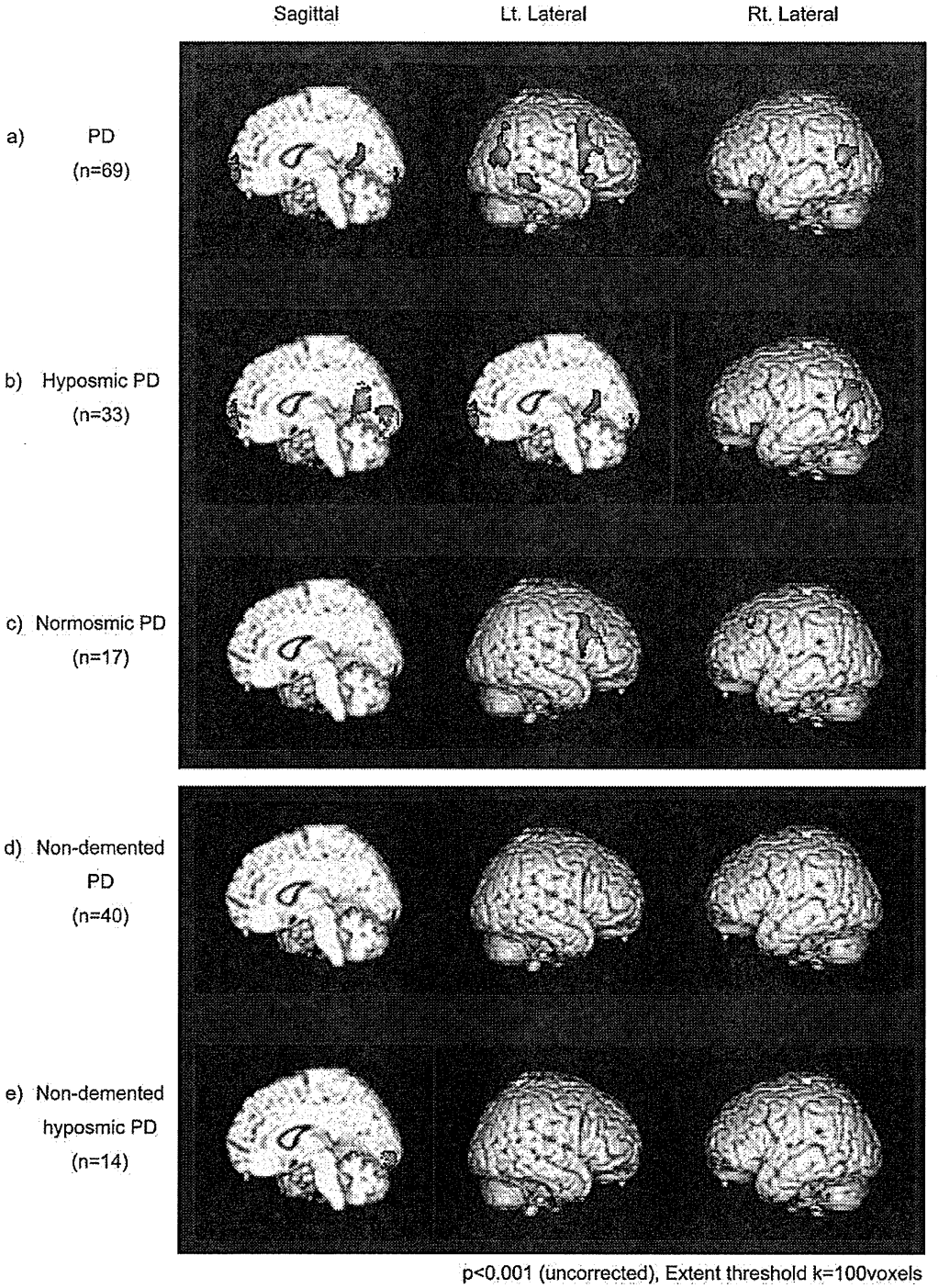

FIG. 3. *Brain*. regions showing reduced glucose metabolism in PD subgroups compared with the normal control group. **a:** Total PD group showed reduced metabolism bilaterally in the medial prefrontal cortex, dorsolateral prefrontal cortex (DLPFC), medial occipital cortex, and lateral parieto-temporo-occipital area. **b:** Hyposmic PD group demonstrated additional, broader occipital hypometabolism. **c:** Normosmic PD group showed metabolic reductions only in the bilateral DLPFC. **d:** Nondemented PD group showed no apparent metabolic changes. **e:** Nondemented PD+SH group showed metabolic reductions in the medial occipital cortex ($P < .001$ uncorrected with an extent threshold of 100 voxels).

seems to reflect the distribution of the pathological process that alters neuropils and causes functional deficits of the synaptic activities. Therefore, it is plausible that functional deficits and metabolic alterations are closely connected to each other. Compared with the normal control group, the total PD group showed mild metabolic reduction in the mPFC, DLPFC, medial occipital cortices, and lateral parieto-temporo-occipital area (Fig. 3a). These findings are consistent with previous studies[14,27,28] and indicate that our participants were

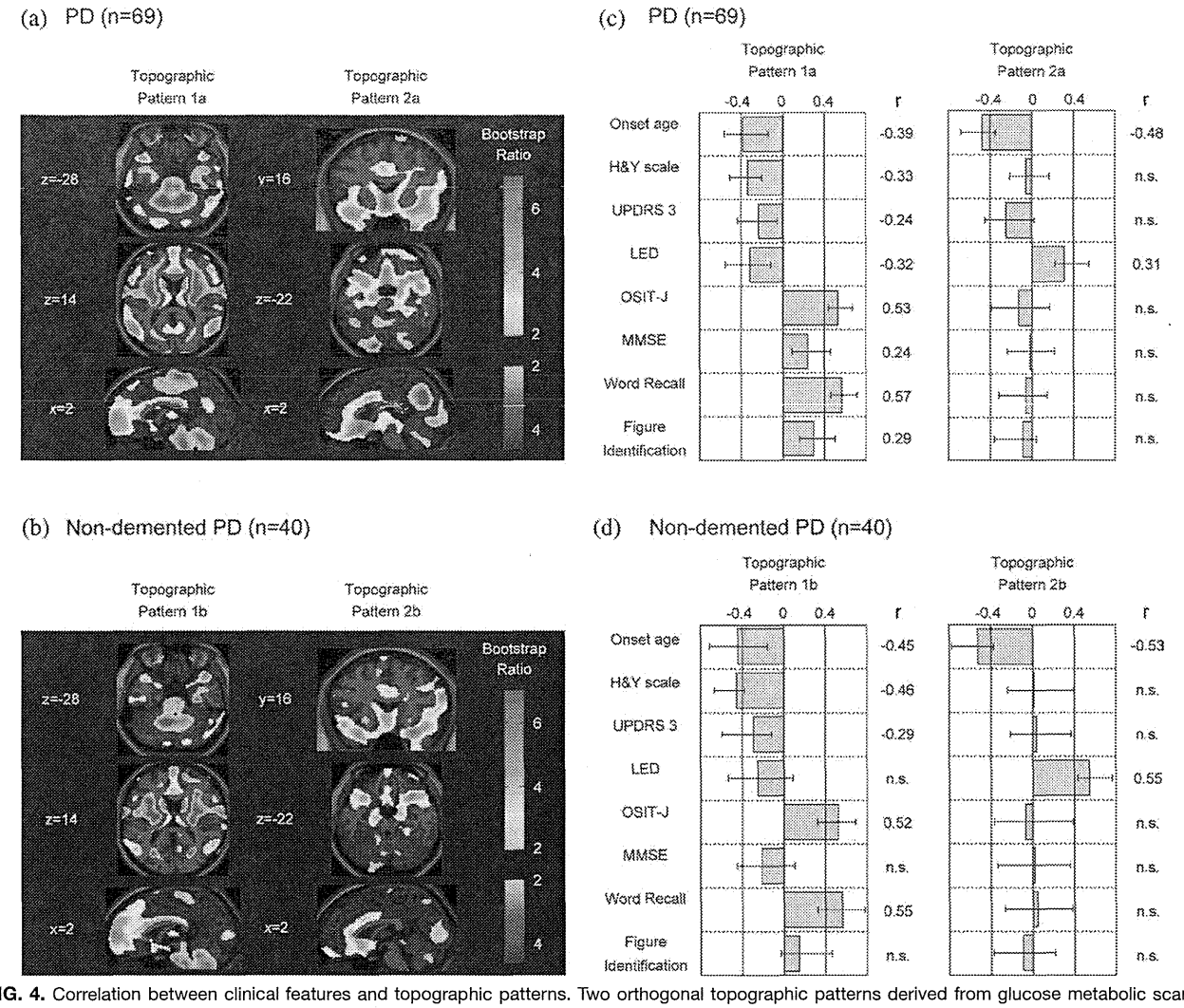

FIG. 4. Correlation between clinical features and topographic patterns. Two orthogonal topographic patterns derived from glucose metabolic scans at rest in (**a**) the total PD group (MMSE > 24) and (**b**) the nondemented PD group (MMSE > 28). Relationships between topographic patterns and clinical ratings in (**c**) the total PD group (MMSE > 24) and (**d**) the nondemented PD group (MMSE > 28). Coordinates along the *x*, *y*, and *z* axes refer to Montreal Neurological Institute standard stereotactic space. The bootstrap ratio is the ratio of the voxel salience value to its standard error (estimated from 100 bootstrap samples). It is a measure of the stability of high (red scale) and low (blue scale) metabolic values, which constitute the topographic pattern. The correlation between a topographic pattern and a clinical rating was not considered significant (n.s.) if the 95% CI crossed zero, as determined by estimation from 100 bootstrap samples.

metabolically typical, as observed in nonadvanced PD. Furthermore, the hyposmic PD group showed more prominent occipital hypometabolism, even in nondemented cases (Fig. 3e). These results suggested that olfactory dysfunction is a sensitive marker of brain hypometabolism in PD.

Next, we performed brain–behavior PLS analysis and identified 2 significant topographic patterns of metabolic alteration at rest that correlated with representative clinical features in PD, including olfactory dysfunction (Fig. 4). A topographic pattern of glucose metabolism at rest is thought to reflect a group of structural and functional types of damage to the neuropil caused by pathological changes. A recent study used PLS analysis to demonstrate correlations among topographic patterns and cognitive and mood functions in moderate to advanced PD.[17] Other studies that used similar spatial covariance analysis confirmed the existence of a disease-specific metabolic pattern at rest in PD.[29,30] In the present study, we demonstrated that 2 significant topographic patterns could be detected even in nonadvanced PD (Fig. 4a,b). Furthermore, we found that the expression of topographic patterns 1a and 1b was positively correlated with olfactory and memory performance. Topographic patterns 1a and 1b were both characterized by altered metabolism in multiple brain regions, including the mPFC, DLPFC, piriform cortex, cingulate cortex, lateral parieto-occipito-temporal area, and caudate. These data suggest that hyposmia and memory impairment are 2 reliable predictors of cortical hypometabolism in PD.

The finding that olfactory and memory dysfunctions in PD were correlated with the same metabolic pattern suggested that these 2 symptoms have a common pathological etiology. Convergent evidence from pathological[5–7] and imaging studies[8–10,31] has suggested that dysfunction of the amygdala and piriform cortex is responsible for olfactory impairment in PD. Furthermore, a recent study demonstrated that central cholinergic dysfunction in the amygdala and hippocampus correlated with olfactory and memory impairment in nondemented PD.[25] Our data showed that the performance of olfaction and memory was highly correlated with topographic patterns 1a and 1b. With respect to olfaction-related brain regions, patterns 1a and 1b both included metabolic changes in the piriform cortex, and pattern 1b encompassed metabolic changes in the amygdala (Fig. 4a,b). Previous studies have suggested that the link between olfaction and memory is mediated by the amygdala[32] and the piriform cortex.[33] Taken together, these findings indicate that dysfunction of these areas, which may be due in part to cholinergic dysfunction, may be responsible for the olfactory and memory impairment in nondemented PD. It was noteworthy that although PLS analysis demonstrated relative hypometabolism of the piriform cortex and amygdala in hyposmic PD patients, the parametric *t* test implemented in SPM5 failed to detect significant metabolic reductions in these areas (Fig. 3b,e). These results are explained by the finding that multivariate methods such as PLS are more suitable for assessing metabolic network abnormalities than is SPM's *t* test,[34] but further study is needed to clarify these points. Interestingly, the correlation between metabolic changes in the amygdala and olfactory performance was observed only in topographic pattern 1b, which suggested that the hypometabolism in the amygdala was one of the earliest metabolic alterations in the PD brain and reached a nadir at later stages.

Recent clinical studies have demonstrated that higher onset age is the best predictor of PD progression rate.[35,36] In the present study, onset age showed comparatively close relationships with all topographic patterns (Fig. 4c,d), which suggested that a higher onset age might be associated with broad cortical metabolic reduction. Furthermore, recent pathological studies indicated that later-onset PD patients often exhibit early limbic and neocortical involvement and develop dementia.[37,38] Our data revealed that topographic patterns 2a and 2b represented metabolic abnormalities in the limbic and prefrontal cortices, consistent with those pathological studies and also suggested that metabolic changes in these areas were present even in nondemented PD patients. Taken together, the present data suggest that hyposmia, memory impairment, and later-onset age are associated with brain hypometabolism affecting broad regions and could potentially predict later development of dementia in PD. Because atrophy correction was not performed in this study, there is a possibility that our data may reflect the combined effect of atrophy and metabolic reduction. However, we verified that all participants did not exhibit apparent focal brain atrophies, and previous studies comparing resting glucose metabolism with and without voxel-based atrophy correction revealed that regional changes of glucose metabolism measured by PET are not simply a reflection of focal brain atrophy.[39] Thus, it is expected that the effect of circumscribed atrophy on metabolic reduction would be relatively small. However, further study is needed to confirm this point.

In conclusion, we investigated the possible relationships among olfactory impairment, representative clinical features, and resting-state brain metabolism in PD. The results suggested that odor-identification impairment in PD is closely associated with cognitive dysfunctions, especially memory impairment. Further analysis revealed that odor-identification deficit and memory impairment are closely associated with disease-specific metabolic changes including changes in the amygdala and piriform cortex. Moreover, we demonstrated that onset age is a highly accurate predictor of cortical hypometabolism even in nondemented PD patients. The results of this study shed light on the complex involvement of the brain in PD and may facilitate the development of better management protocols for patients with PD. ■

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