RESEARCH ARTICLE

Association of Circumscribed Subcortical Gray and White Matter Lesions With Apraxic Deficits in Patients With Left Hemisphere Stroke

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Abstract

Background and Objectives

Apraxia is commonly attributed to left hemisphere (LH) lesions of the cortical fronto-temporo-parietal praxis networks or white matter lesions causing disconnections between cortical nodes. By contrast, the contribution of lesions to the subcortical gray matter, that is, basal ganglia or thalamus, to apraxic deficits remains controversial. Here, we investigate whether damage to these subcortical gray matter structures (i.e., caudate nucleus, putamen, globus pallidus, and thalamus) or the adjacent white matter tracts was associated with apraxic deficits.

Methods

We identified patients with distinct subcortical lesions with and without apraxia from a large retrospective sample of subacute LH ischemic stroke patients (n = 194). To test which subcortical structures (caudate nucleus, putamen, globus pallidus, thalamus, and adjacent white matter tracts), when lesioned, contributed to apraxic deficits, we statistically compared the proportion of lesioned voxels within subcortical gray and white matter structures between the apraxic and nonapraxic patients.

Results

Of the 194 stroke patients screened, 39 (median age = 65 years, range 30–82 years; median time poststroke at the apraxia assessment = 7 days, range 1–44 days) had lesions confined to subcortical regions (gray and white matter). Eleven patients showed apraxic deficits when imitating gestures or pantomiming object use. Region-wise statistical lesion comparison (controlled for lesion size) revealed a more significant proportion of damage ('lesion load') in the caudate nucleus in apraxic stroke patients (mean difference = 6.9%, 95% CI 0.4–13.3, p = 0.038, η_p^2 = 0.11). By contrast, apraxic patients had lower lesion load in the globus pallidus (mean difference = 9.9%, 95% CI 0.1–19.8, p = 0.048, η_p^2 = 0.10), whereas the lesion load in other subcortical structures (putamen, thalamus, and adjacent white matter tracts) did not differ significantly between the apraxic and nonapraxic patients.

Discussion

These findings provide new insights into the subcortical anatomy of apraxia after LH stroke, suggesting a specific contribution of caudate nucleus lesions to apraxic deficits.

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Glossary

AAL = Automated Anatomical Labeling; **AF** = arcuate fasciculus; **CST** = corticospinal tract; **IFOF** = inferior fronto-occipital fasciculus; **LH** = left hemisphere; **MCA** = middle cerebral artery; **MNI** = Montreal Neurological Institute.

Introduction

As a cognitive motor disorder, which elementary sensorimotor or language comprehension deficits cannot solely explain,[1] apraxia is commonly associated with cortical lesions to frontal, temporal, or parietal regions affecting the left hemisphere (LH) praxis networks[2] or with white matter lesions leading to structural disconnections between these areas.[3-5] Furthermore, studies in LH stroke patients suggest a role of subcortical gray matter structures, including the basal ganglia, in apraxia.[6,7]

However, there is a longstanding debate about whether or to what extent subcortical gray matter lesions alone cause apraxia.[8] A few neuropsychological (case) reports documented apraxic deficits in stroke patients with lesions confined to subcortical regions, including the basal ganglia, often with concomitant damage to the adjacent white matter.[9-12] Besides, apraxia has also been reported in stroke patients with thalamus lesions.[11,13] In a comprehensive review of 82 patient reports in which apraxia due to subcortical lesions was described, Pramstaller and Marsden[8] found that in most cases, the lesions were not confined to the basal ganglia or thalamus but extended into the internal capsule as well as the periventricular and peristriatal white matter. Accordingly, apraxic deficits associated with subcortical lesions have been most often attributed to damage to the subcortical white matter tracts connecting frontal, temporal, and parietal cortices rather than to the basal ganglia per se.[8,14] Notably, the available reports are mainly based on clinico-neuroradiologic lesion descriptions in patients with apraxia lacking a direct comparison with lesion sites in patients without apraxia. Therefore, the contribution of subcortical gray matter damage to apraxic deficits remains elusive.

To inform the debate, this study investigated the contribution of distinct lesions of the subcortical gray matter involving the basal ganglia or thalamus to apraxia. Based on normalized structural lesion data, we tested whether damage to these subcortical gray matter structures (i.e., caudate nucleus, putamen, globus pallidus, and thalamus) or the adjacent white matter tracts (i.e., internal capsule, corticospinal tract [CST], and inferior fronto-occipital fasciculus [IFOF]) was associated with apraxic deficits (or not).

Methods

Patient Sample

We screened the structural lesion data of 194 subacute LH ischemic stroke patients assessed for apraxia in previous studies of the University Hospital Cologne. We retrospectively identified those stroke patients based on the individuals' normalized lesion maps whose lesions affected at least one subcortical gray matter structure (i.e., caudate nucleus, putamen, globus pallidus, or thalamus) but did not extend to cortical structures. Patients were selected based on having circumscribed subcortical gray matter lesions, independent of the presence of apraxia as defined by the Cologne Apraxia Screening (Kölner Apraxie Screening, KAS).[15] Stroke patients whose lesions involved only the white matter, only cortical areas, or subcortical and cortical regions were not included in further analyses. All patients were right-handed and had no other neurologic or psychiatric diseases.

Standard Protocol Approvals, Registrations, and Patient Consents

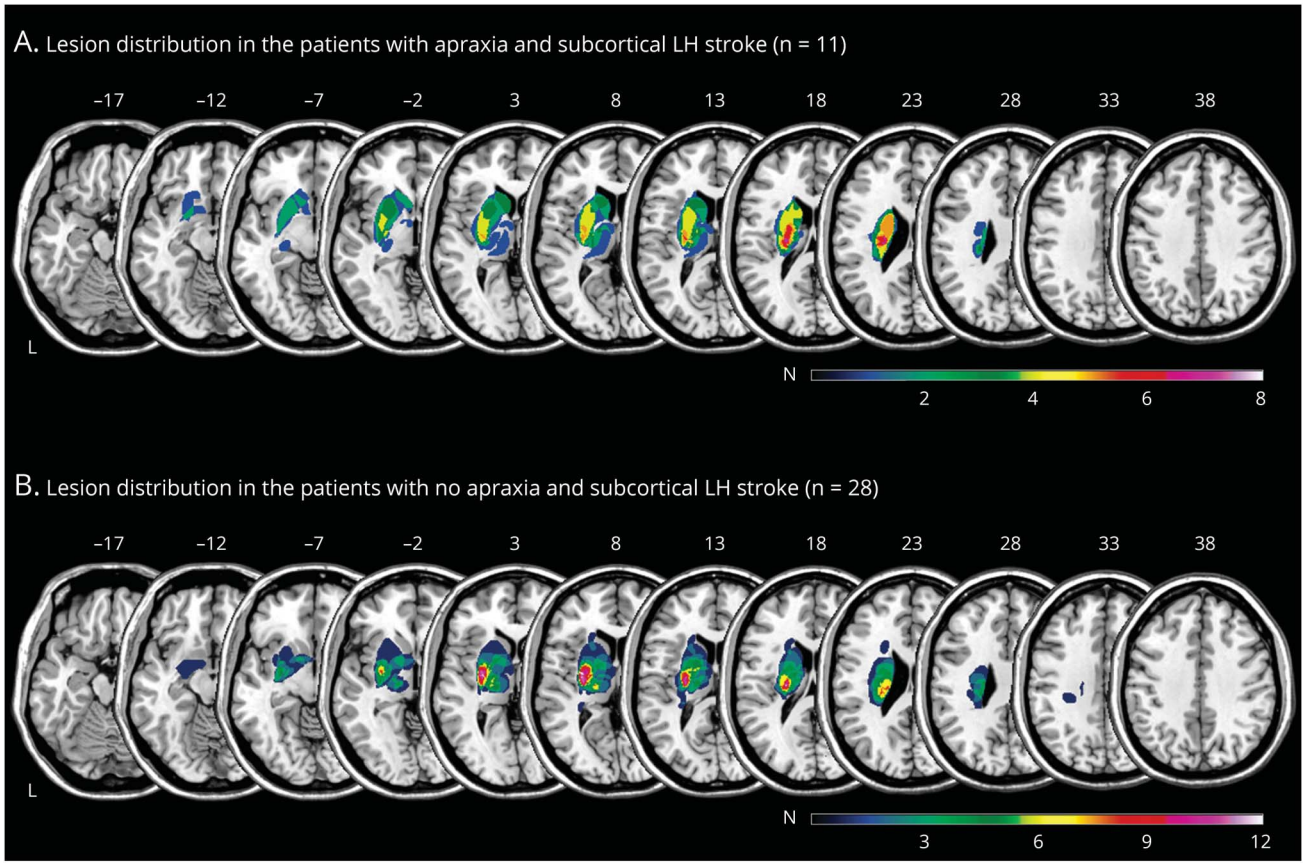
Subjects' consent for reusing their neuropsychological and clinical imaging data was obtained according to the Declaration of Helsinki, and the ethics committee of the Medical Faculty of the University of Cologne approved retrospective data analyses.

Neuropsychological Assessment

The Cologne Apraxia Screening (Kölner Apraxie Screening, KAS) evaluated praxis performance by assessing bucco-facial and arm/hand gestures with pantomime and imitation tasks.[15] In the pantomime test, the patients were shown photographs of 5 objects for actions with the face and 5 objects for actions with the upper limbs and asked to pantomime the use of the depicted objects. The correct execution of certain predefined features of the pantomime was scored, with a maximum score of 4 points per pantomime item. No point was given when movement features were absent. The imitation test required patients to reproduce 5 bucco-facial and 5 arm/hand gestures presented on photographs showing a female person performing the gestures. Four points were given for correctly imitating each gesture on the first trial. If the imitation was incorrect, the photograph was shown again, and 2 points were given for correct imitation on the second trial or no points for an erroneous second attempt. The maximum score of the KAS is 80 points (40 points for the pantomime test and 40 points for the imitation test), and patients are classified as apraxic when they score less than 76 points.[15] Patients always used their ipsilesional left, nonparetic hand for the apraxia assessment.

Besides, language functions were probed with the short version of the Aphasia Check List (ACL-K), which assesses the patient's reading aloud, auditory comprehension, verbal fluency, and verbal communication abilities.[16] The ACL-K's

Figure 1 Lesion Overlays of the Apraxic and Nonapraxic Patients With Subcortical Left Hemisphere (LH) Stroke Affecting the Basal Ganglia or Thalamus



(A) Lesion distribution in the LH stroke patients with apraxia after circumscribed subcortical lesions (n = 11). (B) Lesion distribution in the LH stroke patients without apraxia after circumscribed subcortical lesions (n = 28). Color shades represent the increasing number of overlapping lesions. Axial slices with the MNI z-coordinates from −17 to +38 are shown.

maximum score is 40 points, with a cut-off score of less than 33 points for aphasia.

Lesion Delineation and Extraction of Lesion Data

Stroke lesions were identified based on the patient's routine clinical CT (n = 8) or MRI (n = 31) scans performed at the time of admission to the hospital or within a few days of stroke onset. The median time between stroke onset and structural image acquisition for lesion delineation was 1 day (range 0–15 days). Detailed scanning parameters of the CT and MRI images varied across the sample, which was aggregated from several studies and admitting hospitals. We used diffusion-weighted imaging (DWI, n = 30) or fluid-attenuated inversion recovery (FLAIR, n = 1) images to map the lesions in patients with MRI scans. The lesion boundaries were manually delineated on axial slices of a standard Montreal Neurological Institute (MNI) template with a 1×1 mm^2 in-plane resolution using MRIcron software. Lesions were mapped in steps of 5 mm in MNI space onto the template's axial slices that were identical to or closest matched the slices of each individual's CT or MRI. Two examiners had to jointly agree on the exact location and extent of the lesion in each stroke patient. For the present retrospective analyses, we used lesion masks previously mapped for our original studies on motor cognition/apraxia. Accordingly, the lesion mapping could not be biased toward this study's aim of identifying stroke patients with circumscribed subcortical lesions to investigate their contribution to apraxia.

Involvement of subcortical gray matter structures (basal ganglia and thalamus) was determined based on the individual patient's normalized binary lesion map and verified by the Automated Anatomical Labeling (AAL)[17] atlas template implemented in MRIcron.

For statistical comparison of subcortical gray matter lesion extent between the apraxic and nonapraxic stroke patients, we overlapped the individual lesion maps with the AAL atlas and extracted for each patient the proportion of lesioned voxels (i.e., 'lesion load') within the nuclei of the basal ganglia (caudate nucleus, putamen, and globus pallidus) and the thalamus[18] of the LH. Based on the Natbrainlab white matter atlas[19] provided by MRIcron, we also selected 2 closely adjacent white matter tracts that were additionally lesioned in

almost all the stroke patients (>90%), namely the internal capsule and CST. Besides, we identified the following white matter tracts connecting frontal, temporal, and parietal regions previously associated with apraxia[5]: the fronto-temporal segment of the arcuate fasciculus (AF), the fronto-parietal segment of the AF that partially overlaps with the ventral component of the superior longitudinal fasciculus (i.e., SLF-III),[20] and the IFOF. As the AF and SLF-III had only marginal overlap with the patients' subcortical lesions (mean overlap <2%), they were not included in the primary lesion analysis (but see eAppendix, links.lww.com/WNL/C987: Supplementary Analysis that yielded no differential lesion load in these white matter tracts). The lesion load was calculated per patient and LH tract using the Natbrainlab atlas.[19] To compute the region-wise lesion load, the individual original lesion maps were interpolated to a resolution of $1 \times 1 \times 1$ mm^3 voxel size to match the resolution of the brain atlases. The interpolated lesion maps were also used to estimate the patients' lesion size.

Statistical Analyses of Behavioral and Lesion Data

Statistical analyses of behavioral and atlas-based region-wise lesion data were performed using IBM SPSS Statistics (version 25). Nonparametric independent samples Mann-Whitney *U* tests (2-sided) compared demographic, clinical, and neuropsychological data between the stroke patients with and without apraxia. Nonparametric Spearman correlation analyses (2-sided) were used to assess the association between stroke patients' overall lesion size and the severity of apraxia and aphasia.

To test for a difference in the proportion of lesioned voxels within subcortical gray and white matter structures between the apraxic and nonapraxic patients, the mean percentages of damage ('lesion load') per subcortical region were analyzed in a mixed model analysis of covariance (ANCOVA) with subcortical region (caudate nucleus, putamen, globus pallidus, thalamus, internal capsule, CST, and IFOF) as within-subject factor and apraxia (apraxic and nonapraxic) as between-subjects factor. The patients' total number of lesioned voxels was included as a covariate to control for overall lesion size. Putative group differences in subcortical lesion load were assessed post hoc by simple main effects (controlling for lesion size). An alpha level of $p < 0.05$ was used for all analyses to determine significance. Effect sizes are reported as Cohen *d* or partial eta squared (η_p^2).

Data Availability

The data supporting this study's findings are not publicly available due to the ethical consensus on data protection approved by the local ethics committee and signed by the patients. The authors may provide the data on reasonable request.

Results

Patient Sample Characteristics

Of the 194 subacute LH ischemic stroke patients screened for circumscribed subcortical lesions involving at least one subcortical gray matter structure (i.e., basal ganglia or thalamus), 39 patients were identified (n = 19 female; median age = 65 years, range 30–82 years; see Figure 1 for the lesion overlays). The median time interval between stroke onset and apraxia assessment (hereafter referred to as 'time poststroke') was 7 days (range 1–44 days). Demographic, clinical, and neuropsychological data of the LH stroke patients with and without apraxia are presented in Table.

Based on the KAS[15] performance, 11 of the 39 LH stroke patients (28%) with circumscribed subcortical lesions involving the basal ganglia or thalamus were classified as apraxic. Most apraxic patients (n = 8, 73%) had deficits in imitating gestures and pantomiming object use, 2 patients showed

Table Demographic, Clinical, and Neuropsychological Data of the Left Hemisphere Stroke Patients With and Without Apraxia After Circumscribed Subcortical Lesions Affecting the Basal Ganglia or Thalamus

	Apraxic patients (n = 11)	Nonapraxic patients (n = 28)
KAS total[a]	67 (62–76)	80 (77–80)
ACL-K total	26.5 (7.5–37)	35.5 (11–40)[b]
Age (y)	71 (48–82)	60 (30–81)
Time stroke—assessment (d)	5 (1–24)	10 (1–44)
Time stroke—imaging (d)	0 (0–15)	1 (0–14)
Time imaging—assessment (d)	5 (0–22)	6.5 (0–37)
Lesion size (voxels)	6,128 (224–23,159)	2,199.5 (192–28,995)

KAS = Kölner (Cologne) Apraxia Screening (maximum score = 80 points; cut-off score for apraxia ≤76 points).
ACL-K = Aphasia Check List-short version (maximum score = 40 points; cut-off score for aphasia <33 points).
The median and range (in parentheses) are given.
[a] Classification criterion.
[b] $p < 0.05$ (Mann-Whitney *U* test).

isolated imitation deficits, and 1 patient was impaired in pantomiming only. Bucco-facial and limb apraxia was present in 8 apraxic patients, 2 patients had limb-related praxis deficits only, and 1 patient had isolated bucco-facial apraxia as assessed with the KAS.

Compared with the nonapraxic patient group (n = 28), the LH stroke patients with apraxia were more impaired in language functions, as indicated by the ACL-K[16] ($U = 53.5$, $p = 0.002$, $d = 1.16$). According to the ACL-K, there was only 1 apraxic patient (out of 11) who was not classified as aphasic. Conversely, 10 LH stroke patients without apraxia suffered from aphasia. The apraxic and nonapraxic patients did not differ significantly concerning age ($U = 111.5$, $p = 0.184$, $d = 0.44$), time post-stroke at apraxia assessment ($U = 107.0$, $p = 0.141$, $d = 0.48$), time between stroke and structural image acquisition for lesion delineation ($U = 115.5$, $p = 0.213$, $d = 0.39$), time between image acquisition and apraxia assessment ($U = 104.5$, $p = 0.121$, $d = 0.51$), and lesion size ($U = 111.0$, $p = 0.180$, $d = 0.44$). Moreover, total lesion size did not significantly correlate with the severity of apraxia (as indexed by the KAS score; $\rho = -0.197$, $p = 0.229$), suggesting that apraxia was not solely related to larger lesions but might be associated with specific subcortical damage in the current LH stroke patients. By contrast, there was a significant correlation between stroke patients' overall lesion size and aphasia severity (as indexed by the ACL-K score; $\rho = -0.380$, $p = 0.017$): Larger lesions were associated with more severe aphasia (i.e., lower scores in the ACL-K).

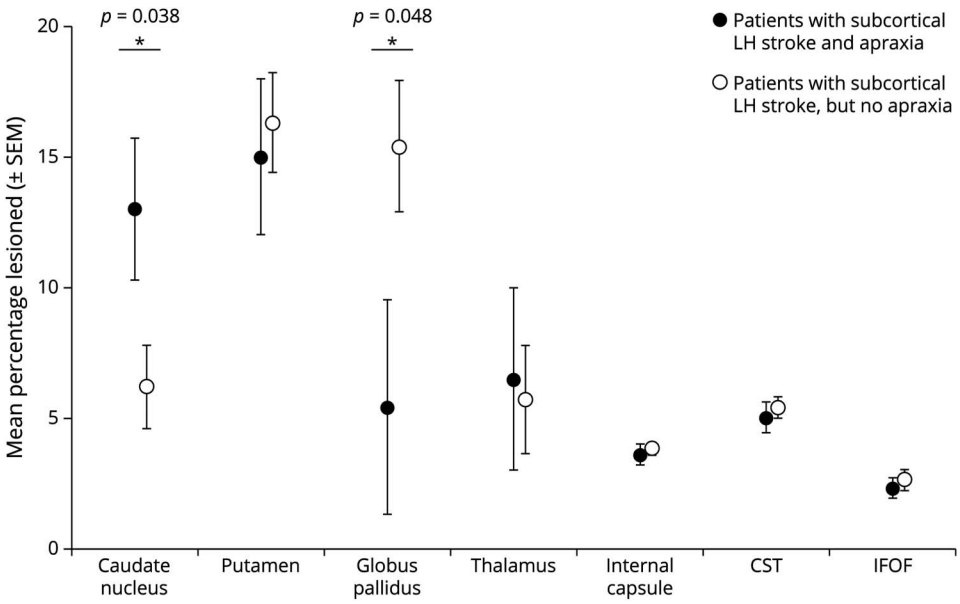
Statistical Lesion Comparison

The ANCOVA testing for a differential proportion of lesioned voxels within the selected subcortical regions between the apraxic and nonapraxic stroke patients, while controlling for overall lesion size, revealed a significant subcortical region × apraxia interaction effect [$F_{(6,216)} = 2.31$, $p = 0.035$, $\eta_p^2 = 0.06$]. Post hoc simple main effects (controlled for lesion size) showed a greater proportion of damage ('lesion load') in the caudate nucleus in the LH stroke patients with apraxia compared with the nonapraxic patients [$F_{(1,36)} = 4.65$, $p = 0.038$, $\eta_p^2 = 0.11$, mean difference = 6.9%, 95% CI 0.4–13.3; Figure 2]. By contrast, apraxic patients had lower lesion load in the globus pallidus [$F_{(1,36)} = 4.18$, $p = 0.048$, $\eta_p^2 = 0.10$, mean difference = 9.9%, 95% CI 0.1–19.8]. There were no significant group differences in lesion load in the other subcortical gray matter structures (putamen [mean difference = 1.3%, 95% CI −6.1—8.6], thalamus [mean difference = 0.8%, 95% CI −7.7—9.2]; all $p > 0.728$, all $\eta_p^2 < 0.01$) or adjacent white matter tracts (internal capsule [mean difference = 0.3%, 95% CI −0.7—1.2], CST [mean difference = 0.3%, 95% CI −1.2—1.9], IFOF [mean difference = 0.3%, 95% CI −1.4—2.0]; all $p > 0.561$, all $\eta_p^2 < 0.01$).

Discussion

This study investigated the contribution of subcortical gray matter damage to apraxia in 39 retrospectively identified subacute LH stroke patients with circumscribed subcortical lesions involving the basal ganglia (caudate nucleus, putamen, and globus pallidus) or the thalamus but sparing the cortex, as apparent on structural brain imaging. Region-wise statistical comparison of the lesion extent in subcortical gray and adjacent white matter between the apraxic and nonapraxic stroke patients revealed that apraxia was explicitly associated with more significant damage ('lesion load') in the caudate nucleus.

Figure 2 Mean Percentage of Damage ('Lesion Load') in Subcortical Gray Matter Structures and Adjacent White Matter Tracts in the Apraxic and Nonapraxic Patients With Subcortical Left Hemisphere (LH) Stroke



Region-wise statistical lesion comparison controlling for lesion size revealed a more significant proportion of lesioned voxels ('lesion load') in the caudate nucleus in the LH stroke patients with apraxia (n = 11; black circles) compared with the LH stroke patients without apraxia (n = 28; white circles). By contrast, apraxic patients had lower lesion load in the globus pallidus. At the same time, there were no significant differences in lesion load between the apraxic and nonapraxic patients in the other subcortical gray matter structures (putamen and thalamus) or adjacent white matter tracts (internal capsule, CST, and IFOF). Adjusted mean percentages after controlling for overall lesion size are given. Error bars indicate the standard error of the mean (SEM). CST = corticospinal tract; IFOF = inferior fronto-occipital fasciculus.

By contrast, after accounting for lesion size, apraxic patients had a lower lesion load in the globus pallidus, while the lesion load in other subcortical structures of the gray (putamen and thalamus) and white matter (internal capsule, CST, and IFOF) was comparable between the apraxic and nonapraxic patients.

The association between caudate nucleus lesions and apraxia aligns with early reports of apraxic (imitation and pantomime) deficits in single patients with LH stroke confined to the caudate nucleus.[10,21] Moreover, our results converge with a crucial role of the caudate in higher-order (cognitive) motor functions, including the selection of appropriate actions and selective inhibition of competing action alternatives,[22] spatio-temporal movement sequencing,[23,24] or generation of detailed task-specific movement/kinematic patterns of ongoing actions,[25] as implicated by neurophysiologic studies in monkeys[23] and rodents,[25] functional imaging studies in healthy subjects,[22] and lesion studies in stroke patients.[7,24]

Notably, the striatum (caudate nucleus and putamen) receives direct topographical input from distributed cortical areas, including the dorsolateral prefrontal and posterior parietal cortices. It is thus involved in multiple, parallel organized cortico-basal ganglia-thalamo-cortical circuits contributing to diverse motor and cognitive control behaviors.[26,27] The features of the basal ganglia and thalamus that support parallel distributed processing are well elaborated in a recent review by Nadeau.[28] This review highlights that basal ganglia dysfunction affects cognitive or motor functions presumably through disturbed dimensionality reduction in cortical systems. Disturbances of cognitive motor functions have been commonly observed in clinical conditions affecting the input nuclei of the basal ganglia, including the caudate nucleus. By contrast, damage to the output structures of the basal ganglia, such as the globus pallidus, seems to have only subtle or imperceptible behavioral effects.[29] In this study, LH stroke patients with apraxia had a lower lesion load in the globus pallidus. In other words, a more significant lesion load in the globus pallidus was found in the patients without apraxia (after accounting for overall lesion size), consistent with observations that a wide range of behavioral functions is spared after transient inactivation or permanent lesion of the globus pallidus.[29] Similarly, deep brain stimulation of the globus pallidus alleviates striatal-associated motor and cognitive symptoms in neurologic disorders, presumably by modulating faulty output signals from the basal ganglia to the cortex.[30]

Apraxic deficits have also been documented in patients with striatal neurodegeneration (including the caudate nucleus), such as corticobasal syndrome[31] or Parkinson[32] and Huntington disease.[33] However, the additional frontal and parietal atrophy associated with corticobasal syndrome[31] and the progressive functional and structural network alterations affecting cortico-striatal circuits in Parkinson[34] and Huntington disease[33] hamper conclusions about the precise role of striatal dysfunction in these conditions.

A similar limitation of this study concerns the fact that we cannot determine whether the apraxic deficits in our stroke patients with subcortical lesions are primarily due to dysfunction of the caudate nucleus per se or whether they reflect indirect dysfunction (i.e., diaschisis) of the cortical regions to which the basal ganglia project, that is, through disrupted cortico-striatal circuits.[27] In this vein, a recent lesion network mapping study in 101 chronic LH stroke patients with apraxia revealed a large number of disconnections affecting the caudate nucleus associated with poor hand gesture performance: These included disconnections of short fibers within the basal ganglia and long fibers between the cortex and the basal ganglia.[5] These findings suggest that structural disconnections to and within the basal ganglia contribute to persistent apraxic deficits. The current stroke patients were assessed in the early subacute phase poststroke (Table). Thus, further research is warranted to investigate the role of basal ganglia disconnections in (sub) acute stroke patients with apraxia.

Another potential mechanism proposed to account for cognitive deficits observed after subcortical lesions due to striato-capsular infarction is cortical hypoperfusion.[35] The 2 subcortical structures (caudate nucleus and pallidum) for which we observed a differential effect on apraxia in this study are mainly supplied by lateral lenticulostriate arteries, long penetrating branches of the M1 portion of the middle cerebral artery (MCA). Considering the basal ganglia vascularization, cognitive deficits after ischemic striato-capsular lesions have been attributed to reduced blood flow to the cerebral cortex in the context of (temporary) occlusion of the M1 portion of the MCA.[35,36] Although adequate end-to-end cortical anastomoses between branches of the MCA, anterior cerebral artery, and posterior cerebral artery enabling an efficient collateral blood supply from the anterior and posterior cerebral arteries to the MCA cortical branches[37] may prevent the occurrence of cortical infarction, transient neuronal dysfunction at the cortical level may still occur, albeit not sufficiently severe to cause cortical structural alterations detectable by standard CT or MRI sequences.[35] Indeed, cortical hypoperfusion has been related to aphasia or neglect in patients with acute subcortical (striato-capsular) stroke lesions.[38-41] However, no specific subcortical lesion site was associated with aphasia or neglect in these studies. Furthermore, other studies did not find a consistent association between cortical hypoperfusion and aphasia after acute subcortical LH stroke.[42,43]

In this study, we identified the caudate nucleus as the only subcortical structure whose amount of damage (independent of total lesion size) was associated with apraxia. Conversely, stroke patients with apraxia had a lower lesion load in the globus pallidus. This pattern of differential effects of the caudate nucleus and globus pallidus renders it unlikely that the apraxic deficits in our subcortical stroke patients were predominantly related to (undetected) cortical lesions or dysfunction. Although previous studies have investigated the role of cortical hypoperfusion for aphasia or neglect in patients with acute subcortical stroke lesions, to the best of

our knowledge, no such study has been performed in apraxia. Therefore, further studies (for example, using PET or arterial spin labeling methodology) are needed to clarify the role of cortical dysfunction in subcortical stroke patients with apraxia.

In conclusion, the present findings suggest that damage to the caudate nucleus—as the principal subcortical input structure embedded in different basal ganglia-thalamus-cortex circuits—can disrupt cognitive motor functions, manifesting clinically as apraxia. The exact contribution of the caudate nucleus to praxis warrants further investigation as the present lesion analysis approach cannot differentiate direct or indirect (i.e., diaschitic) effects.

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Disclosure

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