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Involvement of Thalamocortical Networks in Patients With Poststroke Thalamic Aphasia

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Abstract

Background and Objective

Theories assume that thalamic stroke may cause aphasia because of dysfunction in connected cortical networks. This takes into account that brain functions are organized in distributed networks, and in turn, localized damage may result in a network disorder such as thalamic aphasia. With this study, we investigate whether the integration of the thalamus into specific thalamocortical networks underlies symptoms after thalamic stroke. We hypothesize that thalamic lesions in patients with language impairments are functionally connected to cortical networks for language and cognition.

Methods

We combined nonparametric lesion mapping methods in a retrospective cohort of patients with acute or subacute first-ever thalamic stroke. A relationship between lesion location and language impairments was assessed using nonparametric voxel-based lesion-symptom mapping. This method reveals regions more frequently damaged in patients with compared with those without a symptom of interest. To test whether these symptoms are linked to a common thalamocortical network, we additionally performed lesion-network-symptom mapping. This method uses normative connectome data from resting-state fMRI of healthy participants (n = 65) for functional connectivity analyses, with lesion sites serving as seeds. Resulting lesion-dependent network connectivity of patients with language impairments was compared with those with motor and sensory deficits as baseline.

Results

A total of 101 patients (mean [SD] age 64.1 [14.6] years, 57 left, 42 right, and 2 bilateral lesions) were included in the study. Voxel-based lesion-symptom mapping showed an association of language impairments with damage to left mediodorsal thalamic nucleus lesions. Lesion-network-symptom mapping revealed that language compared with sensory deficits were associated with higher normative lesion-dependent network connectivity to left frontotemporal language networks and bilateral prefrontal, insulo-opercular, midline cingular, and parietal domain-general networks. Lesions related to motor and sensory deficits showed higher lesion-dependent network connectivity within the sensorimotor network spanning prefrontal, precentral, and postcentral cortices.

Discussion

Thalamic aphasia relates to lesions in the left mediodorsal thalamic nucleus and to functionally connected left cortical language and bilateral cortical networks for cognitive control. This suggests that dysfunction in thalamocortical networks contributes to thalamic aphasia. We propose that inefficient integration between otherwise undamaged domain-general and language networks may cause thalamic aphasia.

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Glossary

BA = Brodmann area; **BOLD** = blood-oxygenation-level dependent; **DWI** = diffusion-weighted imaging; **FC** = functional connectivity; **FLAIR** = fluid-attenuated inversion recovery; **FWE** = family-wise error; **LNC** = lesion-dependent network connectivity; **LNSM** = lesion-network-symptom mapping; **MNI** = Montreal Neurological Institute; **ROI** = region of interest; **SPM12** = Statistical Parametric Mapping, version 12; **VLSM** = voxel-based lesion-symptom mapping.

Thalamic stroke can cause various symptoms that may affect motor and sensory as well as cognitive functions, such as language. In some aspects, these language impairments resemble those observed after left hemisphere cortical stroke and are referred to as thalamic aphasia. Theories assume that thalamic aphasia is caused by dysfunction in connected cortical networks.[1] This takes into account that brain functions are organized in distributed networks, and in turn, localized damage may result in a network disorder such as thalamic aphasia. To date, these theories are derived from small samples, imaging in healthy humans, or animal studies.[1-4] In the absence of empirical evidence from larger populations, the functional contribution of the thalamus to language remains a matter of ongoing debate and challenges its integration into corticocentric models of cognition and language. With this perspective, the study addresses a clinically relevant area of research that takes into account that language is organized in distributed networks that critically engage subcortical structures and, in turn, allows for the possibility that their damage may result in a network disorder such as thalamic aphasia.

Based on case series and reports (for references, see eTable 1, links.lww.com/WNL/C447), lesions in various nuclei of the dominant (left) thalamus are implicated in language impairments. This includes the anterior and, most prominently, ventral anterior nuclei, the ventral lateral nucleus, the mediodorsal and centromedian nuclei as well as the dorsal lateral nucleus and pulvinar. Among the highly variable language impairments reported after thalamic lesions (eTable 1) are fluent output with frequent paraphasias and impaired comprehension, nonfluent or reduced spontaneous speech output, perseverations and word-finding difficulties, decreased verbal fluency, confabulations with incoherent spontaneous speech, and dyslexia. Anosognosia for the impairment may also occur in addition to other cognitive executive deficits.

Despite distinct associations between language impairments and focal lesion locations, an indirect influence of the dominant thalamus on cortical language processing has been favored. This is mainly based on the knowledge of connectivity between thalamic nuclei and cortical regions involved in language and cognitive control in healthy humans without aphasia.[3,5-7] The variety of thalamic language impairments are then interpreted as a consequence of subsequent dysfunction in broader networks for language and cognition in which cortical activation is assumed to be modulated by the thalamus allowing for an allocation of processing resources.[2,3,5-8] In this context, the phenomenon that symptoms emerge from dysfunction in brain regions remote from but functionally connected to the lesioned tissue can be referred to as diaschisis.[9] This translates into the hypothesis that thalamic stroke may cause aphasia due to diaschisis in connected cortical networks for language and cognition. However, it has not yet been systematically demonstrated that thalamic language impairments arise from a functional disconnection between thalamic nuclei and cortical language networks.

With this retrospective study of patients with thalamic lesions, we aimed to investigate the neural basis of thalamic aphasia. To test for associations between lesion location and language impairments, with sensory and motor deficits serving as a control, first we used voxel-based lesion-symptom mapping (VLSM). On a voxel-by-voxel basis, it allows to examine whether certain lesion locations are statistically more frequent in patients with compared with those without a symptom of interest.[10] This method is based on the assumption that certain brain functions and symptoms anatomically localize on circumscribed brain regions. However, it is limited in its ability to explain symptoms that arise from lesions to anatomically or functionally connected distributed networks. Therefore, in a second step, we tested whether lesions associated with these symptoms map on different functional networks potentially affected by diaschisis. To this end, we applied the method of lesion-network-symptom mapping (LNSM), an adapted version of the original lesion-network mapping approach.[11,12] This method uses normative connectome data from resting-state fMRI of healthy participants for functional connectivity (FC) analyses, with lesion sites serving as seeds. The resulting lesion-dependent networks are compared according to the assumption that regions with high normative connectivity to the lesion are vulnerable to diaschisis.[13] Direct comparison of lesion-dependent networks causing language impairments and networks causing other symptoms as baseline thus allows us to attribute the phenomenon of thalamic aphasia to specific thalamocortical networks. We hypothesize that a distinct pattern of thalamocortical connectivity with the left lateralized frontotemporal language network and bilateral networks involved in cognitive control relates to observed language impairments.

Methods

Participants

All patients included in this study were admitted to the University of Leipzig Medical Center between 2011 and 2019. We retrospectively identified patients based on radiologic reports

that contained the keyword "Thalamus" or "thalamisch" (engl. thalamic) or "thalamo" by using an automated review of radiology reports (cranial CT or MRI). Inclusion citeria for further analyses were (1) acute or subacute ischemic, (2) first-ever thalamic stroke lesion in (3) patients aged 18 years or older. Exclusion criteria were defined as (1) chronic, (2) nonischemic (e.g., hemorrhage, tumor, or metastasis), or (3) previous other stroke lesions. We also excluded patients with (4) concurrent anterior circulation lesions or (5) major microvascular brain damage (Fazekas scale >2) or relevant brain atrophy according to the radiology report. Furthermore, patients with (6) other preexisting neurologic disorders affecting the CNS (e.g., dementia and Parkinson disease) were excluded from the analyses. Hemorrhagic or tumor lesions were not included because surrounding edema and/or reorganization processes may weaken lesion-symptom associations.

Assessment of Stroke Symptoms of Interest

The assessment of stroke symptoms of interest was based on a retrospective review of the complete medical report of all patients who met the inclusion criteria. For this purpose, all documented deficits related to the acute or subacute event were reviewed in detail. As part of stroke routine care, patients are examined repeatedly by treating physicians within the first 72 hours of hospital admission. In addition, all patients are evaluated by a trained speech and language therapist, physiotherapist, and occupational therapist at least once within the first 24 hours, resulting in a relatively reliable screening for and complete record of stroke symptoms. Because of the sometimes mild and transient symptoms in thalamic stroke, a symptom was considered present if documented at least once during the initial neurologic examination in the emergency department, repeated medical visits, or therapy sessions. No quantitative language tests were performed as part of routine examination, but a standardized instrument (Aphasia Check List) was applied by speech and language therapists if aphasia was suspected.[14] We interpreted the presence of language impairments based on the documentation of reduced fluency, spontaneous speech or word-finding difficulties, paraphasias, neologisms, lexical-semantic deficits, problems during naming or repetition, and impaired comprehension or reading. Dysarthria included slurred or slow speech. Motor deficits included all documented disorders of movement as follows: altered muscle tone (dystonia or asterixis), impairments of coordination (e.g., ataxia, dysmetria, and dysdiadochokinesia), standing and gait, or weakness (facial, pronation, or downward drift during arm and leg examination) in at least 1 body region (face, arm, or leg). Sensory deficits included unilateral abnormalities in touch, pain, or temperature sensation and reported paresthesias in at least 1 body region.

Brain Imaging and Lesion Delineation

Lesion delineation was performed on clinical routine CT or MRI. Imaging was usually performed within the first hours of admission. In cases without lesion demarcation on CT, MRI was performed within a few days of stroke onset. In all cases, documentation of stroke symptoms and imaging acquisition for lesion delineation was within the first 2 weeks after stroke onset. MRI scans including diffusion-weighted imaging (DWI; voxel size $1.8 \times 1.8 \times 3.0$ mm^3) and fluid-attenuated inversion recovery (FLAIR; voxel size $0.9 \times 0.9 \times 3.0$ mm^3) images were acquired at 3 tesla with a Siemens Magnetom Trio Tim. CTs were obtained with a Philips Ingenuity 128 Scanner, and all scans were reconstructed at a 1.25-mm slice interval during data acquisition. Lesion delineation was performed in MRIcron[15] by a single reviewer (S.H.-R.) blinded to the patients' symptoms on either CT (n = 5) or MRI (n = 96) scans. All lesion maps were supervised by 2 neurologists experienced in stroke imaging (A.S. and M.P.) and used for cost function masking during normalization. Corresponding CT and MRI scans were normalized to MNI152 (Montreal Neurological Institute) space and resliced to 1-mm isotropic voxels using the Clinical Toolbox[16] for SPM12 (v7487, Wellcome Trust Centre for Neuroimaging, London, United Kingdom) under MATLAB (R2018b, The MathWorks Inc, Natick, MA). The resulting normalization parameters were also applied to the native space lesion maps, which were then used for further lesion analyses in MNI space.

Voxel-Based Lesion-Symptom Mapping

To test for associations between the lesion location and stroke symptoms, we performed VLSM using the NiiStat software[17] under MATLAB (R2018b). Voxels damaged in at least 10% of all patients were included in the analyses. We tested for group differences between patients with and without a symptom of interest (language impairments, dysarthria, and right or left sensory or motor deficits) by means of 1-tailed Liebermeister tests for binomial data. To control the family-wise error (FWE) rate, the null distributions of the maximum z-score were obtained by 5,000 random permutations. Results were thresholded at $p(FWE) < 0.05$ on the voxel level. Anatomic labeling was performed with a thalamic nuclei probabilistic atlas.[18]

Lesion-Network-Symptom Mapping

To test whether lesions associated with symptoms of interest map on different functional brain networks, we applied LNSM. This method is based on resting-state fMRI data of unrelated healthy controls. Here we used data of elderly subjects from the publicly available 3-tesla Enhanced Rockland Sample[19] (n = 65, mean age = 56 years, 48% female, 85% right handed, and 11% ambidextrous). Imaging details can be found in ref. 19. Data analysis was performed with SPM12 and in-house tools using MATLAB (R2018b) similar to the procedures described in detail in a previous publication.[11] In brief, the first 4 functional (echo-planar imaging) scans were excluded from further analyses to allow for magnetic field saturation. Preprocessing for the remaining scans included correction for differences in slice time acquisition, motion correction, T1-coregistration, and normalization of all functional scans to MNI space. In addition, all functional images were convolved with an isotropic gaussian smoothing kernel with full width at half maximum of 5 mm to account for residual anatomical variance and for improvement of the signal-to-noise ratio. Signal variance over time explained by nuisance variables was removed using a multiple regression

approach. Nuisance variables were motion parameters (as first- and second-order terms) and the first 5 principal components of the signals from white matter and cerebrospinal fluid (as first-order terms). Residual BOLD time series were bandpass filtered (0.01–0.08 Hz). Regions of interest (ROIs) were defined as individual lesion masks spatially limited to a mask representing the bilateral thalamus and served as seeds for FC analyses.[18] FC was calculated as Fisher-transformed Pearson correlation coefficients between mean ROI time series and the time series of all other voxels in the brain. The resulting connectivity maps were averaged over all patients to obtain a single lesion-dependent network for every patient. To map lesion-dependent networks to symptoms, LNSM was performed with nonparametric permutation testing.[20] To reveal differences in lesion-dependent networks between patient groups (e.g., language impairments vs no language impairments), 2-sample t tests were computed for every voxel. The null distribution of the extent of the largest cluster (given a cluster-defining threshold of $p < 0.001$) was obtained by 5,000 repetitions of the statistical test with randomly assigned group labels. The initial test results (with correct group assignments) were then thresholded at a cluster extent corresponding to p(FWE) < 0.05 at the cluster level. Anatomical labeling was performed with the Laboratory of Neuro Imaging probabilistic brain atlas and the Brodmann maps provided with MRIcron.[21,22]

Standard Protocol Approvals, Registrations, and Patient Consents

In compliance with laws and regulations of the Federal State of Saxony, this retrospective study did not require an ethics committee approval (§34 Sächsisches Krankenhausgesetz). On the legal basis of the University of Leipzig Medical Center admission contract, patients or their legal guardian gave written consent to the storage of all medical data. By law (§34 Sächsisches Krankenhausgesetz), physicians are allowed to process medical data stored within their institution (University of Leipzig Medical Center) for scientific purposes.

Data Availability

We have made all data that support our findings (normalized lesion maps, lesion-dependent networks, and behavioral data that allowed VLSM and LNSM), which we can legally share accessible through FigShare (https://figshare.com/articles/dataset/Thalamic_Aphasia/19154153). This study is reported in accordance with the STROBE checklist.[23]

Results

Demographics and Clinical Characteristics

Of the 267 patients identified in the report review, 101 patients (64.1 ± 14.6 years; mean ± SD, 40 females, 96 right handed) met the inclusion criteria. Fifty-seven patients had left, 42 patients right, and 2 patients bilateral thalamic lesions. The average time between stroke onset and examination documenting stroke symptoms of interest was 1.0 day (SD 1.23; range 0–11 days). A total of 17 patients were found to have language impairments (for a detailed deficit description and imaging of the respective patients, see Table 1 and Figure 1, respectively). Forty-eight patients presented with dysarthria, 44 patients with right and 32 patients with left motor deficits, as well as 34 patients with right and 37 patients with left sensory deficits.

Voxel-Based Lesion-Symptom Mapping

All lesions were distributed in the posterior circulation territory, with a maximum lesion overlap in the left ventral lateral nucleus of the thalamus (n = 24/101 patients, Figure 2A). Only voxels affected in at least 10% (n ≥ 10) of all patients were subjected to the subsequent VLSM analyses. Therefore, parts of both thalami (i.e., the most lateral, posterior, and anterior edges) could not be included in the analyses (Figure 2B).

For patients with compared with patients without language impairments, VLSM identified a significant association in the left mediodorsal thalamic nucleus (102 voxels, MNI: −12, −15, 1). Right motor and sensory deficits were linked to contralateral (left) ventral lateral (819 voxels, MNI: −17, −21, 2) and ventral lateral and posterolateral (660 voxels, MNI: −17, −20, 3) thalamic nuclei, respectively. Although regions associated with language were spatially separate from those associated with right motor or sensory deficits, the latter 2 overlapped in the ventral lateral nucleus (Figure 3). A mirrored pattern emerged in the contralateral (right) ventral lateral and posterolateral nucleus for left motor (871 voxels, MNI: 15, −17, 4) and sensory deficits (894 voxels, MNI: 17, −19, 3). No associations were found for dysarthria. Adding lesion volume as a covariate of no interest to the analyses did not change the results (not shown).

Lesion-Network-Symptom Mapping

Patients with compared with patients without language impairments showed significantly higher lesion-dependent network connectivity (LNC, p(FWE) < 0.05 at the cluster level) with the left superior and middle frontal gyrus (Brodmann areas [BAs] 9, 10, 46, corresponding to the ventral and dorsolateral prefrontal cortex) and the left inferior parietal lobe (BA 39, 40). In addition, these patients had higher LNC with the left insula and the left inferior frontal gyrus (BA 45, 47), the left inferior and middle temporal gyrus (BA 20, 21, 37), as well as the left mediodorsal and anterior thalamic nuclei (Figure 4A and Table 2). All significant clusters were located in the left hemisphere. By contrast, dysarthria was associated with higher right superior and middle frontal gyrus (BA 9, 10, 46) LNC when compared with lesion-dependent networks of patients without dysarthria. Furthermore, it was linked to higher LNC with the bilateral cingulate cortex (BA 24, 32), the right supplementary motor cortex (BA 6), and the left cerebellum (Figure 4B and Table 2).

A different FC pattern emerged for right and left sensory and motor deficits compared with language and dysarthria. For better comparison, in the following, we will focus on right-sided deficits (for left-sided deficits, see eFigure 1, eTable 2, links.lww.com/WNL/C447). Patients with compared with patients without right sensory deficits were characterized by higher LNC with the bilateral prefrontal cortex (middle and

Table 1 Characteristics of Patients With Language Impairments

ID	Sex	Age	Language impairments	Other symptoms
08	f	86	Reduced spontaneous speech and impaired comprehension	Right motor deficits and dysarthria
09	m	79	Reduced spontaneous speech, impaired comprehension, naming difficulties, and impaired lexical-semantic abilities	Dysarthria
10	m	58	Word-finding difficulties, semantic paraphasias, dyslexia, and impaired self-correction	Right motor and sensory deficits and dysarthria
11	f	76	Impaired comprehension, neologisms, semantic paraphasias, word-finding difficulties, paragrammatism, and dyslexia	Right motor deficits
12	f	72	Impaired comprehension and semantic paraphasias	Right motor and sensory deficits
20	f	89	Impaired comprehension, neologisms, and phonemic and semantic paraphasias	Right motor and sensory deficits and dysarthria
37	m	48	Reduced spontaneous speech	Right facial palsy and dysarthria
54	f	25	Impaired comprehension and word-finding difficulties	None
86	m	50	Reduced spontaneous speech and word-finding difficulties	Right motor and sensory deficits and dysarthria
117	f	77	Reduced spontaneous speech, word-finding difficulties, and semantic paraphasias	Right motor deficits and dysarthria
125	f	74	Reduced spontaneous speech	Right motor deficits
131	f	54	Word-finding difficulties, dyslexia, and impaired self-correction	Right motor and sensory deficits and dysarthria
150	f	21	Word-finding difficulties	Right facial palsy
154	f	51	Word-finding difficulties	Right facial palsy
161	m	86	Reduced spontaneous speech, word-finding difficulties, and phonemic paraphasias	None
175	f	86	Reduced spontaneous speech, impaired comprehension, word-finding difficulties, neologisms, and semantic paraphasias	Right motor deficits
183	f	67	Reduced spontaneous speech and word-finding difficulties	Right motor deficits and dysarthria

Patient ID, gender: m = male and f = female, age in years, language impairments according to neurologic or speech and language therapist examination, and other symptoms connected to the acute or subacute event.

superior frontal gyrus and orbitofrontal cortex), postcentral/superior parietal cortex (left > right), and left precentral cortex, as well as with the left ventral lateral thalamic nucleus and pulvinar. In addition, these patients showed higher bilateral cerebellar (right > left), temporal, and mesiotemporal connectivity (Figure 4C and eTable 2). A very similar pattern was found for patients with compared with patients without right motor deficits. It comprised higher LNC with the bilateral middle and superior frontal gyrus, left precentral and postcentral cortex, left ventral lateral thalamic nuclei, and pulvinar. In addition, higher LNC was found with the bilateral basal ganglia (putamen and pallidum) and right cerebellum (Figure 4D and eTable 2).

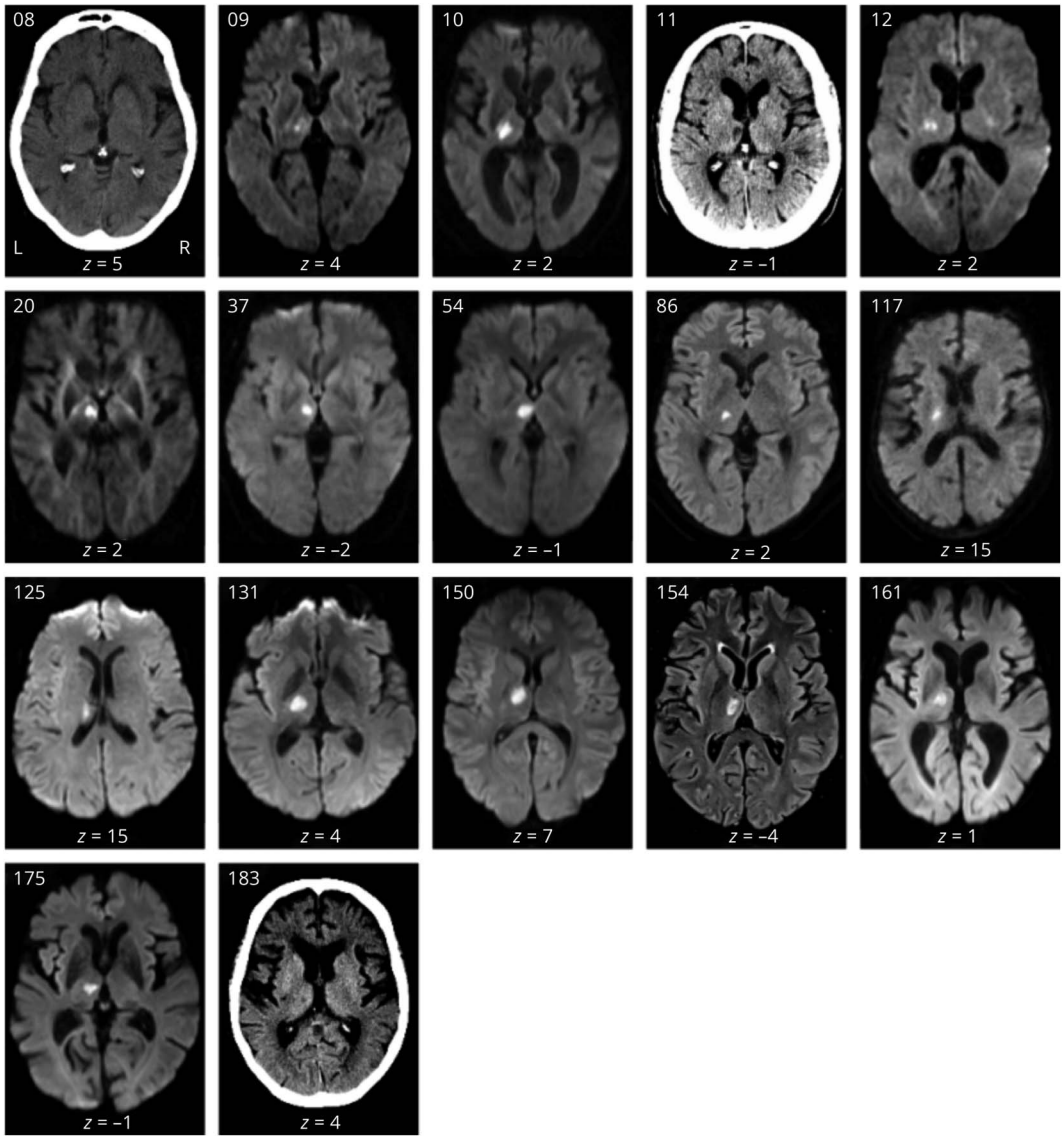
Additional analysis of LNC in which we restricted comparisons to patients with only language impairments with those with one other symptom is displayed in the supplemental information (eFigure 2 and eTable 3, links.lww.com/WNL/C447).

Discussion

In this observational study, we systematically investigated symptoms caused by focal ischemic lesions in a large retrospective cohort of 101 thalamic stroke patients. The application of both VLSM and LNSM allowed us to assess not only the local effect of lesions but also the impact of the lesion on functionally connected networks. In the following, we will first discuss and compare our findings in light of previous studies in which different lesion locations were associated with thalamic aphasia. Second, we will interpret LNC associated with language impairments and evaluate it in relation to known functional brain networks. Third, we will extend the discussion to the possible mechanism of thalamic aphasia within the framework of distributed thalamocortical networks.

Lesions of patients included in this study were distributed across both thalami. Consistent with other studies according to which the lateral thalamus is the most common lesion location, the ventral lateral thalamus was most frequently affected (Figure 2A) in our study population.[24,25] Anterior and posterior medial (pulvinar) thalamic nuclei were affected less frequently and could therefore not be included in the VLSM analyses, although findings of previous case studies indeed reported thalamic aphasia after lesions of these nuclei (eTable 1, links.lww.com/WNL/C447). As a primary result, VLSM analyses revealed that the left mediodorsal nucleus was more frequently damaged in patients with language impairments compared with those with dysarthria and motor or

Figure 1 DW/FLAIR/CT Imaging Showing the Lesion Location of the 17 Patients With Language Impairments

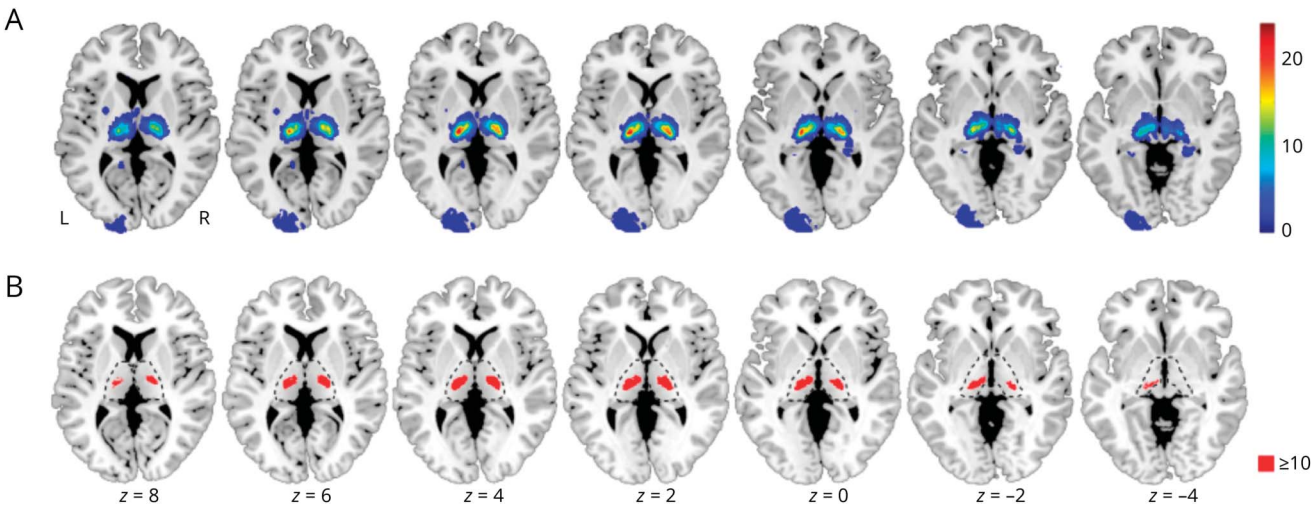


Representative axial slices are in MNI space; z-coordinates are reported below each image. MNI = Montreal Neurological Institute.

sensory deficits (Figure 3, cyan). The latter 2 showed lesion-symptom associations that were spatially distinct from language impairments (Figure 3, red and green) and conform to previous evidence for ventral lateral and posterolateral nuclei involvement in movement and somatosensation.[26] Although in line with case studies reporting left mediodorsal nucleus involvement in thalamic aphasia (eTable 1), our study provides additional empirical evidence based on a voxel-wise statistical comparison in a larger sample. Left mediodorsal nucleus contribution to language has also been demonstrated with task-based fMRI, suggesting a role in semantic memory and lexical-semantic processing.[27-29] Visualization of the distribution of thalamic peaks of several fMRI studies suggested a left-sided clustering near midline regions (intralaminar and mediodorsal nuclei), especially for perceptually challenging language tasks.[30] This might be connected to the overlap between executive and language functions, for example, domain-general executive control over language processing that may come into play with increasing task demands.[31-33] In this context, a regulatory role in cognition, in general, has been attributed to the mediodorsal nucleus.[8,34] In line with this, a lesion study showed that damage to thalamic mediodorsal nucleus caused impaired executive functions and proposed that a dysfunction in thalamocortical networks contributes to these deficits.[35] In the following, we will discuss our LNSM results with a special focus on the identified pattern with involvement of both language and domain-general networks.

LNC was interpreted according to the assumption that regions with higher normative connectivity to the lesion are more vulnerable to diaschisis that causes dysfunction.[13] Symptoms are attributed to regions with higher FC based on statistically significant differences of LNC between patients with and

Figure 2 Lesion Distribution and Visualization of Voxels Included in the Voxel-Based Lesion-Symptom Mapping Analyses

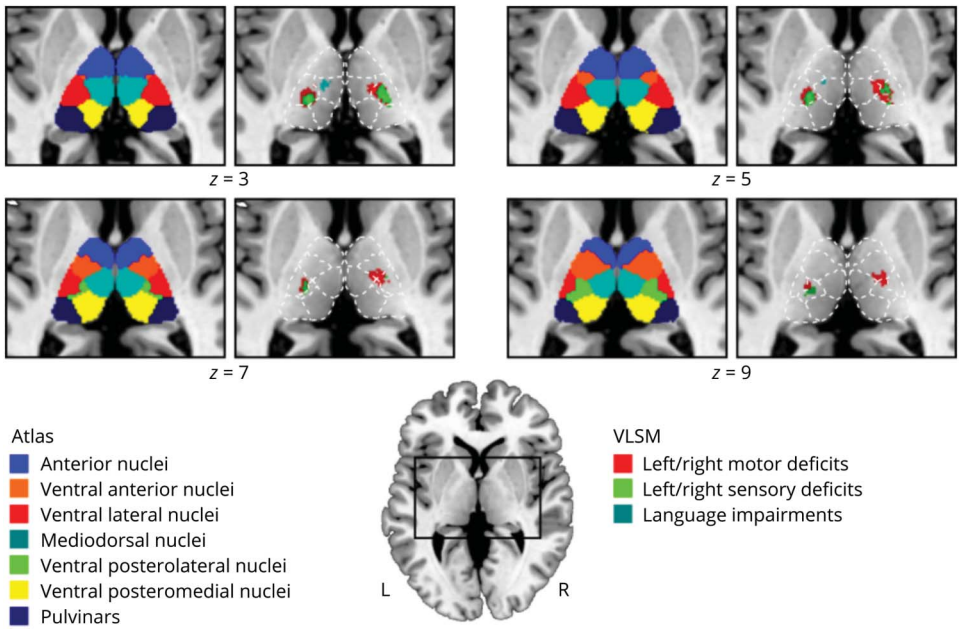


(A) Lesion frequency map: Lesion overlap of the 101 patients superimposed on MRI in MNI space (ch2bet template distributed with MRIcron). Colorbar specifies the number of patients with overlapping lesions in each voxel, with hot colors indicating that a greater number of patients had lesions in this region. Maximum lesion overlap is located in the left ventral lateral nucleus (MNI −16, −20, 2; n = 24). (B) Only regions affected in at least 10% of all patients (n ≥ 10) were subjected to voxel-based lesion-symptom mapping analyses. Dashed lines mark thalamic boundaries. Representative axial slices are in MNI space, z-coordinates are reported below each image. MNI = Montreal Neurological Institute.

without a symptom of interest. As such, this method indirectly describes the networks in which the functional interaction of neural circuits serves the generation and perception of language, articulation, sensation, and movement.

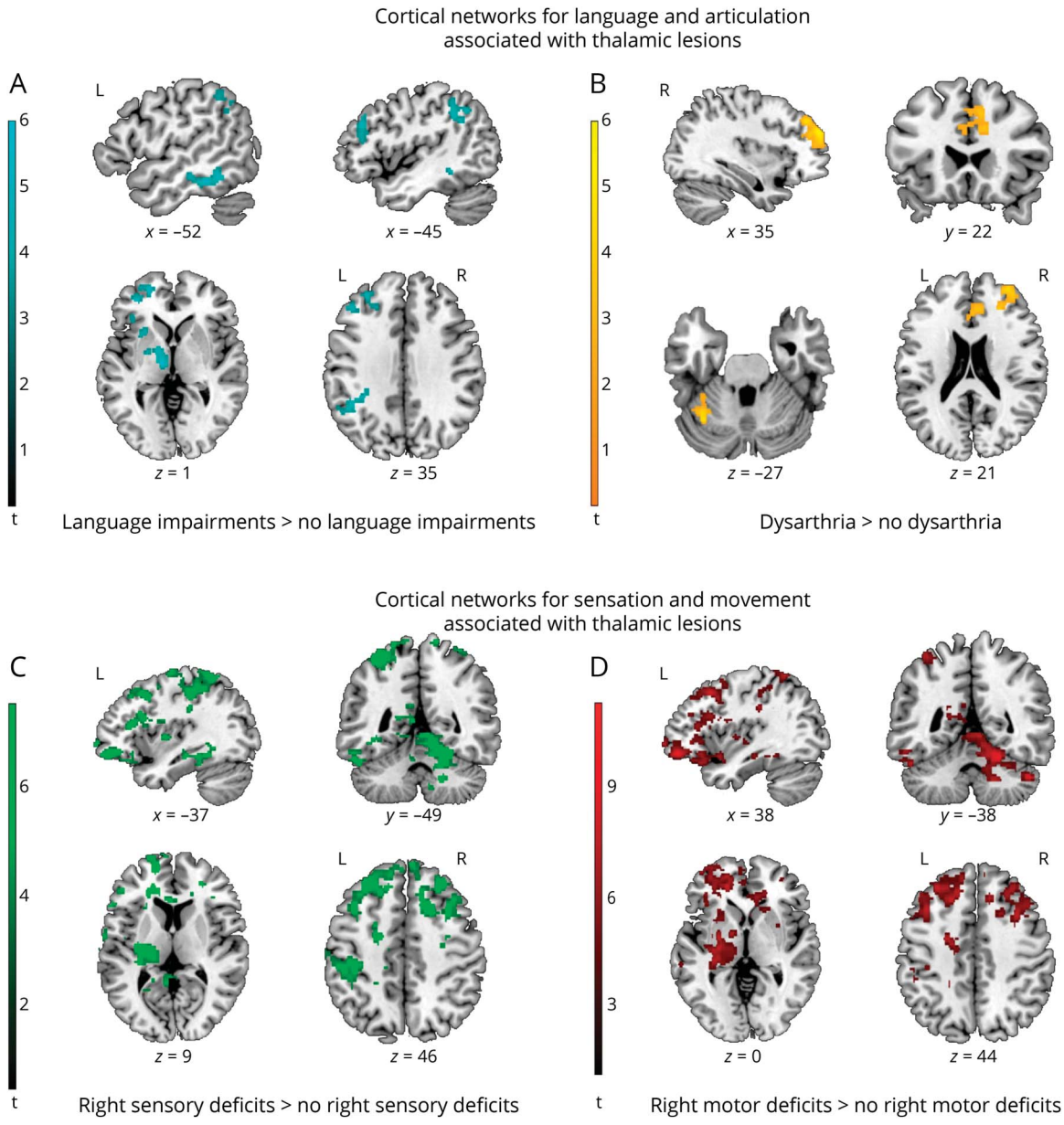
For language impairments, LNSM revealed higher LNC to regions recognized as the left hemisphere frontotemporal language network (left inferior frontal, inferior, and middle temporal gyrus) involved in the representation and processing of speech sounds and their meaning.[36] In addition, higher LNC to regions that can be summarized as domain-general networks (bilateral ventral and dorsolateral prefrontal, middle and anterior cingulate, insulo-opercular, and parietal cortex) also contributed to language impairments. The ability of language requires joint processing between networks for language and bilateral domain-general networks involved in

Figure 3 Thalamic Lesions Associated With Stroke Symptoms



Voxel-based lesion-symptom mapping contrasting lesions of patients with language impairments and motor or sensory deficits. All analyses were performed with nonparametric Liebermeister tests, thresholded at p(FWE) < 0.05. Only significant voxels are displayed for the respective symptoms. Language compared with no language impairments are associated with the left mediodorsal thalamic nucleus (cyan). Motor and sensory deficits map to contralateral ventral lateral (red) and posterolateral (green) thalamic nuclei, respectively. These projections partly overlap in the ventral lateral thalamic nucleus. Each comparison included all 101 patients, for example, patients with right motor deficits were compared with all other patients without right motor deficits including those with left motor deficits. Anatomic labeling was based on a probabilistic atlas of the human thalamus shown as a reference next to the voxel-based lesion-symptom mapping results; dashed lines mark thalamic nuclei boundaries.[18] Representative axial slices are in MNI space; z-coordinates are reported below the images. FWE = family-wise error; MNI = Montreal Neurological Institute.

Figure 4 Thalamocortical Lesion Networks Associated With Stroke Symptoms



Lesion-network-symptom mapping analyses identified regions in which higher normative lesion-dependent network connectivity was associated with (A) language impairments, (B) dysarthria, and (C) right sensory or (D) motor deficits when compared with patients without the respective symptom. Under the assumption that network dysfunction causes impairment, functional interactions within these networks contribute to the generation and perception of language, articulation, sensation, and movement. For all analyses, statistical inference was based on a random permutation test thresholded at p(FWE) < 0.05 at the cluster level. Highlighted voxels are significantly different between groups. Left hemisphere inferior frontal and temporal networks for language and domain-general networks (insular, prefrontal, and parietal cortex) showed significantly greater lesion-dependent network connectivity for patients with language impairments compared with patients with other thalamic stroke symptoms. Coordinates: MNI space. FWE = family-wise error; MNI = Montreal Neurological Institute.

higher-order cognitive processes.[31,32] Reflecting all regions identified in this study, domain-general networks can be further subdivided into a frontoparietal network comprising dorsolateral prefrontal, middle cingulate cortex, precuneus, and inferior parietal lobe and a cingulo-opercular network including anterior prefrontal cortex, anterior insula, frontal operculum, and anterior cingulate cortices.[37] Both networks have been implicated in efficient cognitive processing by providing flexible resources for the initiation and maintenance of cognitive control, respectively.[38] Despite the ongoing debate about how such executive control operations affect language processing, the selection of task- or goal-relevant network components (e.g., to access a word meaning or produce a speech sequence) from multiple sets in the distributed language network may be considered one mechanism mediated by domain-general networks.[31,39,40] Compatible with the notion of dysfunction caused by a focal lesion, disrupted processing within these networks could well contribute to language impairments

Table 2 Lesion-Dependent Network Connectivity Associated With Language Impairments and Dysarthria

Anatomical region	Side	MNI coordinates			Statistics		
		x	y	z	t	*p* Value	k
Language							
Frontal							
Superior frontal gyrus (BA 9, 10)	L	−22	56	4	6.14	0.0048	1,297
Inferior frontal gyrus (BA 45, 47)	L	−32	34	−4	4.21		Subcluster
Insular cortex	L	−28	20	−4	3.74		Subcluster
Middle frontal gyrus (BA 46)	L	−42	32	42	5.44	0.0300	322
Temporal							
Inferior temporal gyrus (BA 20)	L	−52	−38	−18	5.53	0.0420	231
Middle temporal gyrus (BA 21, 37)	L	−59	−52	−4	3.92		Subcluster
Parietal							
Inferior parietal lobe (BA 39, 40)	L	−44	−48	34	4.93	0.0292	332
Subcortical							
Thalamic mediodorsal nucleus	L	−10	−14	0	5.80	0.0338	289
Thalamic anterior nuclei	L	−12	−4	0	4.93		Subcluster
Dysarthria							
Frontal							
Middle frontal gyrus (BA 10, 46)	R	32	52	26	4.97	0.0138	678
Superior frontal gyrus (BA 9)	R	34	40	38	4.34		Subcluster
Anterior cingulate cortex (BA 24)	R	14	28	22	4.02	0.0174	562
Middle cingulate cortex (BA 32)	R	12	30	32	3.56		Subcluster
Supplementary motor cortex (BA 6)	R	12	16	50	3.56		Subcluster
Anterior cingulate cortex (BA 24)	L	−2	26	26	3.74		Subcluster
Subcortical							
Cerebellum	L	−34	−62	−28	4.4	0.0456	197

Abbreviations: BA = Brodmann area; FWE = family-wise error; k = number of voxels; MNI = Montreal Neurological Institute.
List of regions in which higher normative lesion-dependent network connectivity was associated with language impairments and dysarthria when compared with patients without the respective symptom. For all analyses, statistical inference was based on a random permutation test thresholded at p(FWE) < 0.05 at the cluster level. Anatomic labeling was based on a probabilistic atlas of the human thalamus,[18] LONI probabilistic brain atlas,[21] and the Brodmann maps provided with MRIcron.[22] Coordinates: MNI space.

observed after thalamic stroke. Particularly, the characterization of thalamic aphasia as disconnected and incoherent speech[41] may be considered a consequence of less controlled processing between structurally undamaged cortical areas involved in language. Under the limitation that we are unable to provide experimental evidence for the underlying neuronal processes, in the following, we synthesize findings on how the identified thalamocortical networks might collaboratively contribute to language.

To discuss potential mechanisms of thalamic aphasia, the effect of thalamic hubs on cortical information processing must first be considered. A hub is conceptualized as a highly connected network component that mediates concerted processing between multiple regions organized in functional networks that enable complex behavior.[42] The thalamus is one such mediator of corticocortical communication. This is supposed to depend on higher-order thalamic nuclei (e.g., mediodorsal nucleus) that both receive and send afferent and efferent projections from and to various cortical regions.[43] Recent studies in stroke and healthy humans demonstrated that the mediodorsal nucleus shares equal connections to several different networks to which different functions can be attributed.[35,44] These comprised, in addition to the cingulo-opercular and the fronto-parietal network, the default mode network. Analyses of the organization of the default mode network have also shown that

different parts are associated with networks for cognitive control and language networks, providing a further potential link for a functional integration between the mediodorsal thalamus and these networks.[45] This also reinforces the view that the mediodorsal nucleus is a connector hub that interlinks functional networks and thereby supports the integration of different outputs.[46] This general interpretation suits the current concept that language communication necessitates multiple system integration beyond core left frontotemporal language networks.[47] As an example, activation in medial and prefrontal networks controls the goal-directed selection of semantic representations in language core areas.[48] Adding the thalamus to this network perspective, we suggest that one potential mechanism of thalamic aphasia may be seen as a consequence of inefficient integration between otherwise undamaged domain-general and language networks.

In our study, we also describe thalamic lesion–dependent networks for articulation, sensation, and movement. Because our focus was on thalamic aphasia, the inclusion of non–language impairments was primarily for the purpose of a control group to demonstrate that lesion networks for language were specific. Indeed, lesion-dependent networks associated with dysarthria and sensory and motor deficits are consistent with the previously described lateral thalamus-cerebellar-sensorimotor functional networks.[49] This included supplementary motor, precentral and postcentral, as well as parietal association cortices in which activity can be attributed to the planning and generation of (articulatory) movements and the integration of multimodal sensory (feedback) information. However, we also found partly overlapping dorsolateral, ventral, and ventromedial prefrontal regions of lesion-dependent networks that contribute to not only language but also nonlanguage symptoms. Consistent with the notion that also during sensorimotor processing, interactions with networks for executive control, attention, and salience allow for optimal, contextually appropriate, goal-directed behavior, these networks are likely nonspecific for language.[50,51]

This study did have some limitations. First, with about 17%, the frequency of language impairments was higher than that in previous studies on thalamic aphasia.[52] This was likely due to the fact that a language impairment was considered present even if documented only once in the initial neurologic examination on admission to the emergency department. Despite the retrospective study design without standardized language testing, this allowed us to include all patients with a probable thalamic aphasia including transient deficits. In this way, we were unlikely to miss any language impairments. However, it is possible that other mechanisms may have played a role in early transient deficits. For example hypoperfusion may have been present in a wider area than the final thalamic lesion. In particular it may have affected the mesiotemporal cortices that also belong to the posterior circulation and play a role in memory. Also, the accuracy of language assessments may have been biased by other factors that limit the ability to speak, for example, reduced vigilance or confusion. A more detailed characterization and test-based valid diagnosis of thalamic aphasia would have been possible in a prospective study design. Given the low frequency of thalamic strokes and aphasia, though, a sufficient number of patients for network analyses would require a multicenter approach.

Second, our analyses did not cover anterior and posterior medial (pulvinar) thalamic nuclei for which a role in language processing was reported previously (eTable 1, links.lww.com/WNL/C447). A larger number of cases would have been necessary for a more complete lesion coverage of the thalamus. However, the left anterior thalamus showed higher FC with lesions causing language impairments in our LNSM analyses. This suggests that both, mediodorsal and anterior nuclei, may contribute to language in a common functional network. Yet, empirical evidence for an involvement of the anterior nucleus and pulvinar in language would necessitate confirmatory studies.

Third, under the assumption that regions with higher FC are more vulnerable to diaschisis, we provide only indirect evidence for this physiologically defined phenomenon of reduced neuronal activity resulting from deafferentation. However, our results are in line with case studies of left anterior and medial thalamic stroke that directly demonstrate diaschisis by means of hypometabolism in similar left hemisphere cortical regions (eTable 4, links.lww.com/WNL/C447). In addition, further investigations need to demonstrate whether regions that constitute a lesion network which is attributed to language impairments do show altered FC in patients with thalamic aphasia.

Finally, the proposed neuronal mechanism of thalamic contribution to language is not entirely empirically supported by our basic clinical and lesion data. It instead should motivate future research to systematically investigate the effect of thalamocortical integration on different functional networks and its consequence for language functions.

To summarize, our study closes the gap between studies in stroke and healthy humans that propose thalamic contributions to language based on symptoms, correlational evidence of thalamocortical activation, and connectivity related to language processing. We demonstrate that left thalamic lesions associated with language impairments show higher normative connectivity with language and domain-general networks compared with lesions not associated with this symptom. We interpret this as indirect evidence for dysfunction in cortical networks, such that these brain networks contribute to thalamic aphasia. It also emphasizes the importance of the thalamus for language processing, indicating that distributed cortical language networks critically engage this subcortical structure. We propose that one overarching mechanism of the variety of language impairments after thalamic lesions can be summarized as inefficient integration between otherwise undamaged cortical networks for executive control and language caused by a dysfunction in thalamocortical networks.

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References

1. Crosson B. Role of the dominant thalamus in language: a review. *Psychol Bull.* 1984;96(3):491-517. doi: 10.1037/0033-2909.96.3.491
2. Crosson B. Thalamic mechanisms in language: a reconsideration based on recent findings and concepts. *Brain Lang.* 2013;126(1):73-88. doi: 10.1016/j.bandl.2012.06.011
3. Crosson B. The role of cortico-thalamo-cortical circuits in language: recurrent circuits revisited. *Neuropsychol Rev.* 2021;31(3):516-533. doi: 10.1007/s11065-019-09421-8
4. Hebb AO, Ojemann GA. The thalamus and language revisited. *Brain Lang.* 2013;126(1):99-108. doi: 10.1016/j.bandl.2012.06.010
5. Bohsali AA, Triplett W, Sudhyadhom A, et al. Broca's area—thalamic connectivity. *Brain Lang.* 2015;141:80-88. doi: 10.1016/j.bandl.2014.12.001
6. Behrens TE, Johansen-Berg H, Woolrich MW, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat Neurosci.* 2003;6(7):750-757. doi: 10.1038/nn1075
7. Jang SH, Yeo SS. Thalamocortical connections between the mediodorsal nucleus of the thalamus and prefrontal cortex in the human brain: a diffusion tensor tractographic study. *Yonsei Med J.* 2014;55(3):709-714. doi: 10.3349/ymj.2014.55.3.709
8. Schmitt LI, Wimmer RD, Nakajima M, Happ M, Mofakham S, Halassa MM. Thalamic amplification of cortical connectivity sustains attentional control. *Nature.* 2017;545(7653):219-223. doi: 10.1038/nature22073
9. Schmahmann JD, Pandya DN. Disconnection syndromes of basal ganglia, thalamus, and cerebrocerebellar systems. *Cortex.* 2008;44:(8)037-1066. doi: 10.1016/j.cortex.2008.04.004
10. Bates E, Wilson SM, Saygin AP, et al. Voxel-based lesion-symptom mapping. *Nat Neurosci.* 2003;6(5):448-450. doi: 10.1038/nn1050
11. Wawrzyniak M, Klingbeil J, Zeller D, Saur D, Classen J. The neuronal network involved in self-attribution of an artificial hand: a lesion network-symptom-mapping study. *Neuroimage.* 2018;166:317-324. doi: 10.1016/j.neuroimage.2017.11.011
12. Boes AD, Prasad S, Liu H, et al. Network localization of neurological symptoms from focal brain lesions. *Brain.* 2015;138(10):3061-3075. doi: 10.1093/brain/awv228
13. Wawrzyniak M, Schneider HR, Klingbeil J, et al. Resolution of diaschisis contributes to early recovery from post-stroke aphasia. *Neuroimage.* 2022;251:119001. doi: 10.1016/j.neuroimage.2022.119001
14. Kalbe E, Reinhold N, Brand M, Markowitsch HJ, Kessler J. A new test battery to assess aphasic disturbances and associated cognitive dysfunctions—German normative data on the aphasia check list. *J Clin Exp Neuropsychol.* 2005;27(7):779-794. doi: 10.1080/13803390490918273
15. MRIcron. NeuroImaging Tools & Resources Collaboratory, NITRC. Accessed March 14, 2019.https://www.nitrc.org/projects/mricron/
16. Rorden C, Bonilha L, Fridriksson J, Bender B, Karnath HO. Age-specific CT and MRI templates for spatial normalization. *Neuroimage.* 2012;61(4):957-965. doi: 10.1016/j.neuroimage.2012.03.020
17. NiiStat. NeuroImaging Tools & Resources Collaboratory, NITRC. Accessed June 18, 2018.https://www.nitrc.org/projects/niistat/
18. Najdenovska E, Aleman-Gomez Y, Battistella G, et al. In-vivo probabilistic atlas of human thalamic nuclei based on diffusion- weighted magnetic resonance imaging. *Sci Data.* 2018;5(1):180270. doi: 10.1038/sdata.2018.270
19. Nooner KB, Colcombe SJ, Tobe RH, et al. The NKI-Rockland Sample: a model for accelerating the pace of discovery science in psychiatry. *Front Neurosci.* 2012;6:152. doi: 10.3389/fnins.2012.00152
20. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp.* 2002;15:1-25. doi: 10.1002/hbm.1058
21. Shattuck DW, Mirza M, Adisetiyo V, et al. Construction of a 3D probabilistic atlas of human cortical structures. *Neuroimage.* 2008;39(3):1064-1080. doi: 10.1016/j.neuroimage.2007.09.031
22. Rorden C, Brett M. Stereotaxic display of brain lesions. *Behav Neurol.* 2000;12(4):191-200. doi: 10.1155/2000/421719
23. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med.* 2007;147(8):573-577. doi: 10.7326/0003-4819-147-8-200710160-00010
24. Schmahmann JD. Vascular syndromes of the thalamus. *Stroke.* 2003;34(9):2264-2278. doi: 10.1161/01.STR.0000087786.38997.9E
25. Carrera E, Bogousslavsky J. The thalamus and behavior: effects of anatomically distinct strokes. *Neurology.* 2006;66(12):1817-1823. doi: 10.1212/01.wnl.0000219679.95223.4c
26. Bogousslavsky J, Regli F, Uske A. Thalamic infarcts: clinical syndromes, etiology, and prognosis. *Neurology.* 1988;38(6):837-848. doi: 10.1212/wnl.38.6.837

27. Mestres-Misse A, Camara E, Rodriguez-Fornells A, Rotte M, Munte TF. Functional neuroanatomy of meaning acquisition from context. *J Cogn Neurosci.* 2008;20(12):2153-2166. doi: 10.1162/jocn.2008.20150
28. Ketteler D, Kastrau F, Vohn R, Huber W. The subcortical role of language processing. High level linguistic features such as ambiguity-resolution and the human brain; an fMRI study. *Neuroimage.* 2008;39(4):2002-2009. doi: 10.1016/j.neuroimage.2007.10.023
29. Kraut MA, Calhoun V, Pitcock JA, Cusick C, Hart J Jr. Neural hybrid model of semantic object memory: implications from event-related timing using fMRI. *J Int Neuropsychol Soc.* 2003;9(7):1031-1040. doi: 10.1017/S135561770397007X
30. Llano DA. Functional imaging of the thalamus in language. *Brain Lang.* 2013;126(1):62-72. doi: 10.1016/j.bandl.2012.06.004
31. Geranmayeh F, Wise RJ, Mehta A, Leech R. Overlapping networks engaged during spoken language production and its cognitive control. *J Neurosci.* 2014;34(3):8728-8740. doi: 10.1523/JNEUROSCI.0428-14.2014
32. Davis SW, Cabeza R. Cross-hemispheric collaboration and segregation associated with task difficulty as revealed by structural and functional connectivity. *J Neurosci.* 2015;35(21):8191-8200. doi: 10.1523/JNEUROSCI.0464-15.2015
33. Declerck M, Meade G, Midgley KJ, Holcomb PJ, Roelofs A, Emmorey K. On the connection between language control and executive control—an ERP study. *Neurobiol Lang.* 2021;2(4):628-646. doi: 10.1162/nol_a_00032
34. Pergola G, Danet L, Pitel AL, et al. The regulatory role of the human mediodorsal thalamus. *Trends Cogn Sci.* 2018;22(11):1011-1025. doi: 10.1016/j.tics.2018.08.006
35. Hwang K, Bruss J, Tranel D, Boes AD. Network localization of executive function deficits in patients with focal thalamic lesions. *J Cogn Neurosci.* 2020;32(12):2303-2319. doi: 10.1162/jocn_a_01628
36. Hickok G, Poeppel D. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition.* 2004;92(1-2):67-99. doi: 10.1016/j.cognition.2003.10.011
37. Dosenbach NU, Fair DA, Cohen AL, Schlaggar BL, Petersen SE. A dual-networks architecture of top-down control. *Trends Cogn Sci.* 2008;12(3):99-105. doi: 10.1016/j.tics.2008.01.001
38. Dosenbach NUF, Fair DA, Miezin FM, et al. Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci USA.* 2007;104(26):11073-11078. doi: 10.1073/pnas.0704320104
39. Caplan D. Commentary on "The role of domain-general cognitive control in language comprehension" by Fedorenko. *Front Psychol.* 2014;5:629. doi: 10.3389/fpsyg.2014.00629
40. Whitney C, Kirk M, O'Sullivan J, Lambon Ralph MA, Jefferies E. Executive semantic processing is underpinned by a large-scale neural network: revealing the contribution of left prefrontal, posterior temporal, and parietal cortex to controlled retrieval and selection using TMS. *J Cogn Neurosci.* 2012;24(1):133-147. doi: 10.1162/jocn_a_00123
41. Chatterjee A, Yapundich R, Mennemeier M, et al. Thalamic thought disorder: on being "a bit addled". *Cortex.* 1997;33(3):419-440. doi: 10.1016/s0010-9452(08)70228-4
42. van den Heuvel MP, Sporns O. Network hubs in the human brain. *Trends Cogn Sci.* 2013;17(12):683-696. doi: 10.1016/j.tics.2013.09.012
43. Sherman SM. Thalamus plays a central role in ongoing cortical functioning. *Nat Neurosci.* 2016;19(4):533-541. doi: 10.1038/nn.4269
44. Hwang K, Bertolero MA, Liu WB, D'Esposito M. The human thalamus is an integrative hub for functional brain networks. *J Neurosci.* 2017;37(23):5594-5607. doi: 10.1523/JNEUROSCI.0067-17.2017
45. Gordon EM, Laumann TO, Marek S, et al. Default-mode network streams for coupling to language and control systems. *Proc Natl Acad Sci USA.* 2020;117(29):17308-17319. doi: 10.1073/pnas.2005238117
46. Hwang K, Shine JM, Bruss J, Tranel D, Boes A. Neuropsychological evidence of multi-domain network hubs in the human thalamus. *Elife.* 2021;10:1-24. doi: 10.7554/eLife.69480
47. Hertrich I, Dietrich S, Ackermann H. The margins of the language network in the brain. *Front Commun.* 2020;5:1-26. doi: 10.3389/fcomm.2020.519955
48. Binder JR, Desai RH. The neurobiology of semantic memory. *Trends Cogn Sci.* 2011;15(11):527-536. doi: 10.1016/j.tics.2011.10.001
49. Seitzman BA, Gratton C, Marek S, et al. A set of functionally-defined brain regions with improved representation of the subcortex and cerebellum. *Neuroimage.* 2020;206:116290. doi: 10.1016/j.neuroimage.2019.116290
50. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci.* 2002;3:201-215. doi: 10.1038/nrn755
51. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci.* 2001;24(1):167-202. doi: 10.1146/annurev.neuro.24.1.167
52. Fritsch M, Krause T, Klostermann F, Villringer K, Ihrke M, Nolte CH. "Thalamic aphasia" after stroke is associated with left anterior lesion location. *J Neurol.* 2020;267(1):106-112. doi: 10.1007/s00415-019-09560-1

Involvement of Thalamocortical Networks in Patients With Poststroke Thalamic Aphasia

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