Research Paper

Involvement of specific striatal subregion contributes to executive deficits in Alzheimer disease

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Background: There is growing evidence that the striatum plays a central role in cognitive dysfunction. However, it remains unclear whether and how the striatum contributes specifically to executive deficits in Alzheimer disease (AD). We sought to elucidate aberrations in the striatal subregion associated with executive function and its metabolic connectivity with the cortical regions to investigate its role in the pathogenesis of executive deficits in patients with AD. **Methods:** Patients with AD and healthy controls underwent a neuropsychological assessment battery, including assessment of executive function, and a hybrid positron emission tomography/magnetic resonance imaging (PET/MRI) scan. We performed voxel-wise analyses of cerebral metabolism between patients and controls, focusing on the executive subregion of the striatum according to the Oxford–GSK–Imanova Striatal Connectivity Atlas. We assessed the correlation between the [^{18}F]-fluorodeoxyglucose standardized uptake value ratio of the striatal executive subregion and clinical variables, and we analyzed seed-based metabolic connectivity of the striatal executive subregion with the dorsolateral prefrontal cortex (DLPFC) using [^{18}F]-fluorodeoxyglucose PET. **Results:** We included 50 patients with AD and 33 controls in our analyses. The patterns of striatal hypometabolism in patients with AD were specific to executive and caudal motor subregions. Metabolic activity in the executive subregion of the striatum correlated negatively with the severity of executive dysfunction, as measured with the Trial-Making Test (TMT) part B and the difference score TMT B–A, and correlated positively with Digit Span (backward) and Verbal Fluency Test scales, particularly on the left side. Compared with controls, patients with AD showed reduced metabolic connectivity between striatal executive subregions and the dorsolateral prefrontal cortex (DLPFC). **Limitations:** Our study was limited by small sample sizes and cross-sectional findings. **Conclusion:** Our findings show that patients with AD have impairments in the executive subregion of the striatum, and these deficits may be associated with a disconnection between the executive striatum and DLPFC, providing valuable insight into the pathogenesis of this disease.

Introduction

Alzheimer disease (AD), the most common cause of dementia, is pathologically characterized by an accumulation of amyloid-β plaques, neurofibrillary τ tangles and neurodegeneration in the brain.[1,2] Executive deficits characterize the initial phases of AD, following memory impairments and preceding language and visuospatial impairments, and have a negative impact on daily activities and the ability to cope with other cognitive or behavioural disorders.[3] Executive skills have traditionally been linked to prefrontal cortex regions — in particular, the dorsolateral prefrontal cortex (DLPFC) — but recent studies using morphological imaging and functional magnetic resonance imaging (fMRI) have provided evidence for an association between striatal involvement and poor performance on executive function tasks.[4–7] To date, however, it remains unclear whether and how the striatum contributes specifically to executive deficits in AD.

Clinical pathology and neuroimaging studies demonstrate the striatal atrophy, hypometabolism, dopaminergic dysfunction and amyloid deposition in the entire striatum in patients with AD that are associated with cognitive decline.[2,8–12] Notably, aside from executive function, the striatum is involved in a variety of complex functions, including memory, attentional allocation, reward and emotion processing, and motor control.[13] To better target the executive function of the striatum, we used a substriatum parcellation atlas with which striatal subregions associated with executive function could be distinguished based

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on their specific cortical connectivity profiles.[14] Only 1 previous study based on morphological imaging has reported atrophy of the striatal executive subregion in AD, but its contribution to executive dysfunction was not elucidated.[15] Furthermore, brain dysfunction is not solely attributable to the nature of isolated regions; impaired executive functions have been suggested to be hallmarks of frontal–subcortical circuit dysfunction.[16,17] Currently, the pattern of connectivity between the striatum executive subregion and the DLPFC in AD remains unknown, and may be a candidate mechanism for executive deficits. As such, we hypothesized that the specific striatal subregion associated with executive function as well as its connectivity with the DLPFC would be affected, contributing to the apparent executive deficit suggested by the symptomatology of AD.

We investigated the alteration of the striatal executive subregion and its metabolic connectivity with the DLPFC using [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography/magnetic resonance imaging (PET/MRI) data from patients with AD. In addition, we examined associations between the FDG standardized uptake value ratio (SUVR) in the executive subregion of the striatum and the severity of executive deficits in patient groups. We aimed to explore aberrant patterns of the executive subregions of the striatum and specific striatocortical connectivity affected in AD, as well as their possible association with executive dysfunction.

Methods

Participants

Between July 2017 and December 2020, we recruited patients with AD and healthy control participants from the Department of Neurology of Xuanwu Hospital. All participants underwent clinical interviews, physical examinations, neuropsychological assessments, and a brain [^{18}F]-FDG-PET/MRI scan. Diagnoses were established by a panel of cognitive neurologists, trained psychologists and a neuroimaging specialist in a multidisciplinary consensus meeting according to the core clinical criteria of the National Institute on Aging–Alzheimer's Association workgroup for probable AD.[18] The inclusion and exclusion criteria for patients with AD are detailed in Appendix 1, Supplementary Table 1, available at www.jpn.ca/lookup/doi/10.1503/jpn.220164/tab-related-content. Administration of anti-cholinesterase or *N*-methyl-D-aspartate (NMDA) receptor antagonists can interfere with [^{18}F]-FDG uptake and distribution in the brain; thus, we included only patients who were diagnosed for the first time without the use of any prior medication for AD. Our study was approved by the Ethics Committees of the Xuanwu Hospital and Capital Medical University, China, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient or their guardian.

Neuropsychological assessments

The neuropsychological test battery consisted of widely used neuropsychological assessments that measure cognitive function in the domains of memory, execution, language and behavioural abnormalities. Global cognitive screening measures included the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating (CDR) scale. We evaluated word-list memory using Rey's Auditory-Verbal Learning Test (AVLT); executive function with the Trail-Making Test parts A (TMT-A) and B (TMT-B), Digit Span (forward and backward), Verbal Fluency Test, and Stroop Color-naming Test; language with the Boston Naming Test (BNT); and the severity of behavioural abnormalities with the Frontal Behavior Inventory (FBI).

PET/MRI acquisition parameters

All images were acquired on a hybrid 3.0 T time of flight PET/MRI scanner (SIGNA PET/MR; GE Healthcare).[19] The PET and MRI data were acquired simultaneously using a vendor-supplied 19-channel head and neck union coil. The participants received [^{18}F]-FDG (3.7 MBq/kg) intravenously and underwent 3-D T_1-weighted sagittal imaging and [^{18}F]-FDG-PET imaging 40 minutes later during the same session. Patients were asked to relax, not to think of anything, not to fall asleep and to remain as still as possible during scanning.

We used a 3-D T_1-weighted fast field echo sequence (repetition time 6.9 ms, echo time 2.98 ms, flip angle 12°, inversion time 450 ms, matrix size 256 × 256, field of view 256 × 256 mm^2, slice thickness 1 mm, 192 sagittal slices with no gap, voxel size 1 × 1 × 1 mm^3 and acquisition time 4 min 48 s) for data acquisition. Static [^{18}F]-FDG-PET data were acquired using the following scanning parameters: matrix size 192 × 192, field of view 350 × 350 mm^2 and pixel size 1.82 × 1.82 × 2.78 mm^3, and included corrections for random coincidences, dead time, scatter, and photon attenuation.

PET/MRI scan preprocessing and analysis

We performed [^{18}F]-FDG-PET image processing and analyses using SPM12 implemented in the MATLAB software (Mathworks, Inc.). After normalizing the structural MRI scans, the transformation parameters determined by the T_1-weighted image spatial normalization were applied to the co-registered PET images for PET spatial normalization. The images were then smoothed using an isotropic Gaussian kernel with an 8-mm full-width at half-maximum approach. The FDG-PET scan intensity was normalized using a whole-cerebellum reference region to generate SUVR images. We used the preprocessed [^{18}F]-FDG-PET SUVR image data to perform voxel-wise whole-brain comparisons between patients with AD and controls.

Striatal subregion analysis

Each striatal subregion of interest (ROI) was defined using the Oxford–GSK–Imanova Striatal Connectivity Atlas,[14] which is a probabilistic atlas of substriatal regions segmented according to their white matter connectivity to cortical regions. Based on the differential cortical connectivity patterns, the atlas subdivides the striatum into the following 7 subregions: limbic, executive, rostral–motor, caudal–motor, parietal, occipital and

temporal (Figure 1A). We determined mean [^{18}F]-FDG-PET SUVRs separately in the unilateral striatal subregion using ROIs provided by the atlas. We focused on the executive subregion of the striatum (central and dorsal precommissural striatum and central and ventral postcommissural striatum), which is connected with areas 9, 9/46 and 10 of the DLPFC.[14,20]

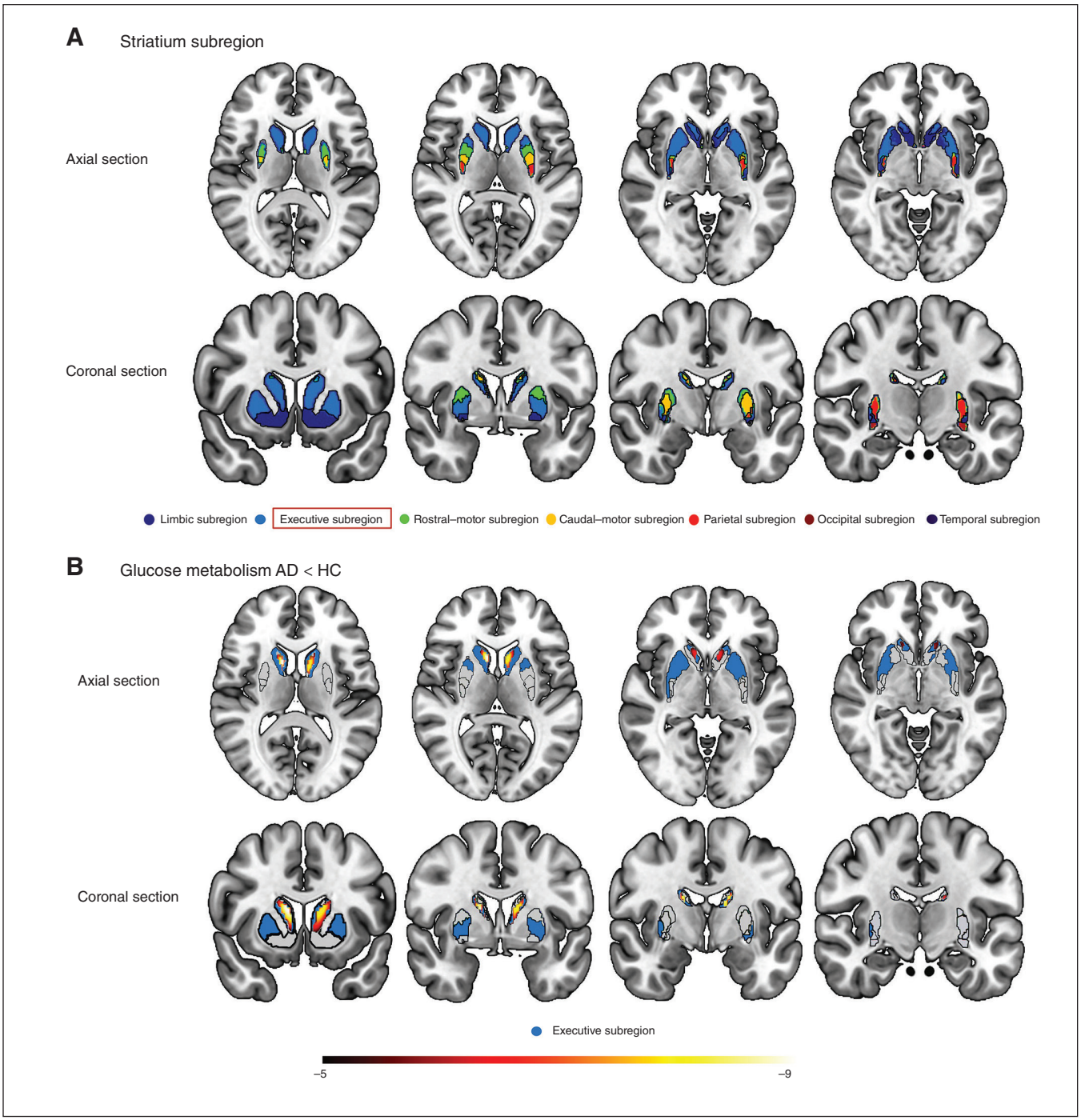

Figure 1: The hypometabolism pattern of the striatal executive subregion in the Alzheimer disease (AD) group. (A) Striatal parcellations based on intrinsic functional connectivity with the cerebral cortex. (B) Projections of areas with relative hypometabolism of the striatal executive subregion in patients with AD compared to healthy controls (HC). *T* values are colour-coded in a red–yellow colour gradient to highlight the differences for AD < controls. Data were analyzed at a height threshold of $p < 0.001$ and were family-wise error–corrected at the cluster level at $p < 0.05$. Compared with controls, patients with AD had hypometabolism in bilateral executive subregions of the striatum. Notably, the involvement of the executive striatum appeared to be specific to the caudate portion.

Metabolic connectivity analysis

We used sparse inverse covariance estimation (SICE), which is a method previously validated by Huang and colleagues.[21] Because our hypothesis was specifically focused on the specific striatocortical connectivity associated with executive function, we performed a seed-based analysis with the preselected striatal executive subregion to investigate the metabolic connectivity between the executive striatum and the DLPFC. We calculated Pearson correlation coefficients between [^{18}F]-FDG SUVRs in the executive subregion of the striatum and DLPFC.

Statistical analysis

We used GraphPad Prism software (version 8.3.0; GraphPad Software Inc.) for all statistical analyses. Numerical variables are presented as means ± standard deviations (SD). Group comparisons of numerical variables were performed using Student *t* tests, and the comparative analysis of categorical variables was completed using χ^2 tests.

The [^{18}F]-FDG-PET data were subjected to voxel-wise whole-brain 2-sample *t* tests based on the framework of a general linear model (GLM) in SPM12, using age and sex as covariates. The brain regions and striatal subregions with significant FDG changes were determined using a voxel threshold of $p < 0.05$ (family-wise error [FWE]–corrected). We then conducted the atlas-based ROI analysis of the PET images to extract the regional SUVRs of the striatal executive subregions for further correlation analyses. To compare metabolic connectivity between groups, we used nonparametric permutation tests with 5000 permutations to determine significance. We calculated *p* values as fractions of the difference in distribution values that exceeded the difference value between the actual groups.

We assessed Pearson correlation between the [^{18}F]-FDG SUVRs of the striatal executive subregion and neuropsychiatric assessment scores, as well as the whole striatum and neuropsychiatric assessment scores using a threshold of $p < 0.05$ (false discovery rate [FDR]–corrected). For all analyses, $p < 0.05$ indicated statistical significance.

Results

Participants

We included 50 patients with AD and 33 healthy controls in our analyses. Demographic, cognitive and behavioural characteristics of the patients with AD and controls are presented in Table 1. There were no significant differences between the

Table 1: Demographic and neuropsychiatric assessment data

Characteristic	AD, mean ± SD* $n = 50$	Control, mean ± SD* $n = 33$	*p* value†
Age, yr	58.86 ± 5.06	55.82 ± 10.05	0.08
Sex, no. male/female	20/30	15/18	0.65
Years of education	10.90 ± 4.05	11.31 ± 3.47	0.25
Duration of disease, yr	3.56 ± 1.78	–	–
MMSE	14.69 ± 7.17	28.65 ± 2.07	< 0.0001
MoCA	9.55 ± 6.39	26.06 ± 3.43	< 0.0001
CDR	8.48 ± 4.25	0 ± 0	< 0.0001
Memory			
AVLT, immediate recall	9.23 ± 5.61	23.81 ± 5.59	< 0.0001
AVLT, delayed recall	1.17 ± 2.21	8.79 ± 2.98	< 0.0001
Executive function			
Digit Span (forward)	6.43 ± 1.70	7.72 ± 1.31	0.0008
Digit Span (backward)	3.05 ± 1.11	4.90 ± 1.15	< 0.0001
TMT-A	126.0 ± 39.54	50.48 ± 24.94	< 0.0001
TMT-B	222.8 ± 96.42	88.44 ± 62.59	< 0.0001
TMT B–A	119.7 ± 50.66	37.96 ± 45.71	< 0.0001
Stroop I	79.25 ± 65.41	88.44 ± 62.59	0.01
Stroop II	79.17 ± 61.68	35.80 ± 12.42	0.0007
Verbal Fluency Test	7.10 ± 4.60	17.16 ± 3.31	< 0.0001
Language			
BNT	15.23 ± 6.94	24.96 ± 3.83	< 0.0001
Behavioural features			
FBI	16.67 ± 11.15	1.67 ± 4.08	0.005

AD = Alzheimer disease; AVLT = Auditory-Verbal Learning Test; BNT = Boston Naming Test; CDR = Clinical Dementia Rating scale; FBI = Frontal Behavior Inventory; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; SD = standard deviation; TMT-A and -B = Trail-Making Test parts A and B.
*Unless indicated otherwise.
†Two-sided *p* values for continuous variables refer to unpaired *t* tests, and 2-sided *p* values for categorical variables refer to the Pearson χ^2 test.

groups with regard to age, gender or years of education (all $p > 0.05$). As expected, the AD group performed worse than controls on neuropsychological assessments, including the MMSE, MoCA, CDR, AVLT, TMT-A, TMT-B, difference score TMT B–A, Stroop I, Stroop II, Digit Span (forward) and Digit Span (backward), Verbal Fluency Test, BNT and FBI (all $p > 0.05$).

[^{18}F]-FDG uptake in the whole brain

Compared with controls, patients with AD had a broader pattern of lowered FDG uptake that involved bilateral parietal, temporal and, to a lesser extent, frontal regions as well as the subcortical nuclei, including the caudate, putamen and thalamus (Appendix 1, Supplementary Table 2 and Supplementary Figure 1).

[^{18}F]-FDG uptake in the striatal subregion

Compared with controls, patients with AD showed significantly lower metabolism in the bilateral striatal executive subregion and the caudal motor subregion, but not in the limbic subregion, rostral motor subregion, parietal subregion, occipital subregion or temporal subregion. Notably, the clusters in the caudal motor subregions are smaller than those in the executive subregion, as shown in Appendix 1, Supplementary Table 3.

The hypometabolism pattern of the striatal executive subregion in the AD group compared to the healthy control group is shown in Figure 1. Interestingly, the involvement of the executive striatum appeared to be specific to the caudate portion.

Correlations between the entire striatum and neuropsychological features

Pearson correlation analysis with false-discovery rate (FDR) correction showed only a weak correlation between the SUVR of the left striatum and Verbal Fluency Test, as well as the SUVRs of the right striatum and Digit Span (backward) (Appendix 1, Supplementary Table 4). No significant correlations were found between the SUVRs and Digit Span (forward), TMT-A, TMT-B or TMT B–A.

Correlations between the striatal subregion and neuropsychological features

As shown in Figure 2, the SUVR of the left executive subregion correlated with the severity of executive dysfunction in the AD group by means of a detailed neuropsychological study involving Digit Span (backward), TMT-B, TMT B–A and Verbal Fluency Test assessments. Pearson correlation analysis showed that SUVRs of the right striatal executive subregion were negatively correlated with TMT B–A, but not with Digit Span (backward), TMT-B or Verbal Fluency Test. There were no significant correlations between the SUVR of the bilateral striatal executive subregion and Digit Span (forward) or TMT-A (Appendix 1, Supplementary Figure 2).

Furthermore, SUVRs of the left executive subregion were positively correlated with AVLT scales and negatively correlated with the CDR sum of boxes scale in the AD group (Appendix 1, Supplementary Figure 2). No significant correlations were found between the SUVR of the right executive subregion and the above neuropsychological scores (Appendix 1, Supplementary Figure 2). Furthermore, the SUVR of the executive subregion was not significantly correlated with the performance on the Digit Span (forward), Digit Span (backward), TMT-A, TMT-B, TMT B–A or Verbal Fluency Test in healthy controls (Appendix 1, Supplementary Table 5).

The SUVR of the striatal caudal motor subregion was positively correlated with Digit Span (backward) and Verbal Fluency Test, and negatively correlated with TMT B–A, particularly on the left side (Appendix 1, Supplementary Table 6). The SUVR of the striatal caudal motor subregion had no significant correlations with Digit Span (forward), TMT-A or TMT-B.

Metabolic connectivity in the entire striatum

When compared with controls, patients with AD exhibited weaker metabolic connectivity between the whole striatum and the DLPFC. Additionally, the whole striatum had reduced connections with other frontal cortex regions, including the ventromedial prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex, rectus gyrus and precentral gyrus (Appendix 1, Supplementary Figure 3).

Metabolic connectivity in the striatal subregion

Compared with controls, patients with AD exhibited decreased metabolic connectivity between the executive subregions of the striatum and the DLPFC (Figure 3).

Discussion

We identified the contribution of striatal executive subregions to the generation of executive deficits in AD, which to our knowledge has never before been empirically demonstrated. Specifically, impairment of the striatal executive subregion and its decreased metabolic connectivity with the DLPFC was detected in patients with AD compared with controls, which was associated with the severity of executive dysfunction, implying that the striatal involvement — particularly its cortical disconnection — underlies the apparent executive deficit suggested by the symptomatology of AD.

We assessed striatal alterations and striatocortical connectivity at the level of executive subregions in patients with AD, then analyzed their roles in executive performance. Most previous studies of AD either suggested striatal impairment in the entire striatum or only made an anatomical dissociation with no functional distinction, limiting the evaluation of the striatal role in different cognitive domains.[13,22] We found that SUVRs of the entire striatum had weak correlations with neuropsychological scores and widespread reduced metabolic connectivity with the frontal cortex, which

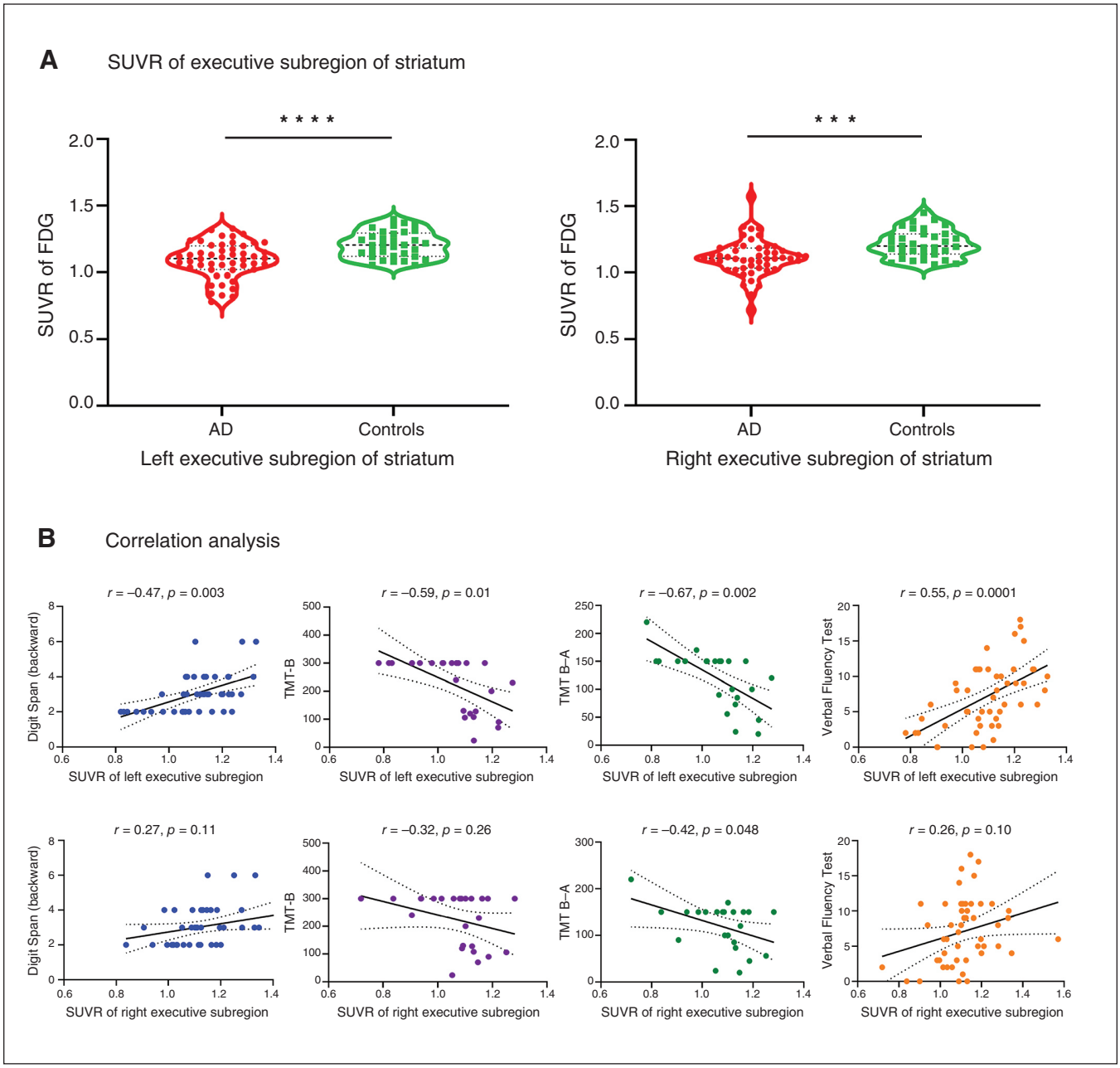

Figure 2: The metabolism in the striatal executive subregion and its association with executive performance in patients with Alzheimer disease (AD). (A) Compared with controls, patients with AD had lower [^{18}F]-fluorodeoxyglucose (FDG) uptake in the bilateral executive subregions of the striatum. Data were analyzed using the Student *t* test, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$. (B) Significant correlations existed between the striatal executive subregion and executive performance in patients with AD. Scatter plots show that standardized uptake value ratios (SUVRs) of the striatal left executive subregion correlated significantly with neuropsychological scores of executive functions assessed using the Digit Span (backward), Trail-Making Test part B (TMT-B), difference score TMT B–A and Verbal Fluency Test. Pearson correlation analysis showed that SUVRs of the right striatal executive subregion were negatively correlated with TMT B–A, but not with the Digit Span (backward), TMT-B or Verbal Fluency Test. Region and scatterplot colours: blue: Digit Span (backward); purple: TMT-B; green: TMT B–A; red: Verbal Fluency Test.

is consistent with the findings of a previous study suggesting that the striatum was involved in a variety of complex functions, including memory, attentional allocation, reward and emotion processing, and motor controls, in addition to the executive function. Therefore, we used a connectivity-based functional striatum atlas instead of anatomically defined discrete striatal regions (e.g., nucleus accumbens, caudate nucleus and putamen) as was previously done, which provides

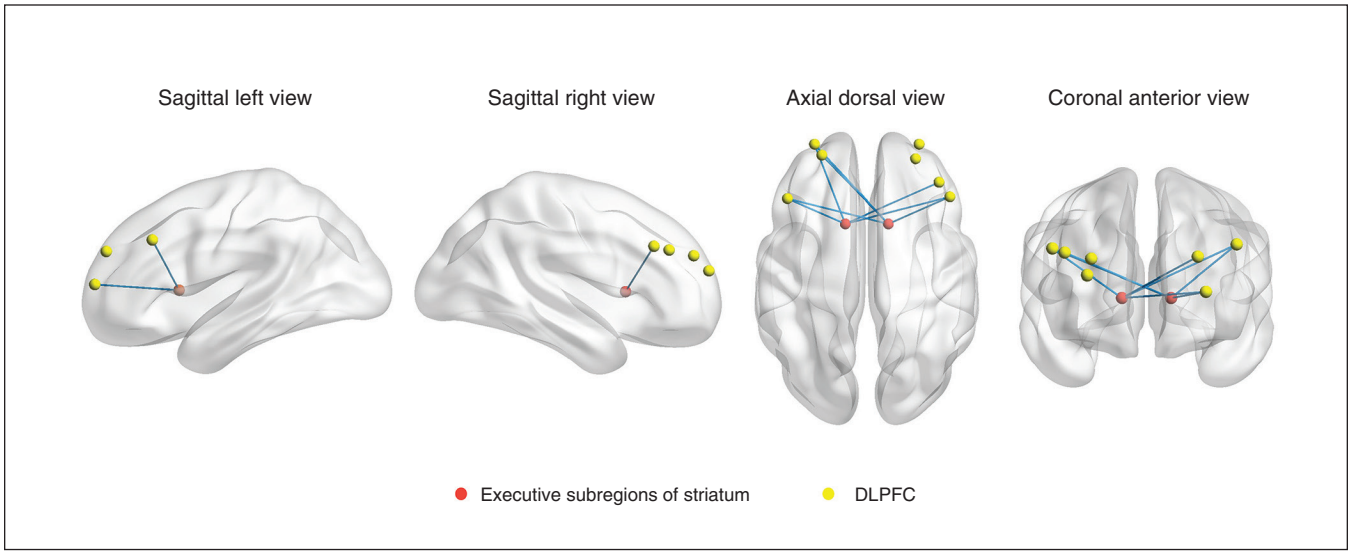

Figure 3: Metabolic connectivity of the striatal executive subregion. Compared with controls, patients with Alzheimer disease (AD) showed decreased metabolic connectivity between executive subregions of the striatum and dorsolateral prefrontal cortex (DLPFC). Weakened metabolic connections are represented by blue lines.

the optimal subdivision to investigate specific functions of the striatum. This study showed a specific relationship between the involvement of striatal executive regions and decreasing executive performance in patients with AD, which is partly consistent with the findings of previous studies on striatum functions that suggested executive function is associated with activity predominantly in the dorsal striatum.[16,23] Furthermore, we identified profiles of the metabolic connectivity of the striatal executive subregion with the DLPFC in patients with AD, which to our knowledge has not been specifically investigated to date. These findings are in line with those of previous studies, suggesting that AD is a more complex disease involving dysfunctions in cortical and subcortical transmission rather than dysfunctions of corticocortical transmission alone.[15,24,25] Taken together, the alterations in metabolism and striatocortical connectivity at the level of the striatal executive subregion may provide new perspectives for understanding of the pathogenesis of AD and could constitute a potential biomarker for the assessment of executive deficit severity.

Our FDG-PET findings showed that the AD group had more significant hypometabolism in the striatal executive subregion than controls, consistent with previous results obtained using morphological imaging, implying the impairment of the executive striatum in patients with AD.[15] Notably, the involvement of the executive striatum appeared to be specific to the caudate portion in patients with AD, which is partly consistent with the findings of a previous study that used morphological imaging based on the anatomical dissociation of the entire striatum, indicating that the caudate was involved early in the presymptomatic stage of AD and that the putamen was then affected as the disease progressed. The distinct pattern of striatal involvement in the AD continuum will require confirmation in larger longitudinal studies.

Furthermore, hypometabolism of the executive striatum in patients with AD was associated with the severity of executive dysfunction measured using the TMT-B, TMT B–A, Digit Span (backward) and Verbal Fluency Test, which are generally thought to be more accurate in detecting executive impairment related to brain damage than the TMT-A and Digit Span (forward).[26,27] This finding is partially consistent with the results of previous studies based on the entire striatum, suggesting that striatal involvement and amyloid-β deposits were related to executive performance.[8,11] Another interesting finding of our study was the larger association with executive deficits in the left executive striatum than the right. Previous pathology and neuroimaging studies in patients with AD have shown asymmetric involvement in different cortical regions as well as hemispheric dominance for specific cognitive cortical functions such as episodic memory, semantic memory and executive dysfunction, which correlated with the lateralization of grey matter loss or hypometabolism to the left hemisphere.[22,28,29] However, assessing executive function depends partially on movement and verbal abilities. It is possible that the use of verbal and motion-mediated executive function tests in the monitoring of AD is biased toward patients with compromised left hemisphere functional integrity. In addition, our study included only right-handed participants, which may have increased the hemispherical dissimilarity of our sample. These findings suggest that the executive subregion of the striatum may serve as a key subcortical region, specifically contributing to the executive deficit suggested by the symptomatology of AD.

Brain dysfunction is not solely due to the nature of isolated regions; rather, the connectivity between regions is critical for information integration in order to carry out goal-directed cognitive and neuropsychiatric functions.[30]

Executive subregions of the striatum receive dense projections from the DLPFC, which has been shown to play a critical role in executive function.[31] However, striatal and DLPFC damage appears to be a sufficient but not necessary cause of executive dysfunction, and current evidence supports circuit-specific sequelae, with aspects of executive function attributable to particular circuits.[32] Our discovery of decreased connectivity of the striatal executive region with the DLPFC suggests the involvement of an executive striatofrontal circuit, which may be responsible for the executive deficits in patients with AD. A previous study using anatomically segregated striatum showed that different levels of damage to the DLPFC–caudate–thalamus–DLPFC circuit in patients with mild cognitive impairment who progressed to AD served as neuroanatomical substrates of executive processing, supporting our findings.[33] Therefore, abnormal profiles of the metabolic connectivity of the striatal executive subregion with the DLPFC in patients with AD are associated with executive dysfunction, implying that involvement of the executive striatum in the generation of executive deficits may be attributable to disconnection of the specific striatocortical circuits resulting in neuron-to-neuron transmission disturbances.

Limitations

Our study has several limitations. First, our sample was relatively small because of the challenges inherent in enrolling a large group of patients who have undergone metabolic neuroimaging using a hybrid PET/MRI system. Second, this was a cross-sectional study. A longitudinal study is warranted to observe hypometabolism of the striatal executive subregion and its cortical disconnection and to understand how each corresponds to symptom progression. Third, although our AD phenotypes were defined using stringent diagnostic criteria, we did not perform pathological verification. Additionally, from a connectivity perspective, the directionality of the striatocortical connectivity could not be separated by FDG-PET imaging, which may have confounded the correlations. Finally, we were unable to investigate the association between executive function and metabolic connectivity in patients with AD because metabolic connectivity was measured at the group level, which lacked specific levels of the metabolic connectivity for each participant to analyze the correlation.

Conclusion

The results of this study further challenge the notion of equating executive skills with cortical function, especially prefrontal lobe function, in patients with AD. Our findings provide evidence of an association between the impairment of striatal executive regions and executive dysfunction as well as reduced metabolic connectivity of the striatum executive regions with the DLPFC, which might cause a specific vulnerability in patients with AD, leading them to develop executive deficits, thus providing valuable insights into the understanding of the pathogenesis of the disease.

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Contributors: L. Liu, P. Rosa-Neto and L. Wu designed the study. L. Liu, S. Yan, K. Xie and J. Lu acquired the data, which L. Liu, M. Chu, B. Nie, K. Xie, Y. Cui, D. Jiang, Z. Chen, H. Nan and L. Wu analyzed. L. Liu and P. Rosa-Neto wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors made substantial contributions to the paper.

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