Involvement of Thalamocortical Networks in Patients With Poststroke Thalamic Aphasia

Author(s):
Anika Stockert, MD; Sophia Hormig-Rauber; Max Wawrzyniak, MD; Julian Klingbeil, MD; Hans Ralf Schneider; Mandy Pirlich, MD; Stefan Schob, MD; Karl-Titus Hoffmann, MD; Dorothee Saur, MD

Corresponding Author: Anika Stockert, anika.stockert@medizin.uni-leipzig.de

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Affiliation Information for All Authors: 1. Language and Aphasia Laboratory, Department of Neurology, University of Leipzig Medical Center, Leipzig, Germany; 2. Department of Neuroradiology, Clinic and Polyclinic of Radiology, University Hospital Halle, Halle (Saale), Germany; 3. Department of Neuroradiology, University of Leipzig Medical Center, Leipzig, Germany.

Equal Author Contribution:
Anika Stockert and Sophia Hormig-Rauber - These authors contributed equally to this work as first authors.

Contributions:
Anika Stockert: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Sophia Hormig-Rauber: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Max Wawrzyniak: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data; Additional contributions: Software Developer
Julian Klingbeil: Drafting/revision of the manuscript for content, including medical writing for content
Hans Ralf Schneider: Drafting/revision of the manuscript for content, including medical writing for content
Mandy Pirlich: Drafting/revision of the manuscript for content, including medical writing for content
Stefan Schob: Drafting/revision of the manuscript for content, including medical writing for content
Karl-Titus Hoffmann: Drafting/revision of the manuscript for content, including medical writing for content
Dorothee Saur: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design

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Abbreviations: BA = Brodmann area; BOLD = blood-oxygenation level dependent; CT = computed tomography; DWI = diffusion-weighted imaging; EPI = echo-planar imaging; FC = functional connectivity; FLAIR = fluid-attenuated inversion recovery; fMRI = functional magnetic resonance imaging; FWE = family-wise error; LNC = lesion-dependent network connectivity; LNSM = lesion-network-symptom mapping; MNI = Montreal Neurological Institute; SD = standard deviation; SPM12 = Statistical Parametric Mapping, version 12; ROI = region of interest; VLSM = voxel-based lesion-symptom mapping.

Abstract

Background and objective
Theories assume that thalamic stroke may cause aphasia due to 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 thalamo-cortical 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 non-parametric lesion mapping methods in a retrospective cohort of patients with acute or subacute first-ever thalamic stroke. Relationship between lesion location and language impairments was assessed using non-parametric voxel-based lesion-symptom mapping.
mapping. This method reveals regions more frequently damaged in patients with, compared to those without a symptom of interest. To test whether these symptoms are linked to a common thalamo-cortical 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 to those with motor and sensory deficits as baseline.

Results

101 patients (mean (SD) age 64.1 (14.6) years, 57 left, 42 right, 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 to sensory deficits were associated with higher normative lesion-dependent network connectivity to left fronto-temporal 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, pre- and postcentral cortices.

Conclusion

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 thalamo-cortical networks contributes to thalamic aphasia. We propose that inefficient integration between otherwise undamaged domain-general and language networks may cause thalamic aphasia.

Introduction

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. To date, theories about the contribution of the thalamus to language are derived from small samples, imaging in healthy humans or animal studies. 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 cortico-centric 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 in the Supplement), 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, non-fluent 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 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 to those without a symptom of interest\(^\text{10}\). 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. Here, we applied lesion-network-symptom mapping (LNSM), an optimized version of the lesion-network mapping approach first introduced by Boes and colleagues\(^\text{11, 12}\). 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\(^\text{13}\). 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 thalamo-cortical networks. We hypothesize that a distinct pattern of thalamo-cortical connectivity with the left lateralized fronto-temporal language network and bilateral networks involved in cognitive control relates to observed language impairments.

**Material and Methods**

**Participants**

All patients included in this study were admitted to the University of Leipzig Medical Centre between 2011 and 2019. We retrospectively identified patients based on radiological reports that contained the keyword ‘Thalamus’ or ‘thalmisch’ (engl. thalamic) or ‘thalamo’ by using an automated review of radiology reports (cranial CT or MRI). Full medical records were then reviewed for the following inclusion criteria: (i) acute or subacute ischemic, (ii) first-ever thalamic stroke lesion in (iii) patients aged \(\geq 18\) years. Exclusion criteria were defined as: (i) chronic, (ii) non-ischemic (e.g., hemorrhage, tumor, metastasis) or (iii) previous other stroke lesions. We also excluded patients with (iv) concurrent anterior circulation lesions, (v) major microvascular brain damage (Fazekas Scale > 2) or relevant brain atrophy according to the
radiology report. Further, patients with (vi) other pre-existing neurological disorders affecting the central nervous system (e.g., dementia, parkinson's 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 that 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. Additionally, all patients are evaluated by a trained speech and language, physio 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 neurological examination in the emergency room, 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. We interpreted the presence of language impairment based on the documentation of reduced fluency, spontaneous speech or word-finding difficulties, paraphasias, neologisms, lexical-semantic deficits, problems during naming or repetition, impaired comprehension or reading. Dysarthria included slurred or slow speech. Motor deficits included all documented disorders of movement: altered muscle tone (dystonia, asterixis), impairments of coordination (e.g., ataxia, dysmetria, dysdiadochokinesia), standing and gait or weakness (facial, pronation or downward drift during arm and leg examination) in at least one body region (face, arm, leg). Sensory deficits included unilateral abnormalities in touch, pain or temperature sensation as well as reported paraesthesias in at least one 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 two weeks after
stroke onset. MRI scans including diffusion-weighted (DWI, voxel size 1.8x1.8x3.0 mm$^3$) and fluid attenuated inversion recovery (FLAIR, voxel size 0.9x0.9x3.0 mm$^3$) images were acquired at 3 Tesla with a Siemens Magnetom Trio Trim. CTs were obtained with a Philips Ingenuity 128 Scanner, all scans were reconstructed at 1.25 mm slice interval during data acquisition. Lesion delineation was performed in MRIcron (https://www.nitrc.org/projects/mricron/) by a single reviewer (SH) blinded to the patients’ symptoms on either CT (n = 5) or MRI (n = 96) scans. All lesion maps were supervised by two neurologists experienced in stroke imaging (AS, MP) 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$^{15}$ 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 lesion location and stroke symptoms we performed VLSM using the NiiStat software (https://www.nitrc.org/projects/niistat/) 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, right or left sensory or motor deficits) by means of one-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$^{16}$.

**Lesion-network-symptom mapping**

To test whether lesions associated with symptoms of interest map on different functional brain networks, we applied LNSM based on resting-state fMRI data of elderly, unrelated healthy controls (n = 65, mean age = 56 years, 48 % female, 85 % right-handed, 11 % ambidextrous) from the publicly available 3-Tesla Enhanced Rockland Sample$^{17}$. Imaging details can be found in$^{17}$. 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 four functional (EPI) 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. Additionally, 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 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) as well as the
first five principal components of the signals from white matter and cerebrospinal fluid (as
first order terms). Residual BOLD time series were band-pass filtered (0.01 - 0.08 Hz). ROIs
were defined as individual lesion masks spatially limited to a mask representing bilateral
thalamus and served as seeds for FC analyses. 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 subjects to obtain
a single lesion-dependent network for every patient. To map lesion-dependent networks to
symptoms, LNSM was performed with non-parametric permutation testing. To reveal
differences in lesion-dependent networks between patient groups (e.g., language
impairments vs. no language impairments), two-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 cluster-level. Anatomical
labeling was performed with the LONI probabilistic brain atlas and the Brodmann Maps
provided with MRICron.

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 Centre 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 Centre) for scientific purposes.
Data availability and reporting

We have made all data that support our findings (normalized lesion maps, lesion-dependent networks and behavioral data that allowed VLSM and LNSM) and which we can legally share accessible via FigShare (10.6084/m9.figshare.19154153). The study is reported in accordance with the STROBE checklist\textsuperscript{21}.

Results

Demographics and clinical characteristics

Out of the 267 patients identified in the report review, 101 patients (64.1 ± 14.6 years; mean ± SD, 40 female, 96 right handed) met the inclusion criteria. 57 patients had left, 42 patients right and 2 patients bilateral thalamic lesions. 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, Figure 1). 48 patients presented with dysarthria, 44 patients with right and 32 patients with left motor deficits, 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, see 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 to 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. While regions associated with language were spatially separate from those associated with right motor or sensory deficits, the latter two 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 covariate of no interest to the analyses did not change the results (not shown).

**Lesion-network-symptom mapping**

Patients with, compared to patients without language impairments showed significantly higher lesion-dependent network connectivity (LNC, p(FWE) < 0.05 at cluster-level) with the left superior and middle frontal gyrus (Brodmann areas (BA) 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 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, Table 2). All significant clusters were located in the left hemisphere. In contrast, dysarthria was associated with higher right superior and middle frontal gyrus (BA 9, 10, 46) LNC when compared to lesion-dependent networks of patients without dysarthria. Furthermore, it was linked to higher LNC with bilateral cingulate cortex (BA 24, 32), right supplementary motor cortex (BA 6) and the left cerebellum (Figure 4B, Table 2).

A different FC pattern emerged for right and left sensory and motor deficits compared to 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 in the Supplement). Patients with, compared to patients without right sensory deficits were characterized by higher LNC with the bilateral prefrontal cortex (middle and superior frontal gyrus, orbitofrontal cortex), postcentral/superior parietal cortex (left > right), left precentral cortex as well as with left ventral lateral thalamic nucleus and pulvinar. In addition, these patients showed higher bilateral cerebellar (right > left), temporal and mesio-temporal connectivity (Figure 4C, eTable 2). A very similar pattern was found for patients with, compared to patients without right motor deficits. It comprised higher LNC with bilateral middle and superior frontal gyrus, left pre- and postcentral cortex, left ventral lateral thalamic nuclei and pulvinar. In addition, higher LNC was found with bilateral basal ganglia (putamen, pallidum) and right cerebellum (Figure 4D, eTable 2).

Additional analysis of LNC in which we restricted comparisons to patients with only language impairments to those with one other symptom are displayed in the supplemental information (eFigure 2, eTable 3).
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 thalamo-cortical 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\textsuperscript{22, 23}. 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). As primary result, VLSM analyses revealed that the left mediodorsal nucleus was more frequently damaged in patients with language impairments compared to those with dysarthria, motor or sensory deficits (Figure 3, cyan). The latter two 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\textsuperscript{24}. While in line with case studies reporting left mediodorsal nucleus involvement in thalamic aphasia (eTable 1), our study, for the first time, 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\textsuperscript{25-27}. 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\textsuperscript{28}. 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\textsuperscript{29-31}. In this context, a regulatory role in cognition in general has been attributed to the mediodorsal nucleus\textsuperscript{8, 32}. In line with this, a lesion study by Hwang and colleagues showed that thalamic mediodorsal lesions caused impaired executive functions. They also proposed that dysfunction in thalamo-cortical networks contribute to the executive deficits\textsuperscript{33}. 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\textsuperscript{13}. Symptoms are attributed to regions with higher FC based on statistically significant differences of LNC between patients with and without a symptom of interest. As such, this method indirectly describes the networks in which functional interaction of neural circuits serve the generation and perception of language, articulation, sensation and movement.

For language impairments, LNSM revealed higher LNC to regions recognized as the left hemisphere fronto-temporal language network (left inferior frontal, inferior and middle temporal gyrus) involved in the representation and processing of speech sounds and their meaning\textsuperscript{34}. 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 higher-order cognitive processes\textsuperscript{29, 30}. Reflecting all regions identified in this study, domain-general networks can be further subdivided into a fronto-parietal 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\textsuperscript{35}. Both networks have been implicated in efficient cognitive processing by providing flexible resources for the initiation and maintenance of cognitive control, respectively\textsuperscript{36}. 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\textsuperscript{29, 37, 38}. Compatible with the notion of dysfunction caused by a focal lesion, disrupted processing within these networks could well contribute to
language impairments observed after thalamic stroke. Especially, the characterization of thalamic aphasia as disconnected and incoherent speech 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 thalamo-cortical 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 a highly connected network component that mediates concerted processing between multiple regions organized in functional networks which enable complex behaviour. The thalamus is one such mediator of cortico-cortical 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. 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. 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. This also reinforces the interpretation of Hwang and colleagues of the mediodorsal nucleus as a connector hub that interlinks functional networks and thereby supports the integration of different outputs. This general interpretation suits the current concept that language communication necessitates multiple system integration beyond “core” left fronto-temporal language networks. As an example, activation in medial and prefrontal networks controls the goal-directed selection of semantic representations in language core areas. 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, sensory and motor deficits are consistent with the previously described lateral thalamus - cerebellar - sensorimotor functional networks\textsuperscript{47}. This included supplementary motor, pre- 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 both language but also non-language 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 non-specific for language\textsuperscript{48,49}.

**Limitations**

First, with about 17\%, the frequency of language impairments was higher than in previous studies on thalamic aphasia\textsuperscript{50}. This was likely due to the fact that a language impairment was considered present even if documented only once in the initial neurological examination upon admission to the emergency room. 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 in a wider area than the final thalamic lesion, in particular of mesiotemporal cortices also belonging to the posterior circulation. Also, 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). A larger number of cases would have been necessary for a more complete lesion coverage of the thalamus. However, 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 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). 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.

Lastly, 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 thalamo-cortical integration on different functional networks and its consequence for language functions.

**Conclusion**

Here, we close the gap between studies in stroke and healthy humans that propose thalamic contributions to language based on symptoms, correlational evidence of thalamo-cortical 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 to 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 thalamo-cortical networks.
References

## Tables and Figures

### Table 1. Characteristics of patients with language impairments.

<table>
<thead>
<tr>
<th>ID</th>
<th>Sex</th>
<th>Age</th>
<th>Language impairments</th>
<th>Other symptoms</th>
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<td>08</td>
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<td>86</td>
<td>reduced spontaneous speech, impaired comprehension</td>
<td>right motor deficits, dysarthria</td>
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<td>09</td>
<td>m</td>
<td>79</td>
<td>reduced spontaneous speech, impaired comprehension, naming difficulties, impaired</td>
<td>dysarthria</td>
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<td>right facial palsy, dysarthria</td>
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<td>right motor and sensory deficits,</td>
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<td>right motor and sensory deficits,</td>
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<td>reduced spontaneous speech, impaired comprehension, word-finding difficulties,</td>
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<td>reduced spontaneous speech, word-finding difficulties</td>
<td>right motor deficits, dysarthria</td>
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</table>
Patient ID, gender: m - male, f - female, age in years, language impairments according to neurological or speech and language therapist examination and other symptoms connected to the acute or subacute event.

### Table 2. Lesion-dependent network connectivity associated with language impairments and dysarthria.

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>Side</th>
<th>MNI coordinates</th>
<th>Statistics</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>x   y    z   t  p   k</td>
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<tr>
<td><strong>Language</strong></td>
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<tr>
<td>Frontal</td>
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<tr>
<td>Superior frontal gyrus (BA 9, 10)</td>
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<td>-22</td>
<td>56</td>
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<tr>
<td>Inferior frontal gyrus (BA 45, 47)</td>
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<td>34</td>
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<tr>
<td>Insular cortex</td>
<td>L</td>
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<td>Middle frontal gyrus (BA 46)</td>
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<td><strong>Temporal</strong></td>
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<td>Inferior temporal gyrus (BA 20)</td>
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<td>-38</td>
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<tr>
<td>Middle temporal gyrus (BA 21, 37)</td>
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<td><strong>Parietal</strong></td>
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<td>Inferior parietal lobe (BA 39, 40)</td>
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<td>-48</td>
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<tr>
<td><strong>Subcortical</strong></td>
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<tr>
<td>Thalamic mediodorsal nucleus</td>
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<td>Thalamic anterior nucleus</td>
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<td><strong>Dysarthria</strong></td>
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<tr>
<td>Frontal</td>
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<tr>
<td>Middle frontal gyrus (BA 10, 46)</td>
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<tr>
<td>Superior frontal gyrus (BA 9)</td>
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<td>40</td>
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<td>Anterior cingulate cortex (BA 24)</td>
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<td>Supplementary motor cortex (BA 6)</td>
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<td>Cerebellum</td>
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</table>

List of regions in which higher normative lesion-dependent network connectivity was associated with language impairments and dysarthria when compared to 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 human thalamus, LONI probabilistic brain atlas and the Brodmann Maps provided with MRlcron. Coordinates: MNI space; Abbreviations: L = left, R = right, BA = Brodmann area, k = number of voxels.
Figure 1. DW-/FLAIR-/CT-imaging showing lesion location of the 17 patients with language impairments. Representative axial slices are in MNI space, z-coordinates are reported below each image.
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 an MRI image in MNI space (ch2bet template distributed with MRIcon). 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. L = left, R = right.
Figure 3. Thalamic lesions associated with stroke symptoms. Voxel-based lesion-symptom mapping contrasting lesions of patients with language impairments, motor or sensory deficits. All analyses were performed with non-parametric Liebermeister tests, thresholded at p(FWE) < 0.05. Only significant voxels are displayed for the respective symptoms. Language compared to no language impairments are associated with 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, e.g., patients with right motor deficits were compared to all other patients without right motor deficits including those with left motor deficits. Anatomic labeling was based on a probabilistic atlas of human thalamus shown as reference next to the voxel-based lesion-symptom mapping results, dashed lines mark thalamic nuclei boundaries. Representative axial slices are in MNI space, z-coordinates are reported below the images. L = left, R = right.
Figure 4. Thalamo-cortical 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, (C) right sensory or (D) motor deficits when compared to 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 (insula, prefrontal and parietal cortex) showed significantly greater lesion-dependent network connectivity for patients with language impairments compared to patients with other thalamic stroke symptoms. Coordinates: MNI space; Abbreviations: L = left, R = right.
Involvement of Thalamocortical Networks in Patients With Poststroke Thalamic Aphasia
Anika Stockert, Sophia Hormig-Rauber, Max Wawrzyniak, et al.

Neurology published online October 27, 2022
DOI 10.1212/WNL.0000000000201488

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