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Cerebral blood flow patterns underlying the differential impairment in category vs letter fluency in Alzheimer's disease

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Abstract

Verbal fluency tasks are used to assess language functioning in Alzheimer's disease (AD), and performance typically declines as the disease progresses. However, several studies have shown that Category Fluency performance (produce words from a category) declines faster than Letter Fluency performance (produce words beginning with a certain letter), which is not the case for other dementias. The purpose of this study was to determine if each of these two types of fluency tasks was associated with different patterns of cerebral blood flow abnormality in AD. A resting, Xenon-inhalation regional cerebral blood flow measurement (^{133}Xe rCBF) and neuropsychological evaluation was administered to 25 patients with probable AD and 24 healthy elderly controls. Stepwise regression using rCBF measures as predictor variables was used to predict Category and Letter Fluency performance, in both a combined group of patients and controls, and in the patient group alone. Correlations were also computed between rCBF variables and the difference between normatively corrected scores on each task for each subject, which characterized the extent of the discrepancy between them. In full sample regressions, both Category and Letter Fluency were predicted by education and the decline in left inferior parietal flow, a focal AD-related deficit. Additional variance in Category fluency, however, was predicted by global mean flow, while additional variance in Letter Fluency was predicted by frontal flow. Within the patient sample, in turn, the primary predictor of Category Fluency was mean flow; the primary predictor of Letter Fluency was left-sided frontal flow. Analysis of the fluency difference score revealed that relatively greater impairment of Category Fluency was associated with more typical, AD-related deficits in posterior temporal and parietal perfusion. When the two were equivalently impaired, typical AD-related deficits were accompanied by marked deficits in frontal perfusion. These findings are consistent with the underlying neuropsychology of these tasks, and suggest that Category Fluency's stronger association to the most typical CBF deficits of AD account for its greater sensitivity to this disease. Letter Fluency deficits, on the other hand, carry significant information about the degree to which perfusion deficits have spread to frontal cortex.

Keywords: Verbal fluency; Alzheimer's disease; Cerebral blood flow

1. Introduction

Verbal fluency tasks are sensitive measures of language dysfunction in Alzheimer's disease (AD). However, several studies have shown that different types of fluency tasks (Category and Letter) are differentially impaired in AD. Category fluency tasks require subjects to produce, as rapidly as possible, words falling into a specific category (e.g., animals), while Letter Fluency tasks require subjects to produce words beginning with a specific letter.

Rosen [31] was the first to examine this discrepancy using an animal-naming Category task and C-F-L Letter task and found that mild AD patients produced more words to the category than to any of the letters, and that most productions came within the first 15 s of the task, a pattern similar to controls. Severe AD patients, in contrast, produced few words on either

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task, at a constant rate over a 60 s trial. These data suggested that Letter fluency might be more impaired earlier in the disease, since the raw number of productions on Letter fluency was lower and the task intrinsically harder. However, Wilson, et al. [40] showed that Category fluency was more significantly impaired in age-matched groups of dementia patients and controls, even if the most productive period of an extended-time trial was compared. Butters et al. [8] were the first to observe that correcting for appropriate age-group norms revealed that even mildly affected AD patients were significantly impaired on Category Fluency, but no different from healthy elderly controls on Letter Fluency. Rosser and Hodges [32] observed a similar pattern of normatively-corrected performance in their sample of AD patients. While these patients were impaired on both tasks relative to age-matched controls, their Letter Fluency performance was close to that of the normal control group. Rosser and Hodges also observed that this pattern of performance was somewhat specific to AD: patients with other types of dementia, such as Huntington's disease and progressive supranuclear palsy, were found to be equally impaired on each type of fluency task.

Monsch et al. [22] used this information to demonstrate that standardized Category Fluency performance was a much more efficient discriminator of patients with AD than standardized Letter Fluency, even for mildly impaired cases. They also confirmed [21] that neither were superior for discriminating other types of dementia. Devanand et al. [10], in turn, observed that Category Fluency was a stronger predictor of an ultimate diagnosis of dementia in a sample of questionable cases followed over time (87% probable AD); Letter Fluency was not significantly related to a final diagnosis of dementia.

At least one recent study found that this differential impairment of Category vs Letter fluency is not universal in AD: Suhr and Jones [35] examined groups of Alzheimer's, Huntington's and Parkinson's disease patients, as well as controls, and found no differences in patterns of fluency impairment. Another recent study [24] questioned the specificity of the association between AD and relatively poorer Category fluency, finding that patients with frontotemporal (FTD) dementia exhibit the same pattern. Most recent studies, though, suggest that Category Fluency is much more sensitive to the dementing changes of AD.

Neuropsychologically, Category Fluency is thought to be more sensitive because semantic abilities decline faster than the simple auditory and verbal–motor skills that are needed to perform a Letter Fluency task [8]. Compared with other dementias, there appears to be a selective breakdown in semantic knowledge in AD [16,30,37]. Pathophysiologically, however, these tasks may reflect dysfunction in dissimilar cortical areas. In lesion studies, Category fluency impairment is associated with damage to both temporoparietal and frontal cortical [23], while Letter Fluency impairment is classically associated with more circumscribed frontal lobe lesions [5,20]. Because the primary neuropathological deficits in AD tend to originate in the parietal and temporal lobes in most cases [13,25], Category Fluency could reasonably be expected to decline earlier. The one functional imaging study comparing activation during the two types of fluency performance in healthy controls, however, revealed a similar pattern of activation and deactivation in a network involving both left frontal cortex and superior temporal regions [11]. Also, a study by Goodwin, et al. [12] using Letter Fluency as an activation during SPECT in a sample of AD patients, revealed a circumscribed association between performance and left frontal activity at baseline, but a spreading of this association to incorporate temporopartietal regions on the right side during administration of the adrenergic α-2 receptor antagonist idazoxan, which impaired performance. Letter fluency performance appears to be affected, then, by regional brain activity beyond what is suggested by lesion studies. An association between regional pathophysiology in AD and differential fluency performance has not yet been shown.

The purpose of the present study was to determine if measures of regional cerebral blood flow derived from ^{133}Xe rCBF could be used to explain the superiority of Category Fluency tasks vs Letter Fluency tasks in discriminating AD patients. The relationship between performance on a Category Fluency (animal naming) and a Letter Fluency (CFL) task was examined in relation to blood flow indices that are associated with either AD or with declining fluency (e.g., declining frontal flows). Stepwise regression analysis was used to generate optimal equations for predicting fluency performance on each type of task, in both a combined sample of AD patients and controls, as well as in the patient group alone. Also, because Category and Letter Fluency are discrepant in AD, the difference between the scores was examined in relation to rCBF, to determine if patients who are relatively more impaired on one task (typically Category) or equally impaired on both show different patterns of perfusion deficit. Results are discussed in terms of the underlying neuropsychology of these tasks.

2. Methods

2.1. Subjects

The sample consisted of 25 probable AD patients (NINCDS-ADRDA criteria [19]) and 24 elderly controls, selected because they had been administered—

Table 1
Sample characteristics[a]

	AD Patients	Controls
N	25	24
Age	69.4 ± 10.2	65.8 ± 9.3
Sex ratio	76% Female	58.3% Female
	24% Male	41.7% Male
Racial composition	96% White	95.8% White
	4% African–American	4.2% African–American
Native language	64% English	75% English
Handedness	88% Dextral	87.5% Dextral
Education (years)	10.5 ± 3.9	14.5 ± 3.1***
Occupation rating	4.4 ± 1.3	5.4 ± 1.4**
Estimated premorbid IQ	101.5 ± 10.0	112.2 ± 7.9***
Current WAIS-R IQ	75.9 ± 11.8	112.6 ± 15.4***
Buschke selective reminding test (Total)	39.0 ± 14.9	113.8 ± 15.2***
Age of onset	66.1 ± 10.5	N/A
Duration of illness (years)	3.5 ± 1.7	N/A
Modified mini-mental state exam	32.0 ± 8.3	53.5 ± 3.2***
Estimated folstein mini-mental score	16.7 ± 4.6	28.6 ± 1.8***
Blessed dementia rating scale	8.9 ± 3.7	0.48 ± 0.56***
Systolic blood pressure (mm/Hg)	132.8 ± 16.2	135.9 ± 18.0
Diastolic blood pressure (mm/Hg)	75.9 ± 13.2	79.3 ± 8.5
End-tidal pCO_2 (%)	35.8 ± 3.9	37.1 ± 2.8

[a] *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

and had completed—both a Category and Letter Fluency task. Subjects in this study were drawn from a larger sample consisting of 62 patients with probable Alzheimer's disease and 42 controls who were participating in a longitudinal study of regional cerebral blood flow (rCBF) in AD (only the subsample analysed here were administered fluency measures). Data was taken from each subject's initial assessment.

All subjects with any history of significant medical, neurologic, or psychiatric disease were excluded from participation. Blood samples were drawn prior to imaging procedures, and a standard biochemical profile including hematocrit and hemoglobin concentrations was obtained. Subjects were excluded for any abnormal value. All patient subjects were outpatients (non-institutionalized).

Participants were assessed with regard to AD symptomatology using the modified Mini-Mental State Examination (mMMS: [18], from which a Folstein Mini-Mental State score can be derived), Blessed Dementia Rating scale (BDRS: [7]), and rCBF measurement, in addition to the fluency tasks administered. The characteristics of the patient and control samples are presented in Table 1. Subjects were also administered a battery of standard neuropsychological tasks; results of this assessment and correlations with cerebral blood flow data have been presented previously [15]. The WAIS-R and Buschke SRT data from this assessment are presented in Table 1, to illustrate the level of deficit in this sample.

The AD patients in this sample have a mean age of onset of 66 years, and span a wide range of dementia severity levels (MMS range = 8–24), with most appearing moderately demented. Controls, however, have higher estimated education and occupational achievement, and, as a result, a higher estimated premorbid intelligence level (which is estimated primarily from education and occupational status [4]). The AD patients exhibited a substantial decline in IQ, as well as severely impaired memory performance.

2.1.1. Verbal fluency assessment

Subjects were administered tests of Category Fluency (Animal Naming: [34]) and Letter Fluency (CFL: [6]), using standard procedures, and scores were transformed to *Z*-scores using age, sex (for Letter Fluency only), and education stratified norms (for Category [34]; for Letter [6]). Both performance measures, then, were converted to a common demographically-corrected metric for direct comparison.

2.1.2. Regional cerebral blood flow assessment

Subjects' rCBF was assessed using the ^{133}Xe inhalation technique using methods described in previous publications [2,14,15,29]. Data was obtained with subjects' supine, eyes closed, in a darkened, quiet room. Xenon was administered for one minute followed by an 11-minute acquisition period. Cortical counts in 32 brain regions (16 per hemisphere) were obtained with NaI (Tl) scintillation detectors using the NOVO Cerebrograph 32c. Perfusion was quantified using the gray-matter weighted Initial Slope Index (ISI) calcu-

lated via the M2 four-compartment model [27,28]. Subjects were carefully monitored during all procedures, and data carefully evaluated for artifact according to procedures established in our lab [26].

Blood pressure, end-tidal pCO_2, and respiratory rate were recorded by a computerized system. Neither blood pressure nor p_eCO_2 values differed between patients and controls (Table 1). Nonetheless, CBF values were p_eCO_2 corrected according to a procedure described in Maximillian, et al. [17] to eliminate artifact. Whole-cortex mean flow was computed, using the average of the absolute ISI estimates for each detector. An index of inferior parietal perfusion, the most sensitive measure of AD pathology derived from cortical CBF, was computed bilaterally and for each hemisphere by dividing the sum of flows to inferior parietal detectors (P1 and P3) by the sum of flows to perirolandic (C1) and occipital (O2) detectors. Both the mean flow and the PI are sensitive to deterioration in AD [29] and carry significant variance for intellectual decline in the disease [14]. Moreover, the extent of lateralized pathology observed in the PI predicts different types of neuropsychological performance impairment [15]. In addition to these typical AD-related rCBF measures, a general index of relative perfusion to frontal regions was calculated by dividing the average of the five frontal detectors (F1 to F5) in each hemisphere by the whole brain mean flow, similar to procedures used by Alexander, et al. [3]. This index was calculated bilaterally and again for each hemisphere separately. Because our preliminary analyses revealed that left and right sides of the brain made what appeared to be inverse contributions to the prediction of fluency, we also computed a Parietal Asymmetry score and Frontal Asymmetry score, to characterize the relationship between left and right sides for the PI's and Frontal Indices. These scores were computed using the following formula: $[L—R]/[L+R] \times 100$.

2.1.3. Statistical analyses

Fluency scores and rCBF measures were first examined for evidence of group differences using simple *t*-tests. Standardized fluency scores and blood flow indices were then correlated with one another.

Each of the fluency scores was then subjected to stepwise regression analyses in both (a) the combined sample of patients and controls ($N = 49$) and (b) the sample of patients only ($N = 25$) in order to determine if similar predictive equations could be obtained in both. Regressions were run in both the full sample and patient sample because score distributions may be attenuated in the patient sample, if patient subjects are uniformly impaired on a particular measure. A model developed in the combined group may, therefore, be informative about general associations between dependent and independent variables. However, the full sample regression could potentially be misleading if the two distinct groups produced a bimodal distribution of scores. These analyses were only run, though, after it was established that the distributions of pooled scores did not deviate from normality. One sample Komolgorov–Smirnov tests run on each variable were all non-significant, with *P*-values >0.8 in all cases (distributions closely approximating normality).

Table 2
rCBF index values and fluency scores[a]

	AD Patients	Controls
Parietal index	0.92 ± 0.06	$1.0 \pm 0.04^{***}$
Left parietal index	0.92 ± 0.06	$1.01 \pm 0.05^{***}$
Right parietal index	0.93 ± 0.08	$0.99 \pm 0.04^{**}$
Parietal asymmetry	-0.75 ± 3.7	$1.27 \pm 2.88^{*}$
Frontal index	1.04 ± 0.06	1.03 ± 0.03
Left frontal index	1.03 ± 0.05	1.02 ± 0.04
Right frontal index	1.04 ± 0.06	1.03 ± 0.04
Frontal asymmetry	-0.58 ± 1.88	-0.57 ± 2.08
Mean flow (ml/100 g/min)	41.8 ± 8.1	$47.4 \pm 8.3^{*}$
Category fluency (animals), *Z*-Score	-2.16 ± 1.13	0.45 ± 1.30
Letter fluency (CFL), *Z*-score	-1.15 ± 0.99	0.53 ± 1.04

[a] $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Criteria for stepwise entry into all equations was set at $P = 0.075$, slightly higher than the standard $P = 0.05$. This more liberal criteria was used because variables that, when considered by themselves, were weakly correlated with fluency measures often were more strongly correlated when evaluated in conjunction with others. To overcome suppression effects, *P*-to-enter was raised slightly. Final equations, though, contain only one variable with a *T*-value at $P > 0.05$.

In addition to all CBF indices ($=9$), age, education, and gender were included in the pool of potential predictors in each regression equation, to account for any residual demographic influences on test scores after normative adjustment. This pool of predictors is large for the number of subjects available, but incorporates the major potential sources of variation in fluency score. Final equations generally included only a small subset of these predictors.

Following regression analyses, a difference score was computed for each subject between standardized Category Fluency and Letter Fluency scores. The distributional properties of this difference score was then examined, and correlated with demographic, clinical severity, and rCBF data. Subjects showing relatively greater impairment on one task (Category Fluency more than 1 SD below Letter) and equivalent impairment on both tasks (less than 1 SD difference, with at least one fluency score below -1 SD from norms) were then compared.

Table 3
Zero order correlations of rCBF indices with category and letter fluencies[a]

	Full sample ($N = 49$)		AD Patients ($N = 25$)	
	Category	Letter	Category	Letter
Parietal index	0.62***	0.48***	0.37 ([a]$P = 0.069$)	0.02
Left parietal index	0.67***	0.58***	0.43*	0.25
Right parietal index	0.45***	0.28*	0.29	−0.10
Parietal asymmetry score	0.28*	0.36**	0.09	0.36 ($P = 0.073$)[a]
Frontal index	−0.08	0.12	−0.25	0.29
Left frontal index	−0.01	0.13	−0.08	0.38 ($P = 0.064$)[a]
Right frontal index	−0.10	0.09	−0.38*	0.15
Frontal asymmetry score	0.10	0.03	0.44*	0.33
Mean flow (ml/100 g/min)	0.56***	0.36**	0.46*	0.31

[a] *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; †$P < 0.10$.

Because non-native English speaking subjects comprised more than 25% of both the patient and control samples, all analyses were rerun with these subjects excluded. Since their exclusion had virtually no effect on the results (with the exception of reducing statistical power slightly), data on the complete sample are reported. Also, because results were not altered by the exclusion of non-dextral subjects ($N = 3$), they are included in all analyses as well.

3. Results

3.1. Comparison of fluency and rCBF scores in AD patients and controls

AD Patients and Controls differed in terms of their fluency and rCBF indices in predictable ways (Table 2). Patients were impaired on both fluency tasks relative controls. However, as in previous studies, AD patients were relatively more impaired on Category Fluency, with their scores on this measure falling a full standard deviation (Z-unit) below their Letter Fluency scores ($t(24) = -4.90$, $P < 0.001$). This difference was equivalent in both males ($t(5) = -3.35$, $P < 0.020$) and females ($t(18) = -4.00$, $P = 0.001$) and means were equivalent in each group (Gender × Task interaction, $F(1,23) = 0.07$, $P = 0.791$). As in previous studies, Category Fluency was a more efficient predictor of disease status: a cut score at −1.5 SD identified 72% of AD patients and 4.2% of controls, while a similar cutoff identified only 40% of AD patients with an identical false positive rate, 4.2%, for controls.

Both indices were equivalently correlated with dementia severity as measured by the Mini-Mental State score ($r = 0.51$, $P = 0.009$ for Category; $r = 0.48$, $P = 0.019$ for Letter), but neither were significantly correlated with the Blessed Dementia Scale (BDRS), illness duration, or age at onset. Fluency scores, then, do not appear differentially sensitive to these standard measures of severity. If Mini-Mental State scores are expressed as the degree of decline from age, sex, and educationally stratified norms [9], however, Category Fluency was more strongly associated with this 'decline' score ($r = 0.53$, $P = 0.006$; with Letter Fluency $r = 0.34$, $P = 0.098$).

The rCBF indices differ between AD patients and controls in typical ways. Patients had significantly lower Left and Right PI's, as well as lower mean flow. Patients also had significantly lower Parietal Asymmetry scores, indicating that left-sided flows are relatively reduced in this patient sample. Frontal Indices, however, did not differ between the groups, nor did Frontal Asymmetry scores.

3.2. Zero-order correlations between fluency and rCBF scores

Zero-order correlations between fluency scores and CBF indices are presented in Table 3. In the full sample, these correlations reflect differences between the groups on both the fluency and CBF measures. The PI's and mean flow showed uniformly strong associations to both types of fluency performance. The Parietal Asymmetry score was also positively associated with both types of fluency, indicating that relatively reduced left sided flow was more important to the prediction of fluency decrements.

In the AD sample alone, Category Fluency remained strongly associated with standard AD measures, although the association to PI was now only significant with the Left PI. Frontal flows now also play a role in prediction of Category Fluency, in the form of a negative association to right sided flow and a positive association to Frontal Asymmetry. Associations to Letter Fluency are now only marginal, but include cor-

Table 4
Summary of stepwise regressions

Variable entered (entry order)	β	T	$P(T)$	Partial correlation
Full sample ($N = 49$); predicting Category Fluency				
1. Left PI	0.48	4.57	0.000	0.56
2. Mean flow	0.40	3.96	0.001	0.51
3. Education	0.20	2.01	0.050	0.29
Equation statistics: Multiple $R = 0.78$; $R^2 = 0.61$; $F = 22.98$, $P < 0.001$				
Full sample ($N = 49$); predicting Letter Fluency				
1. Left PI	0.57	4.82	0.000	0.58
2. Education	0.29	2.52	0.016	0.35
3. Frontal index	0.24	2.09	0.042	0.30
Equation statistics: Multiple $R = 0.70$; $R^2 = 0.49$; $F = 14.42$, $P < 0.001$				
AD sample ($N = 25$); predicting Category Fluency				
1. Mean flow	0.48	3.03	0.006	0.55
2. Right frontal index	−0.81	−3.26	0.004	−0.58
3. Left frontal index	0.47	1.90	0.072	0.38
Equation statistics: Multiple $R = 0.70$; $R^2 = 0.49$; $F = 6.75$, $P = 0.002$				
AD sample ($N = 25$); predicting Letter Fluency				
1. Left frontal index	0.65	3.42	0.003	0.59
2. Left PI	0.57	2.97	0.007	0.54
Equation statistics: Multiple $R = 0.62$; $R^2 = 0.39$; $F = 6.94$, $P = 0.005$				

relations with the Left Frontal Index and Parietal Asymmetry.

These zero-order correlations are suggestive of differences in the association of these two fluency measures to CBF, in that Category Fluency was more strongly correlated with typical AD perfusion deficits. Intercorrelation of these indices, however, could mask contributions to variance in the test scores. The independence of these relationships was explored more fully in regression analyses.

3.3. Prediction of fluency scores from rCBF data in combined sample

Stepwise regressions using all subjects ($N = 49$) with rCBF indices and demographic measures as independent variables and each of the two fluency scores as dependent variables produced the results summarized at the top of Table 4. For Category Fluency, the regression was completed in three steps and produced an equation with three variables, the Left Parietal Index, mean flow and education. For Letter Fluency, an equation with three variables was also produced in three steps, and also included the Left Parietal Index and education, but the Frontal Index in place of mean flow.

In each case, the Left PI was the first variable entered, which is predictable given that both patients and controls are included in the sample. Left PI characterizes both the pathophysiology of the AD group as well as the AD group's poorer performance on both fluency tasks. Education was entered even though fluency scores have already been normatively adjusted for education level, but this variable also differentiates the samples. The remaining variance in each task, however, is predicted by different flow measures. For Category Fluency, additional variance is predicted by mean flow, a measure of diffuse reduction of cortical perfusion. Additional variance in Letter Fluency, on the other hand, is predicted by frontal flow, an area of the brain linked to both types of fluency task, but more specifically to Letter Fluency tasks. The models generated by these full sample regressions, then, suggest differing sensitivity to flow reductions that are typically associated with AD.

3.4. Prediction of fluency scores from rCBF data in AD patient sample

Stepwise regressions were also computed in the AD group alone, to compare equations with those obtained in the full sample. Summaries of these analyses are presented at the bottom of Table 4. For Category Fluency, an equation including Mean Flow, the Right Frontal Index (negatively weighted) and the Left Frontal Index is generated; while for Letter Fluency, an equation with the Left Frontal Index and Left Parietal Index was produced.

In each case, the first variable entered was no longer the Left Parietal Index. Though this variable clearly

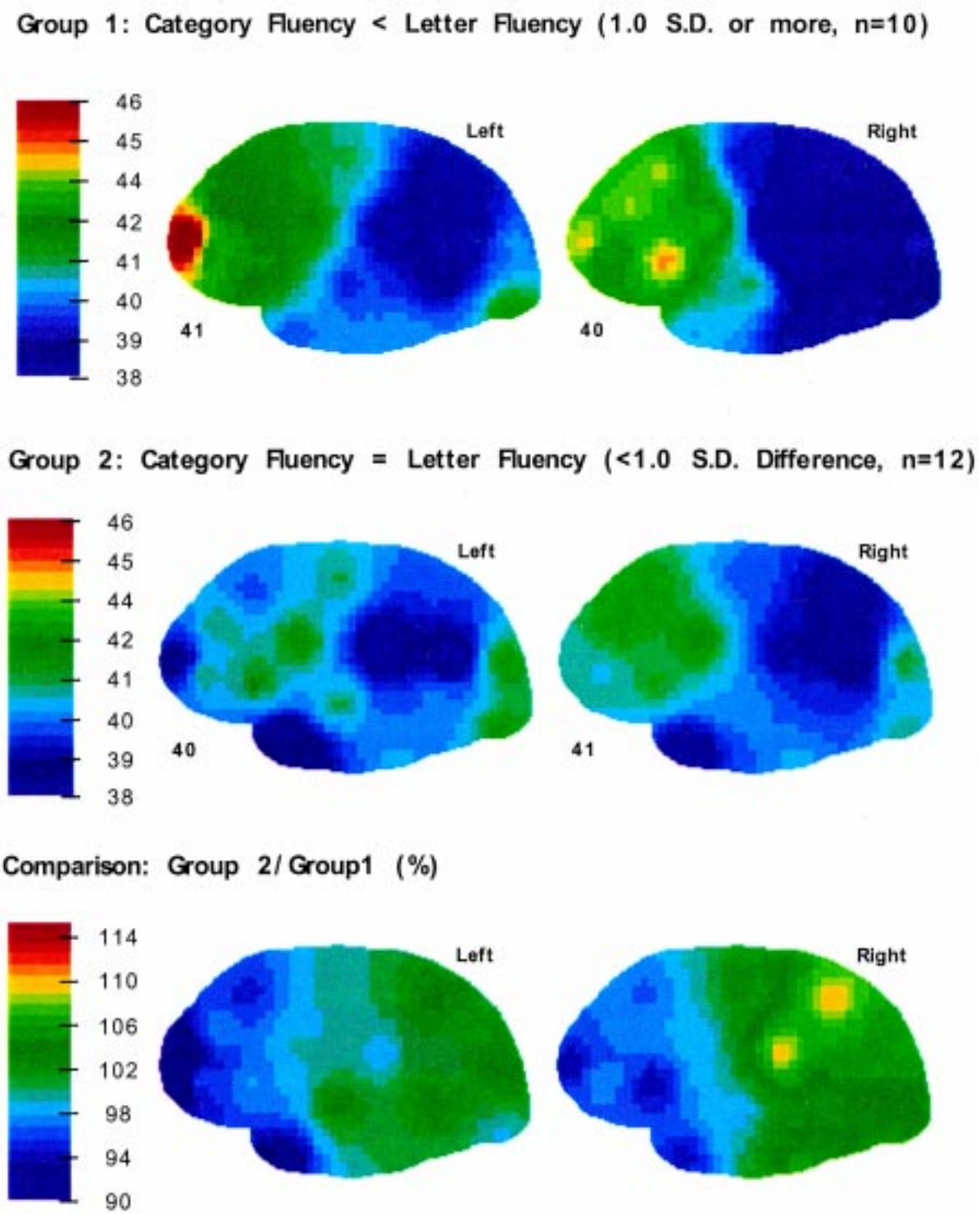

Fig. 1. Cortical perfusion topographies in AD subjects relatively more impaired on Category than Letter Fluency (Group 1), approximately equally impaired on both (Group 2), and the comparison between the two. Those equally impaired on both show comparative reductions of perfusion throughout the frontal cortex. Red indicates higher flow, blue lower. All values are pCO_2-corrected.

discriminates between AD patients and controls, it was no longer as prominent in the patient-only group. Also, education was no longer included in either equation, suggesting that its value in the full sample was based on education differences between patients and controls, rather than its association to already normatively corrected scores. On the other hand, the first variable entered in both equations was either the same (mean flow for Category) or similar (Left Frontal Flow for Letter) to that in the full-sample re-

gression that explains additional variance beyond Left PI and education. The models developed in the full sample regressions, then, illustrate a contrast in the strongest predictors of the unique variance in each.

In the case of Category Fluency, remaining variance in the patient sample is explained by frontal flows, as might be expected for a fluency task. Note that the Right Frontal Flow is entered first and negatively weighted in the equation. The next variable entered, however, is Left Frontal Flow which predicts positively. The negatively-weighted right sided contribution appears contradictory, but can be better understood if the Frontal Asymmetry score is substituted for both of the lateralized frontal measures. An equation containing only two predictors, mean flow and the Frontal Asymmetry score, performs almost as well as the three variable equation: Multiple $R = 0.61$; $R^2 = 0.38$; $F = 6.68$, $P = 0.005$ (r_{Partial} for Frontal Asymmetry $= 0.47$, $T = 2.45$, $P(T) = 0.023$). Thus, a plausible case can be made for the contribution of frontal asymmetry to declining Category Fluency, rather than a confusing association to rising contralateral frontal flow.

In the case of Letter Fluency, the second step in the AD sample regression included the Left PI, and the final equation was very similar to that in the full sample. The predictors were both lateralized and their entry order reversed, but the general association to focal, disease-related inferior parietal flow deficits, and frontal flow deficits remained.

These patient-only regressions suggest that Category Fluency is only related to diffuse perfusion changes in AD (mean flow), while Letter Fluency is related to more focal AD-related changes in left inferior parietal flow. Letter Fluency would appear to be a better indicator of specific AD pathology, then, by virtue of its association to the PI. However, if mean flow is removed from the pool of predictors of Category Fluency, it is replaced by the Left PI in an equation including Left PI and Frontal Asymmetry (Multiple $R = 0.60$; $R^2 = 0.36$; $F = 6.25$, $P = 0.007$; r_{Partial} for Left PI $= 0.45$, $T = 2.39$, $P(T) = 0.026$; r_{Partial} for Frontal Asymmetry $= 0.47$, $T = 2.47$, $P(T) = 0.022$). Category Fluency, then, is predicted by what appears to be shared variance between mean flow and Left PI (the significant zero order correlations between each and Category Fluency become non-significant if the other is partialled out). No similar association can be demonstrated between Letter Fluency performance and mean flow.

3.5. Predictive value of fluency score differences

In the patient sample, Category Fluency performance on average was a full standard deviation below Letter Fluency, but subjects varied around this mean, with some showing very little difference. This difference ranged from −3.05 SD to +0.49 SD, with a distribution that was mildly negatively skewed (skewness $= -0.44$), but approximately normal (Komolgorov–Smirnov statistic $Z = 0.787$, $P = 0.566$).

Correlations with demographic and clinical severity measures revealed that those with a smaller difference tended to be older ($r = 0.45$, $P = 0.024$ with difference), but otherwise demographically very similar (correlations with other demographic and clinical severity measures non-significant). When the difference between Category and Letter Fluency performance was associated with perfusion indices, it was uncorrelated with mean flow ($r = 0.21$, $P = 0.319$), and weakly correlated with the PI ($r = 0.38$, $P = 0.060$), but strongly and negatively correlated with the Frontal Index ($r = -0.55$, $P = 0.004$), on both the left ($r = -0.45$, $P = 0.026$) and right ($r = -0.57$, $P = 0.003$) sides. These correlations were significant as well among those who are impaired (normed score < -1.0 SD) on at least one fluency task ($r = -0.61$, $P = 0.003$ with Frontal Index; $r = -0.56$, $P = 0.007$ with Left Frontal; $r = -0.57$, $P = 0.005$ with Right Frontal). As frontal flows decline, then, the difference between the two fluency measures diminished. This association remained significant even when age was partialled out (with bilateral Frontal Index $r_{\text{Partial}} = -0.57$, $P = 0.007$; with Left $r_{\text{Partial}} = -0.51$, $P = 0.019$; with Right $r_{\text{Partial}} = -0.57$, $P = 0.010$).

The association of this difference score to reduced frontal flow may be illustrated by dividing the patient sample into those who are significantly more impaired on Category than Letter Fluency (Group 1, $N = 10$), and those who are not as differentially impaired but impaired on at least one of the Fluency measures (Group 2, $N = 12$). These groups did not differ significantly on any demographic, clinical severity, or non-frontal flow measure except Letter Fluency ($t(20) = -4.20$, $P < 0.001$; Group $1 = -0.58 + 0.85$, Group $2 = -1.90 + 0.60$; Groups were equally impaired on Category Fluency, approximately −2.5 SD). Frontal Flow differences, using this crude division of the sample, were marginally different bilaterally ($t(20) = -1.99$, $P = 0.061$), borderline significantly different on the left side ($t(20) = -2.06$, $P = 0.053$), and tending in this direction on the right ($t(20) = -1.70$, $P = 0.106$). These differences are illustrated in Fig. 1.

If the standardized fluency difference score is subject to the stepwise regression procedures described above, an equation including only the Frontal Flow Index and Parietal Asymmetry is obtained (Multiple $R = 0.69$; $R^2 = 0.47$; $F = 8.58$, $P = .002$; r_{Partial} for Frontal Index $= -0.65$, $T = -3.75$, $P(T) = 0.001$; r_{Partial}

for Parietal Asymmetry = −0.41, $T = -1.96$, $P(T) = 0.065$).

4. Discussion

In this study, we are able to demonstrate a complex double dissociation between cerebral blood flow patterns that underlie performance on two different types of fluency tasks in the context of Alzheimer's disease. Category Fluency, which has been shown to be more sensitive to early deterioration in AD, is associated with measures of both the focal pathophysiology of AD (reduction in inferior parietal flow), as well as with the more diffuse reduction in flow that generally accompanies these focal changes. Letter Fluency performance, on the other hand, is associated with the focal AD deficit in flow as well as with a decline in frontal perfusion that is less characteristic of typical AD cases. Category Fluency, then, appears to be a more sensitive, but less specific correlate of AD-related perfusion deficits, while Letter Fluency is less sensitive, but more specific for lateralized focal deficits in inferior parietal and frontal regions.

In previous studies [14,15], we have demonstrated that both the index of inferior parietal flow as well as the mean flow make independent contributions to cognitive decline in AD. Thus, Category Fluency's association with both—or at least with some shared variance in both—and Letter Fluency's primary association with only one suggests the principal reason that Category Fluency is a better discriminator of early AD. Letter Fluency, on the other hand, may reflect the degree to which blood flow abnormalities have progressed to the frontal lobes. When Category Fluency alone is impaired, or significantly more impaired than Letter Fluency, perfusion abnormalities may be restricted to posterior brain regions. When both Category and Letter Fluency are impaired, as they are in other dementias such as Huntington's disease and progressive supranuclear palsy, blood flow deficits extend to the frontal lobes, the same regions affected by these other dementias.

Both fluency measures show stronger associations to declining cerebral perfusion on the left side (in the AD sample especially), further supporting our conclusion from an earlier analysis of this data [15] that lateralization of perfusion deficits in AD has ramifications for the types of deficits observed. Moreover, and surprisingly, the pattern of deficits associated with Letter Fluency impairment is strikingly similar to the patterns of activation found in functional imaging studies using this task. Studies using ^{15}O PET [10] and ^{133}Xe cerebrography [38,39] have each shown a pattern of left frontal activation and left superior temporal deactivation during Letter Fluency tasks, suggesting that these two regions are functionally linked during performance. Another study using split dose $^{99\ m}$Tc-HMPAO SPECT and comparing Letter Fluency performance with simple counting also showed deactivation of left superior temporal regions, but no differences in left frontal activation [33]. An additional SPECT study of healthy controls without a comparison task showed correlative associations between performance and left frontal activation, but no associations with any other region [12]. While these SPECT studies contained other manipulations that may have reduced power to detect relationships between perfusion and task performance, this literature is consistent in identifying left frontal and superior temporal regions—which are adjacent to the inferior parietal regions affected by AD—as critical to Letter Fluency performance. In the data reported here, the joint degree of dysfunction in these regions predicted impairment on this task.

Category fluency is also associated with both activity [11] and, as demonstrated here, dysfunction in these same brain regions, but its reliance on semantic information appears to make it more sensitive to other types of cortical pathology. This pathology appears to be non-specific, but a recent study by Tranel, Damasio, and Damasio [36] suggests that semantic stores, particularly for information about animals, are located in regions of the mesial temporal lobe and temporo-occipital junction. These regions, adjacent to primary sites of AD-related neuropathology, especially the hippocampus, are not visualizable with 2-dimensional cortical imaging, and flow reductions to them may only be manifest as diffuse effects across wide areas of the lateral cortex. This is, perhaps, one reason why Category Fluency, especially for animals, is such a sensitive measure of AD pathology, and why widespread posterior flow reductions are found in those who are selectively impaired on this task.

Results here should be interpreted with some caution since the sample sizes are relatively small for the number of predictor variables being entered into stepwise procedures. In addition, there is a significant amount of overlap in the variance contained in various predictors. In many cases, partial correlations are much higher than raw correlations. With variables that are so overlapped, and relatively small sample sizes, spurious associations can occur, although it can also be argued that the underlying associations observed here would have to be quite robust to overcome redundancy. In addition, findings here, derived from planar, 2-dimensional cortical imaging, must be replicated with tomographic, 3-dimensional imaging techniques.

Despite these limitations, these data shed some light on discrepant findings regarding the specificity of relative Category Fluency impairment in AD. Suhr and Jones [35], who found a lack of differential impairment in AD, studied a sample that was relatively old (mean

age = 75.5 years). In this study, we observed that increasing age was related to an equilibration of impairment level, hypothetically because frontal perfusion declines with age. Similarly, the study which found relatively greater impairment of Category Fluency performance in both AD and frontotemporal dementia [24] studied an FTD sample whose parietal perfusion was reduced to the levels of AD. This reduction in posterior flow, atypical for FTD [1], would tend to impair Category Fluency as it does in AD.

Overall, these data suggest that previously hypothesized differences in the cortical mechanisms underlying each of the two types of fluency tasks contribute to their differential predictive value in AD. Category Fluency's sensitivity to cortical pathology that may reflect the deterioration of semantic stores, and its association with frontal and temporoparietal cortical integrity, make it a strong correlate of typical AD-related perfusion deficits. Letter Fluency's more specific association with left frontal and left temporoparietal regions make it a superior localizing measure. Therefore, information from both types of fluency tasks may be combined to gauge the nature and extent of underlying cerebral pathology in AD. Future studies are encouraged to investigate the predictive value of performance discrepancies in separate AD samples.

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