietal measures. In this light, this person's performance on the frontal measure is unexpectedly low. Thus, it is possible that a measure that takes into account the overall cognitive performance across all three areas would be a more sensitive measure for detecting a relationship between cognitive function and neuropathologic burden in targeted regions.

The correlations between the neuropathologic proportional and the psychometric proportional factor scores are shown in table 6.

NFTs. As seen in the top third of table 6, there were no significant correlations between the NFT proportional scores and the proportional factor scores for the psychometric measures.

TSPs. The TSP density assessments included both the number of cored and noncored (neuritic) plaques and the number of diffuse plaques present. As shown in the center third of table 6, there were no significant correlations be-

Table 6 *Correlations between neuropathology proportional scores and proportional scores from the factor analysis*

Psychometric factor scores	Temporal*			Parietal	Frontal
	Mid	CA1	EC		
Neurofibrillary tangles					
Temporal	−0.11	−0.22	0.20	−0.03	0.13
Parietal	−0.10	0.28	−0.16	−0.05	−0.08
Frontal	0.23	−0.12	−0.01	0.10	−0.04
Total senile plaques					
Temporal	−0.11	−0.06	−0.06	0.04	0.13
Parietal	−0.04	0.13	0.09	−0.17	0.05
Frontal	0.16	−0.10	−0.05	0.16	−0.19
Cored senile plaques					
Temporal	−0.05	0.09	**−0.30** (p = 0.057)	0.15	0.07
Parietal	−0.02	−0.14	0.15	**−0.33** (p = 0.035)	0.27
Frontal	0.08	0.08	0.13	0.25	**−0.39** (p = 0.011)

Bold indicates predicted correlations.

* The three temporal areas for which neuropathology markers were measured were the superior and midtemporal gyrus (Mid), area CA1 of the hippocampus (CA1), and the perforant pathway and entorhinal cortex (EC).

tween the TSP proportional scores and the proportional factor scores for the psychometric measures.

CSPs. The results from the CSP analysis are quite different (see the bottom third of table 6). A pattern of significant correlations emerged for the CSP burden in particular regions of cortex with the neuropsychological factors predicted to be associated with those regions. More specifically, a greater proportional CSP burden in the perforant pathway/entorhinal cortex was related to lower proportional scores on measures associated with the temporal region, a greater proportional CSP burden in the parietal region was related to lower proportional scores on tasks subserved by the parietal region, and a greater proportional CSP burden in the frontal region was associated with lower proportional scores on measures thought to be dependent on frontal areas. All these correlations are in the predicted direction.

If considered independently, these correlations of $r = -0.30$, $r = -0.33$, and $r = -0.39$ appear only marginally statistically significant ($p = 0.057$, $p = 0.035$, and $p = 0.011$, respectively) due to the multiple statistical testing performed. However, it is important to note that the *pattern* of correlations emerged in the predicted direction. Moreover, the relatively low reliability (0.56) of the cored senile plaque counts would actually diminish the systematic relation found in these data. Thus, if anything, the strength of the correlations may be an underestimate of the real relation.

Discussion. The results indicated that individuals with DAT decline in functionally meaningful patterns that relate to specific cerebral cortical areas. The areas investigated were frontal, parietal, and temporal and the respective functions that they subserve are executive/mental control, visuospatial, and verbal/memory. Thus, at least concerning cored plaques, the initial predictions concerning the relation of cortical areas to psychometric performance were upheld.

It is intriguing to note that the predicted, nonrandom pattern emerged from the data in the CSPs. Of course, the relationship between CSP pathology in a particular area and breakdown of functional abilities that are subserved by those areas and measured on average 5.1 years earlier does not necessarily mean that CSPs actually caused the dysfunction. CSPs may be the result of a pathologic process that occurred years earlier when the psychometric testing actually took place. Some researchers believe that plaques progress from the immature diffuse stage to the neuritic stage and finally to the mature cored stage.[32] If this account of plaque progression is correct, then at the time in which the psychometric measures were taken there may have been diffuse plaques in the targeted areas that eventually became cored plaques in these same areas 5 years later at autopsy. Our findings that control participants with incipient AD dementia have a dramatic increase of cortical diffuse plaques support this account.[4] Although the present results are consistent with this possibility, further evidence is clearly needed regarding this important hypothesis.

Despite our inability to answer questions regarding etiology, some conclusions are suggested by these results. There appears to be a homogeneous pattern of ability in the nondemented control subjects when the selected set of psychometric tests is used. If control subjects do poorly on one of these tests, they are likely to perform poorly on the other tests. Conversely, good performance on one of these tests is related to good performance on the other tests. This homogeneous performance is possibly due to differences in sensitivity at different points in the measurement scale. In contrast to the nondemented control subjects, performance by individuals with DAT on the *same* set of tests is heterogeneous. When people with early DAT score poorly on one of these tests, they do not perform poorly on all tests but are more likely to perform poorly on tests that are subserved by the same anatomic region. This result implies that the presence of AD may place performance in a more sensitive region of the psychometric measures that reflect common cognitive operations.

A number of aspects of the current study reduced the possibility of finding evidence of a relation between neuropathologic burden and the functional measures. First, an average of 5.1 years passed between psychometric testing and death. Dementia and probably the neuropathologic burden were more severe and widespread at time of death than at the time of testing. Second, the marker density assessments were taken from constrained areas of cortex. It would be unrealistic to believe that every task analyzed relied on the specific region of cortex that was sampled for successful performance. For example, although a task may be "frontal," the area of frontal cortex sampled may not have been specifically involved in performing that task. Third, in constructing the neuropsychological battery, we were constrained by the tests already being used in the larger psychometric battery and could not take advantage of more recent advances in neuropsychological assessment. Fourth, we did not examine other markers associated with cognitive decline in AD such as synapse decline and cell loss that may have a strong relationship to psychometric performance. Moreover, the fact that distributed cerebral interactions are probably necessary for successful performance on psychometric tasks suggests that attributing a "focal" deficit with damage to a constrained cortical area is incomplete. In fact, it is precisely these noted difficulties that make the systematic relation between cored senile plaques and factor loadings on a priori hypothesized areas so compelling and deserving of further study.

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