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A functional neuroimaging study of appetite loss in Alzheimer's disease

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Abstract

Background: Alzheimer's Disease (AD) is frequently associated with changes in appetite. This study investigated the relationship between regional cerebral perfusion and appetite loss in AD.
Methods: 64 patients with possible or probable AD were characterized as being with ($n=22$) or without ($n=44$) appetite loss based on the Neuropsychiatric Inventory (NPI) Appetite subscale. 99mTc-ECD SPECT scans were coregistered to a standardized template in Talairach space generating mean ratios of uptake referenced to the cerebellum. Regions of interest (ROIs) included anterior cingulate cortex (ACC), middle mesial temporal cortex (MTC-m), inferior mesial temporal cortex (MTC-i), insula (INS), orbitofrontal cortex (OFC) and thalamus–hypothalamus (THAL).
Results: Backward stepwise logistic regression analysis of these ROIs showed hypoperfusion in the L-ACC ($p=0.015$) and L-OFC ($p=0.015$), relative sparing of perfusion in the R-ACC ($p=0.010$), R-OFC ($p=0.010$) and L-MTC-m ($p=0.006$), and greater anxiety ($p=0.005$) independently predicted loss of appetite ($\chi^2=22.24$, $p=0.001$, Nagelkerke $R^2=0.41$).
Conclusions: Hypoperfusion in the left anterior cingulate and left orbitofrontal cortices, and relative sparing of perfusion in the right anterior cingulate, right orbitofrontal and left middle mesial temporal cortices emerged as predictors of appetite loss in this sample of patients. These findings are consistent with impairments in the extrinsic motivational pathways of eating and impaired reward value of food as components of appetite loss in AD.

Keywords: Alzheimer's Disease; Appetite disturbance; SPECT

1. Introduction

Though Alzheimer's Disease (AD) is primarily described as a cognitive disorder, the non-cognitive components of this illness are important in function, outcome and management. These components are collectively called the behavioral and psychological symptoms of dementia (BPSD) and include appetite disturbances, most commonly appetite loss [1,2]. Since Alzheimer's first description of Auguste D, it has been noted that AD patients lose weight and this weight loss can be remarkable [3,4]. Approximately 40% of AD patients at all stages have weight loss [5]. Cross sectional studies have consistently shown that demented elderly weigh less and have lower body mass indices (BMI) than non-demented elderly [6]. Longitudinal studies have shown that weight loss frequently occurs in the first stages of disease [7] and may precede a clinical diagnosis of dementia by several years [8,9]. In a 10-year prospective study, higher BMI at baseline was associated with a decreased risk of AD, and low BMI predated dementia onset. It is postulated that common factors lead to both AD and weight loss and low BMI may be a phenotypic marker of dementia [10].

Despite the establishment of appetite loss as a significant feature of dementia, the neuroanatomical correlates remain

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to be elucidated. It has been hypothesized that a change in eating behaviors in dementia reflects involvement of an integrated network including the ventral (orbitobasal) frontal lobe, temporal pole, amygdala, insula and orbitofrontal cortex (OFC) [11]. Neuroimaging studies have implicated mesial temporal cortex (MTC) atrophy [12] and anterior cingulate cortex (ACC) hypometabolism [13] with low BMI in dementia. Neuroimaging studies in non-demented populations have looked at the motivation to eat and related it to intrinsic mechanisms related to hunger and satiety as well as extrinsic mechanisms based on appetitive incentive values of individual foods. Regions involved include the hypothalamus, amygdala, insula, medulla, striatum, ACC, and temporal cortex [14].

Our objective was to investigate regional changes in brain perfusion associated with appetite loss in AD. Using single-photon emission computed tomography (SPECT), we hypothesized that appetite loss in AD is associated with dysfunction in circumscribed frontal and temporal circuits.

2. Methods and materials

2.1. Participants

The Sunnybrook Dementia study is a longitudinal study of patients with AD and other dementias. Patients who met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria for possible or probable AD [15] were included in this substudy. BPSD and eating behavior in particular was assessed via the appetite/eating disorders subscale of the Neuropsychiatric Inventory (NPI) [16]. Patients were characterized as having appetite loss (AL) only if they scored 3 or greater on the appetite/eating disorders subscale of the NPI and caregivers specifically endorsed a poor appetite; otherwise patients were characterized as having no appetite loss (NAL). SPECT scans were performed within 3 months of the behavioral assessment.

2.2. SPECT scans and regional perfusion ratios

The SPECT scans were obtained with a triple detector gamma camera (Prism 3000XP; Philips Medical Systems Inc, Cleveland, Ohio) 30 min after injection of 0.02 Ci (740 Mbq) of the radiopharmaceutical technetium Tc 99 m ethyl cysteinate dimer. Scans were reconstructed by ramp-filtered back projection, followed by a 3-dimensional postfilter (Wiener filter, multiplier 1.0). Reconstructed images were coregistered to a standardized SPECT template in Talairach space, generating mean rations of uptake in 79 regions of interest (ROIs) referenced to the cerebellum, thereby providing regional perfusion ratios for each patient. Details of this procedure have been published elsewhere [17]. Technetium Tc 99 m ethyl cysteinate dimer uptake is approximately proportional to regional cerebral blood flow (rCBF) [18] thus allowing a semi-quantitative measure of rCBF when referenced to a standard region, which in this case was the cerebellum.

2.3. Regions of interest

Six bilateral regions of interest were chosen *a priori* on the basis of their previous associations with appetite and weight loss in AD and non-AD patients: the anterior cingulate cortex (ACC) [13,14], the middle and inferior mesial temporal cortices (MTC-m and MTC-i) [12,19], the hypothalamus (THAL) [14], the orbitofrontal cortex (OFC) [14]

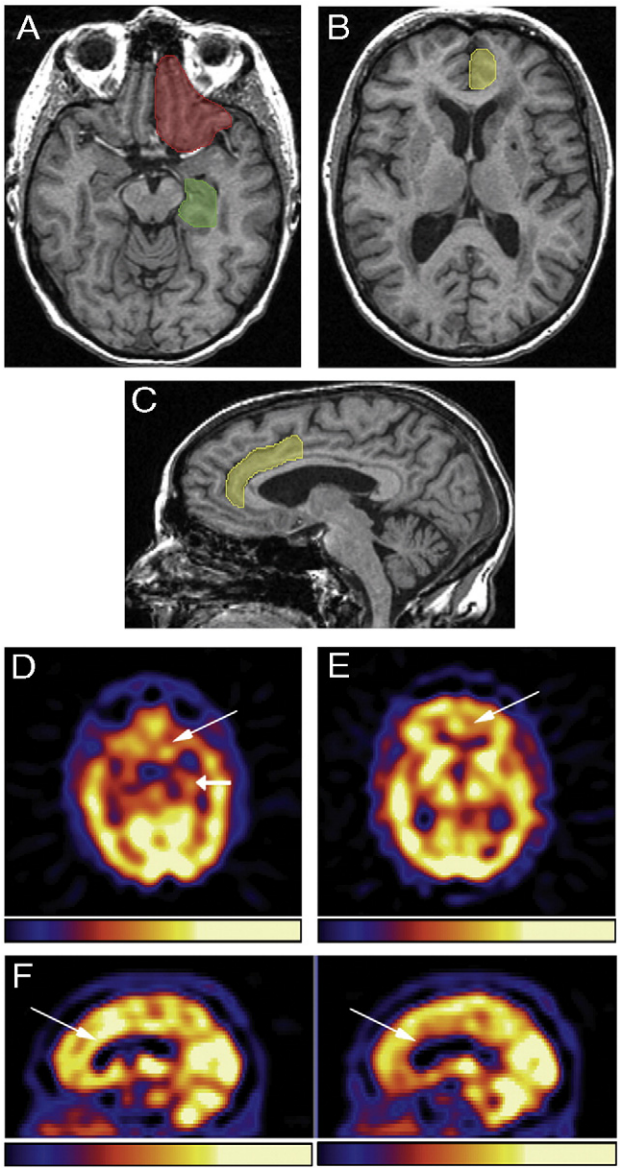

Fig. 1. Panel A: Representative coregistered MRI scan indicating the location of the L-OFC (red) and L-MTC-m (green) ROIs on SPECT. Panels B and C: Representative coregistered MRI scans (axial, B; sagittal, C) indicating the location of the L-ACC ROI on SPECT. Panel D: Representative SPECT scan from a patient with appetite loss, indicating hypoperfusion to the L-OFC and relative sparing of perfusion to the L-MTC-m. Panel E: Axial view of a representative SPECT scan from a patient with appetite loss, indicating hypoperfusion to the L-ACC. Panel F: Sagittal views of a representative SPECT scan from a patient with appetite loss, indicating hypoperfusion to the L-ACC (right panel), as compared to the R-ACC (left panel).

Table 1
Baseline demographic characteristics and medication use

	No appetite loss (n=42)	Appetite loss (n=22)	p-value*
Age	77.4±7.0	75.8±9.4	0.45
Male gender	38.1%	63.6%	0.05
MMSE	23.9±3.0	22.6±6.7	0.39
Cognitive enhancers	43.5%	57.1%	0.53
Antidepressants	4.3%	14.3%	0.36
Antipsychotics	4.3%	0%	0.58

MMSE=Mini Mental State Examination, NPI=Neuropsychiatric Inventory. All data are means±SD * based on independent samples t-tests for continuous data and chi-square tests for categorical data.

and the insula (INS) [14]. The volumes of the anterior cingulate ROIs were 12.29 cm^3 (right) and 11.65 cm^3 (left) and included the combined ventral (BA 25), medial (BAs 24/32/33), and dorsal (BAs 24/32/33) regions of the anterior cingulate. The volumes of the middle medial temporal ROIs were 13.58 cm^3 (right) and 13.46 cm^3 (left) and included the hippocampus, parahippocampus, and posterior amygdala (BAs 28/35/36). The volumes of the inferior medial temporal ROIs were 11.87 cm^3 (right) and 8.80 cm^3 (left) and included the posterior hippocampus, posterior parahippocampal gyri, and fusiform gyrus (BAs 28/35/36/37). The volumes of the orbitofrontal ROIs were 11.73 cm^3 (right) and 14.37 cm^3 (left) and included the orbital frontal gyrus (BA 11). The volumes of the insula were 15.53 cm^3 (right) and 12.65 cm^3 (left). The volumes of the hypothalamus/thalamus ROIs were 10.73 cm^3 (right) and 10.75 cm^3 (left).

In order to establish comparability between the AL and NAL groups, demographic characteristics, psychotropic medication use, and the individual neuropsychiatric symptoms assessed by the NPI were compared between appetite groups using independent samples t-tests or chi-square tests. Because there was a significantly greater proportion of males in the AL group, and because AL patients tended to display more anxiety than NAL patients, gender and NPI anxiety scores were included as covariates in subsequent analyses. Multivariate Analysis of Covariance (MANCOVA–SPSS version 14.0; SPSS Inc, Chicago, Ill) was used to compare rCBF in the ROIs between AD patients with or without AL, with gender and NPI anxiety scores as covariates. Next, logistic regression with forced entry of gender, NPI anxiety scores and rCBF to all ROIs, with subsequent stepwise removal of nonsignificant ROIs ($p>0.05$), was performed until only the best predictors of appetite loss remained in the final model. A subanalysis was repeated in only those patients meeting criteria for probable AD. A secondary backward stepwise linear regression was also performed to assess any link between rCBF changes and the severity of appetite loss in AD. rCBF to all ROIs, as well as gender and NPI anxiety scores were entered in a single step and the variables contributing least to the model were removed in subsequent steps until only significant variables ($p<0.05$) remained.

2.4. Image analyses by statistical parametric mapping

Data analysis was also conducted using statistical parametric mapping (SPM) software (SPM5; Wellcome Department of Cognitive Neurology, London, England) running under the MATLAB environment (MATLAB version 6.0; The MathWorks Inc, Natick, Mass). SPM5 provides p-values corrected for multiple comparisons using random field theory. Voxel level p-values corrected for multiple comparisons were used for statistical inference. The SPM approach was used to identify functionally specialized brain regions associated with appetite loss. As the SPM analyses did not directly test the ROI hypotheses of the study, they were exploratory.

Images in each group were normalized (transformed) into a standardized stereotaxic space using a template image supplied by SPM5. This template image conforms to the Montreal Neurological Institute template. These normalized images were then smoothed to accommodate intragroup subject differences in anatomy using an isotropic Gaussian kernel of 12 mm. Resulting coordinates were converted into Talairach space [20] using the method of Brett et al. [21] and then superimposed onto the T1 template of SPM to confirm that the localization was accurate. MANOVA was used to compare the smoothed images in the appetite loss and non-appetite loss groups. Statistically significant differences in regional perfusion were analyzed by setting opposite contrasts for each group.

3. Results

3.1. Demographics

Demographic data are presented in Table 1. Sixty-four patients with AD were included in this analysis (30 M/34F, age 76.8±7.9 years). Patients had mild-to-moderate AD with MMSE scores of 23.5±4.6. Forty-seven patients were diagnosed with probable AD, while 17 were diagnosed with

Table 2
NPI subscales in appetite loss and non-appetite loss patients

	No appetite loss n=42	Appetite loss n=22	p-value
NPI delusions	0.88±2.33	0.55±1.74	0.56
NPI hallucinations	0.05±0.31	0.05±0.21	0.98
NPI agitation	0.86±1.39	0.86±1.58	0.99
NPI depression	0.83±1.21	1.59±2.22	0.15
NPI anxiety†	0.81±2.02	2.27±3.55	0.08
NPI elation/euphoria	0.07±0.34	0.09±0.43	0.84
NPI apathy/indifference	1.55±2.67	2.73±3.07	0.12
NPI disinhibition	0.26±0.59	0.95±2.08	0.14
NPI irritability/lability	1.50±2.18	1.41±2.86	0.89
NPI aberrant motor behaviour	0.98±2.55	1.91±3.39	0.22
NPI night time behaviours	0.90±2.31	1.68±2.82	0.24
NPI appetite/eating disorders*	0.48±0.86	6.45±2.65	<0.0005
NPI total*	9.17±11.38	20.55±15.91	0.002

NPI=Neuropsychiatric Inventory * Indicates significant (<0.05) or trends towards significant †(<0.10) p-values using independent samples t-tests, adjusting for unequal variances between groups where necessary.

possible AD. Twenty-two patients were characterized as having AL and 42 as NAL. While there was a strong trend for a greater proportion of males in the AL group (63.6% v.s. 38.1%, $p=0.05$), there were no significant differences between groups with respect to age and cognitive status (Table 1; $p>0.05$). There were no significant differences in the proportion of AL and NAL patients treated with cognitive enhancers, antidepressants, or antipsychotics at the time of the scan. Besides having significantly higher scores on the NPI-appetite subscale (Table 2; $p<0.0005$), AL patients displayed a trend for having more anxiety than NAL patients (Table 2; $p=0.08$). AL and NAL patients were otherwise comparable on the remaining NPI subscales (Table 2).

3.2. Predictors of appetite loss in AD

Mean rCBF for the ROIs are presented in Table 3. MANCOVA considering gender and anxiety as a covariates and comparing patients with and without AL on rCBF values showed a trend towards a significant effect of appetite group on rCBF ($F_{12,49}=1.82$, $p=0.07$), with no significant effect of gender ($F_{12,49}=0.95$, $p=0.51$) and a significant effect of anxiety ($F_{12,49}=2.43$, $p=0.02$). When individual ROIs were considered in between subject effects, anxiety had a significant effect on R-MTC-m perfusion ($F_{1,60}=5.15$, $p=0.03$) and gender had a trend for an effect on R-ACC perfusion ($F_{1,60}=3.19$, $p=0.05$).

Backward stepwise logistic regression assessing the contribution of gender, anxiety and rCBF on the presence or absence of AL revealed that hypoperfusion to the L-ACC ($p=0.015$) and L-OFC ($p=0.015$), relative sparing of perfusion to the R-ACC ($p=0.010$), R-OFC ($p=0.010$) and L-MTC-m ($p=0.006$), and greater anxiety ($p=0.005$) emerged as significant predictors of AL in this patient population (Fig. 1). All remaining ROIs, including male gender ($p=0.061$), were removed from the overall model (Table 4; $\chi^2=22.24$, $p=0.001$, Nagelkerke $R^2=0.41$). A subanalysis including only those patients with a diagnosis of probable AD ($n=47$) yielded similar findings: forced entry of rCBF to each ROI, gender and NPI anxiety scores with backward stepwise removal found that hypoperfusion to the L-ACC ($p=0.011$) and L-OFC ($p=0.050$), and sparing of perfusion to the R-ACC ($p=0.010$), R-OFC (p=0.031) and L-MTC-m ($p=0.019$), as well as NPI anxiety scores ($p=0.015$) were all significant predictors of presence of AL in those with probable AD ($\chi^2=19.66$, $p=0.003$, Nagelkerke $R^2=0.47$).

Table 3
Comparison of regional cerebral blood flow (rCBF) ratios in regions of interest for AD patients with and without appetite loss

ROI	Hemisphere	Appetite loss ($n=22$)	No Appetite Loss (n=42)
Anterior cingulate	Right	0.74±0.06	0.72±0.10
	Left	0.79±0.06	0.79±0.10
Orbitofrontal cortex	Right	0.78±0.06	0.77±0.06
	Left	0.77±0.05	0.78±0.07
Middle mesial temporal cortex	Right	0.63±0.10	0.60±0.08
	Left	0.68±0.09	0.66±0.09
Inferior mesial temporal cortex	Right	0.78±0.08	0.76±0.07
	Left	0.81±0.07	0.80±0.08
Thalamus/Hypothalamus	Right	0.70±0.07	0.70±0.07
	Left	0.68±0.08	0.67±0.08
Insula	Right	0.73±0.08	0.74±0.06
	Left	0.77±0.07	0.77±0.06

Data are means±SD.

Table 4
Final logistic regression model assessing predictors of appetite loss in Alzheimer's disease

	R^2	χ^2	*df*	*p*-value	B	SE
Overall model	0.41	22.24	6	0.001		
L-ACC				0.015	−24.41	10.07
R-ACC				0.010	23.44	9.05
L-OFC				0.015	−30.23	12.47
R-OFC				0.010	33.56	13.01
L-MTC-m				0.006	14.65	5.33
NPI-anx				0.005	0.40	0.14

3.3. Predictors of severity of appetite loss in AD

Similarly, backward stepwise linear regression assessing whether rCBF to each ROI, as well as gender and NPI anxiety scores, was predictive of the degree of appetite loss in AD also found that appetite loss severity was negatively associated with perfusion to the L-OFC ($p<0.0005$) and R-INS ($p=0.001$), while it was positively associated with perfusion to the R-ACC ($p=0.003$), R-OFC ($p<0.0005$), L-MTC-m ($p<0.0005$) and NPI anxiety scores ($p=0.003$) ($F_{6,57}=6.10$, $p<0.0005$, $R^2=0.33$).

3.4. SPM results

Similar to the MANCOVA results, SPM analysis showed no significant differences in rCBF between AL and NAL groups at the voxel level.

4. Discussion

We investigated the neurobiological correlates of appetite loss in AD using SPECT. We found that hypoperfusion to the left orbitofrontal cortex and left anterior cingulate cortex, and relative sparing of right orbitofrontal, right anterior cingulate, and left middle mesial temporal cortex perfusion emerged as predictors of appetite loss in our study sample. These findings suggest that distinct pathologic processes in these regions may contribute to appetite loss in AD. These findings are consistent with the putative functions of these regions and provide important information on the circuitry that may be involved in appetite loss in AD. The implicated regions have been previously suggested to be important in the extrinsic motivational pathways of eating, whereas perfusion to regions associated with intrinsic hunger mechanisms do not appear to contribute to appetite loss among AD patients.

The OFC is defined as part of the prefrontal cortex that receives projections from the magnocellular medial nucleus of the mediodorsal thalamus [22]. While the OFC localizes to BA 10/11/47 [23], we have focused our analysis on BA 11 [17], which represents more of the medial aspect of the OFC than BA 10/47 [24]. In both primates [25,26] and humans [27–32] the OFC receives auditory, gustatory, olfactory, somatosensory, visual and visceral sensory inputs. Further, there are medial–lateral and anterior–posterior distinctions in the OFC [23]. The medial OFC appears to be related to the rewarding value of reinforcers, whereas the lateral OFC evaluates punishers or aversive stimuli. Posteriorly, the OFC receives somatosensory inputs and evaluates less complex reinforcers such as taste, whereas the anterior OFC appears to evaluate more complex or abstract reinforcers. Specific to food, there exists a secondary taste cortex in the OFC, the output of which may be important in determining the rewarding or appetitive value of food [33,34]. For example, fMRI investigations have found that pleasant odors and flavors activate the left medial rostral OFC whereas the left lateral OFC is activated by the unpleasant odors and flavors [35,36].

A functional PET study of healthy adults suggested that the intrinsic state of satiety (versus hunger) is localized to the L-lateral OFC while the extrinsic presentation of high (versus low) incentive foods, regardless of hunger state, is localized to the L-medial OFC [14]. There is also evidence localizing satiety to the right ventro-medial prefrontal cortex (i.e. BA 11–OFC) [37]. The hypoperfusion we observed in the L-OFC among AL patients may therefore reflect a dysregulation in the extrinsic pathway of appetite control via a decreased rewarding value of food; however, behavioral ratings of food pleasantness were not specifically conducted. This would result in a decreased motivational response to high incentive foods and thus decreased intake. Conversely, the relative sparing of perfusion to the R-OFC observed among AL patients in our study may indicate that the intrinsic pathway, specifically the feelings of hunger and satiety, are not affected in our patient population. Impaired reward value of food often precedes impaired hunger and thus, in this study, L-medial OFC neurodegeneration resulting in hypoperfusion may represent a neural correlate for decreased appetite due to decreased reward and pleasure from eating. Our finding of L-medial OFC hypoperfusion predicting appetite loss in AD is consistent with the demonstrated role of the OFC in satiety and the motivation to eat.

The ACC is part of the brain's limbic system and can be characterized as "executive" in functioning. It is subdivided into a dorsal cognitive division (BA 24, 32) and rostral (BA 24, 32) and ventral (BA 25, 33) affective divisions [38]. We have combined all these areas into one ACC region [17]. As part of the broader prefrontal cortex, the ACC is also involved in reinforcement and reward and has connections with the OFC [39–41]. The dorsal ACC in humans is important in linking reward-related information to the selection of alternative actions, especially in the context of a diminished return [42]. Reduced ACC activity post-infarct or surgery has been associated with depression [43] and functional neuroimaging studies have demonstrated reductions of rCBF in L-ACC in apathetic versus non-apathetic AD patients [44].

Specific to food, the neural substrate specialized for processing information about food includes circuits involving the ACC as well as the medial OFC, amygdala, superior temporal gyrus, parahippocampal gyrus, hippocampus, insula, and the ventral forebrain [35,45,46]. Hunger has been localized to the ACC both bilaterally [37] and right unilaterally [14] in non-demented adult subjects. Because of this, decreased ACC activity observed among AL patients in this study may reflect a decreased hunger sensation. In support of this, Hu and colleagues [13] performed an FDG–PET study in a sample of 27 patients with AD (12 patients with BMI <21 and 15 with a normal BMI of ≥ 21) and found that the low BMI group had hypometabolism in the ACC. This study combined mean values of both right and left hemispheric metabolic ratios thus precluding assessment of laterality making comparisons with our study difficult. The low BMI group also had a longer duration of illness and there was a trend towards correlation of lower BMI and illness duration ($p=0.068$). It is possible that decreased appetite contributed to lower BMI, but this is not certain. Furthermore, the ACC has extensive projections to the prefrontal cortex, insula, premotor cortex, amygdala, entorhinal cortex, parahippocampus, hippocampus, hypothalamus/thalamus and brainstem [47]. Dysfunction anywhere along this communicating network may result in an abnormal drive to eat and subsequent weight loss and lower BMI.

The MTC-m localizes to BAs 28/35/36 and includes the hippocampus, parahippocampus, and posterior amygdala. This ROI is involved in postulated neural networks associated with eating. Specifically, hunger has been associated with increased rCBF to the amygdala [14] and the hippocampal and parahippocampal gyri [37]. The sparing of L-MTC-m perfusion found among AL patients in our study would therefore suggest an intact hunger mechanism, although this would require confirmation through behavioral study. A previous MRI morphometric analysis correlated atrophy of the mesial temporal cortex with low BMI in 58 AD patients [12]. Mean MMSE $\pm$ SD in that study was 19.2 ± 5.7, indicating that those patients were of moderate disease severity and had progressed further in their illness than our patients had. Furthermore, structural and functional loss may not necessarily correlate, which could account for the differences between studies. A longitudinal study of morphological and functional changes in AD showed that the medial temporal regions showed a faster and more extensive reduction of gray matter volume than of rCBF [48] and this discordance makes comparison of structural and functional studies difficult. One can speculate that the ability to increase rCBF persists in the Grundmann study, despite morphological changes.

Our functional neuroimaging study has shown that hypoperfusion in the L-OFC and L-ACC and relative sparing of perfusion to the R-OFC, R-ACC and L-MTC-m emerged as predictors of appetite loss in AD patients. These regions

and/or circuits may be involved in appetite regulation in this relatively large sample of AD patients. More specifically, we postulate that there is a dysregulation in the functional network controlling appetite. L-OFC and L-ACC hypoperfusion may impair the motivation to eat or pursue food in response to extrinsic cues to eat in this group of mildly demented patients. The relative sparing of L-MTC-m rCBF may be due to the early stage of illness in our study population; with illness progression, losses of perfusion to this area may further decrease drive to eat by impairing the intrinsic sensation of hunger.

While analyses using logistic regression were able to detect significant differences in AL versus NAL patients, SPM, which is not restricted by ROIs, and MANOVA, which compared group differences in mean rCBF for the selected regions, did not find significant differences. The brain appears to adhere to two fundamental principles of functional organization, functional integration and functional specialization, where the integration within and among specialized areas is mediated by effective connectivity [49]. The SPM and MANOVA analyses addressed functional specialization, that is, localization of function to specific areas. Our findings imply loss of functional integration rather than a targeted loss in a single area of specialization, and are consistent with the presence of integrated networks controlling the extrinsic and intrinsic motivations responsible for appetite.

Several factors are important in interpreting the results of this study. While this is the largest neuroimaging study of AL in AD to date, only 22 of the 64 patients had AL. As a result, statistical power to detect subtle differences in perfusion may be limited. Second, while a strength of this study was recruiting a group within a narrow range of cognitive impairment, results cannot be generalized to patients with moderate to severe AD. Third, the observed correlation between decreased appetite and increased anxiety as measured by the NPI may influence the findings in spite of statistically covarying for anxiety. One could speculate that increased anxiety may impair appetite or the ability to eat but the mechanism is unclear and warrants further exploration. Similarly, it is also possible that the greater proportion of males observed in the AL group may have influenced the ROI findings. However, there were no significant differences between genders in mean NPI appetite scores or in rCBF to any individual ROI. Although there was a trend for male gender to predict appetite loss in the regression model, its exclusion from the models did not change the outcome of the ROI findings. Thus, although significantly related to appetite loss, anxiety and gender do not appear to be related to the relationship between perfusion to specific ROIs and the presence or absence of appetite loss. Fourth, our use of predefined ROIs based on a previously published ROI template may have obscured functionally important divisions in appetite regulation. However, this analysis was supplemented with SPM, which allowed us assess regional perfusion differences in the absence of anatomical boundaries and *a priori* hypotheses. Fifth, behavioural ratings of food, pleasantness, feelings of hunger and satiety were not measured. As a next step, such ratings would be an important component of evaluating the functional sense of the reported perfusion patterns in patients with mild AD and related disorders in whom these measurements are still possible. Finally, patients were not free from concomitant psychotropic medications. While the proportions of patients in AL and NAL groups on each therapeutic group were similar, an effect of medications cannot be ruled out.

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