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Can Pure Thalamic Strokes Lead to Severe Impairment of Arousal?

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ABSTRACT

Background: The thalamus has been considered critical for maintaining consciousness, but it is not clear if thalamic strokes can lead to severe impairment of arousal. The aim of this study was to investigate whether thalamic damage alone is sufficient to cause severe impairment of arousal in stroke patients.

Methods: Patients with new-onset ischemic stroke without mass effect, leading to severe impairment of arousal, were identified retrospectively from the electronic medical records of patients treated 2004–2019 at Turku University Hospital. In addition, 500 stroke patients without impairment of arousal were included as controls.

Results: We identified nine patients with coma or stupor following an acute stroke involving the thalamus. Five of these patients remitted following endovascular therapies but had residual lesions intersecting the thalamus. In the four patients with long-term coma or stupor, the thalamic lesions extended into the brainstem and overlapped in regions considered part of the reticular formation. These brainstem regions were specific for patients with long-term coma or stupor, as none of the five patients who remitted following endovascular therapy or 500 control stroke patients (including 39 patients with stroke lesions intersecting the thalamus) had lesions intersecting these regions.

Conclusions: These results demonstrate that thalamic strokes without extension into the brainstem are not sufficient to cause severe impairment of arousal.

1 | Introduction

The thalamus has generally been considered one of the main relay structures for the human arousal system, but the role of the thalamus in human consciousness is still not fully understood [1]. However, the critical role of the thalamus in arousal has been questioned by findings from animal and human lesion studies, suggesting that thalamic damage alone may not be sufficient to cause loss of consciousness [2].

Brain lesions can offer a unique insight by providing a causal relationship from focal brain damage to resulting symptoms. Thus,

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studying acute brain lesions resulting in severe impairment of arousal could shed light on the role of the thalamus in human consciousness. Using this approach in patients with stroke, Hindman et al. showed that all thalamic stroke lesions causing coma or stupor extended into the brainstem, supporting the idea that thalamic damage alone is not sufficient to cause severe impairment of arousal [3]. However, as strokes without mass effect leading to severe impairment of arousal are rare, their extensive database from two centers only included four such cases, limiting the confidence of this finding [3].

Here we aimed to critically test the findings by Hindman et al. in an independent dataset collected from all patients with stroke involving the thalamus and severe impairment of arousal poststroke, including also a large control dataset of stroke patients without impairment of consciousness, treated at Turku University Hospital during 15 years.

2 | Methods

2.1 | Case Selection

Adult patients with new-onset ischemic stroke based on stroke ICD-10 diagnosis codes (I63*), treated at the intensive care unit (ICU) were searched from the electronic medical records of Turku University Hospital from the inception of the current imaging database in 2004 to April 2019. Only patients treated at the ICU were included because all patients with strokes with reduced consciousness without a hopeless prognosis, such as those associated with exceedingly large space-occupying lesions, are treated at the ICU at our hospital.

The initial search resulted in 335 patients, whose medical records were carefully reviewed by the investigators. The inclusion criteria were: (1) age at least 18 years, (2) acute ischemic stroke, (3) decreased consciousness reaching coma or stupor within 12 h from the beginning of the acute stroke symptoms, (4) there was no other cause for the decreased level of consciousness than the stroke (e.g., lesion mass effect, epileptic seizures, or intoxication), and (5) brain CT or MRI obtained during (patients with long-term coma or stupor) or after (patients with reversible coma or stupor) severe impairment of arousal. Patients with massive lesions with mass effect or no brain parenchymal lesions were excluded. The level of consciousness for each patient during the first 12 h after the onset of symptoms was evaluated similarly as in Hindman et al., by reviewing the patient records based primarily on neurological exam findings and rating on a previously defined 6-point scale (coma, 1; stupor, 2; obtunded, 3; somnolent, 4; lethargic, 5; awake, 6) [3, 4]. From the cases returned by the initial search, 55 patients fulfilled these criteria but three had no brain imaging data available (Figure S1). The lesion locations were carefully visually evaluated by the investigators from the remaining 52 patients, and nine patients were found to have their stroke lesion extending into the thalamus, consistent with the inclusion criteria.

The data collection was approved by the Hospital District of Southwest Finland with a waiver for the need for a separate ethics committee evaluation because of the retrospective nature of the study, according to the national and institutional regulations.

2.2 | Control Stroke Lesion Dataset

For the control dataset of stroke lesions not leading to impairment of consciousness, we included the first 500 patients from an ongoing prospective study consecutively enrolling all patients from the stroke ward with new-onset stroke who were willing to participate in the study [5]. At baseline, the subjects were screened for preexisting brain disorders and clinically interviewed and examined by a study neurologist/neurology resident in consultation with a senior neurologist as needed. None of the patients had severe impairment of arousal because of their stroke.

The prospective part of the study was approved by the local ethics committee and received approval from the Hospital District of Southwest Finland. All subjects signed an informed consent form before participating in this study, and the study was conducted according to the Declaration of Helsinki.

2.3 | Lesion Segmentation

The stroke lesions were manually segmented by the clinical investigators with expertise in neurology and neuroimaging. The lesions were manually drawn on the individual native space images using ITK-SNAP [6] and registered to MNI 152 space, as described previously [5]. More detailed information is available in the Supporting Information.

3 | Results

The demographical and clinical data of the included patients together with the control stroke patients is presented in Table 1.

TABLE 1 | Demographic and clinical characteristics of the patients.

	Reversible coma/stupor ($n=5$)	Long-term coma/stupor ($n=4$)
Patients with coma/stupor		
Male/female	3/2	3/1
Age years, median [range]	68 [32–79]	78 [77–83]
MRI/CT	2/3	1/3
Thrombolysis	4	2
Thrombectomy	5	1
Control stroke patients without coma/stupor ($n=500$)		
Male, *n* (%)	305 (61%)	
Age years, mean ± SD	66.7 ± 13.2	
NIHSS score, median (range)	1.0 (0–15)	
Ischemic stroke, *n* (%)	439 (89%)	
MRI/CT, *n* (%)	328/172 (66/34%)	

Abbreviation: NIHSS, National Institute of Health Stroke Scale.

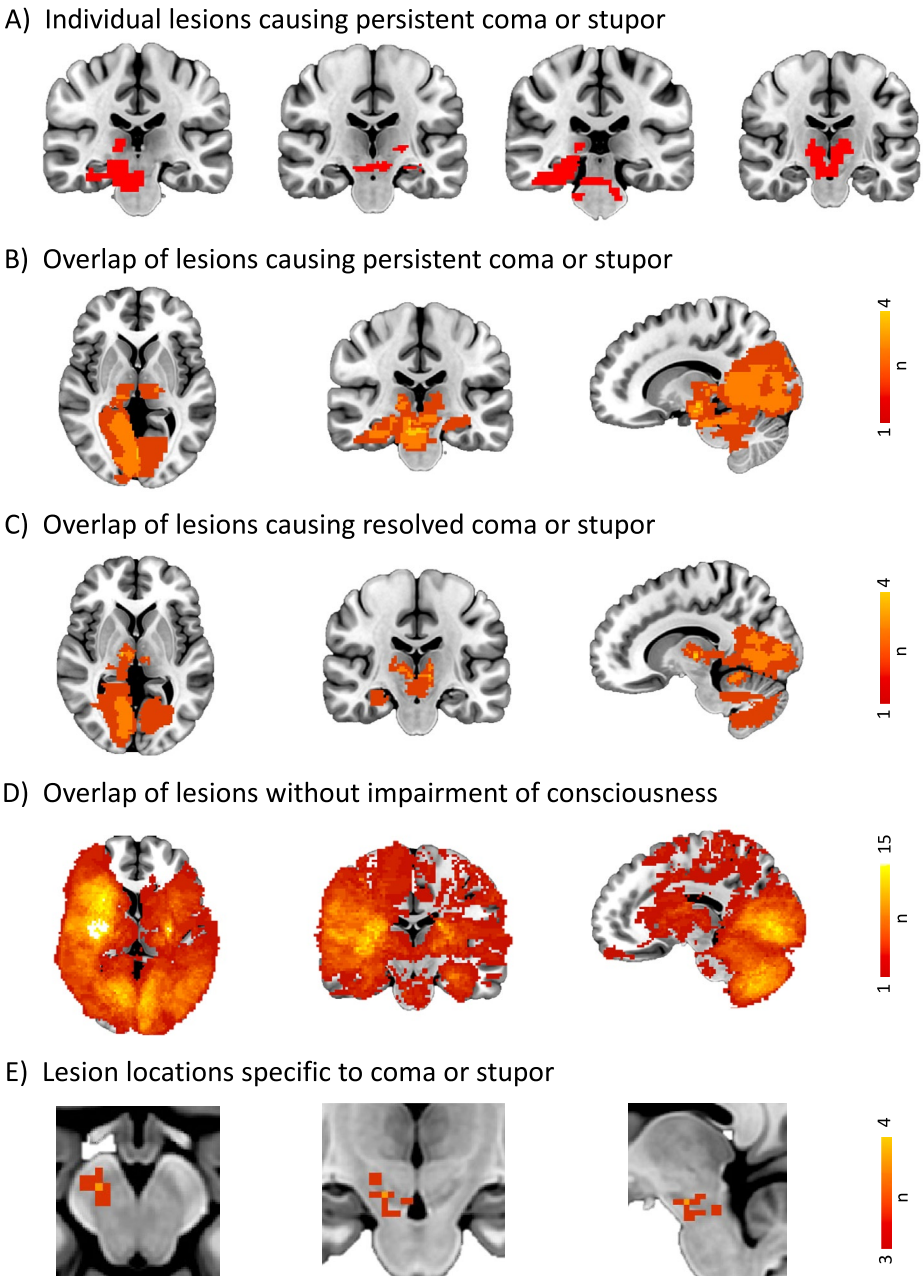

FIGURE 1 | Lesion locations. Individual (A) and overlap (B) of lesion locations in causing long-term coma or stupor. Lesion locations in stroke patients with resolved coma or stupor after intravascular rescue therapy ($n = 5$, C) and no severe impairment of consciousness ($n = 500$ of which 39 intersected the thalamus [22 patients with isolated thalamic strokes of whom one was somnolent], D). Common lesion locations in patients with long-term coma or stupor, but not involved in any of the patients with reversible or no impairment of consciousness (E).

Five of the nine patients with stroke lesions involving the thalamus with severe impairment of arousal had reversible coma or stupor, resolving after mechanical thrombectomy, indicating that the severe impairment of arousal was not caused by their residual stroke lesions. Four of the patients had long-term coma/stupor. One of these patients had received thrombolysis, one thrombolysis and thrombectomy. Three out of four patients with long-term coma or stupor, three out of five patients with transient coma or stupor, and 231 out of 500 control patients also had prior strokes.

All four thalamic lesions causing long-term severe impairment of arousal extended into the brainstem (Figure 1A,B) and all nine cases with long-term or reversible severe impairment of arousal had posterior circulation strokes (Figure 1B,C). The overlap of the four lesions causing long-term severe impairment of arousal (Figure 1B) included a small region in the brainstem that was not affected by any of the lesions in either of the control datasets (Figure 1C,D), suggesting that these regions may be causally related to impairment of consciousness (Figure 1E). These regions intersected several brainstem structures, including the

pedunculopontine nucleus, ventral tegmental area, substantia nigra, red nucleus, and their surrounding white matter tracts (Figure 1E).

4 | Discussion

This study aimed to investigate the role of the thalamus in maintaining human consciousness by testing whether thalamic lesions alone are sufficient to cause severe impairment of arousal, as questioned by Hindman et al. [3]. Our results support their observations, demonstrating that thalamic strokes without extension into the brainstem are not sufficient to cause severe impairment of arousal. Our findings have implications for understanding the role of the thalamus in consciousness and provide valuable information for neurocritical care. In addition, our results suggest critical involvement of upper brainstem regions, intersected by lesions leading to severe impairment of arousal but not by any of the control lesions, in maintaining arousal.

The thalamus has been thought to play an important role in human consciousness, acting as the main relay point between the brainstem and cortex [1]. Thalamic infarcts may lead to disorders of consciousness, but coma or stupor seems to be relatively rare, and it has not been clear if thalamic lesions alone are sufficient to cause severe impairment of arousal [7–9]. Together with the previous findings, our results instead support a critical role for the brainstem reticular formation, including the pedunculopontine nucleus, ventral tegmental area, and likely most importantly, axons ascending through the central midbrain, for sustaining human wakefulness [10, 11]. This view is also supported by an earlier study investigating brainstem lesions, showing that injury to a small region in the pontine tegmentum is associated with coma [12]. In addition, our results show that lesions causing long-term severe loss of consciousness also overlapped in the substantia nigra, which dopaminergic projections may have a role for promoting wakefulness, although dopamine or any other individual neurotransmitters do not seem to be necessary for maintaining arousal [11]. As noted before, in practically all prior reported cases of coma caused by thalamic lesions, the lesions likely extended into the brainstem [3].

There are some limitations to acknowledge. First, despite including all cases from a university hospital from a 15-year period, we only identified four cases with severe, long-term impairment of arousal following strokes involving the thalamus, matching the number of these patients in the earlier study [3]. Thus, the localization to the brainstem should be interpreted with caution. However, the localization is supported by the fact that these regions were not intersected by any of the lesions in the patients of the two control cohorts. Second, we did not exclude patients with prior strokes and, therefore, it is possible that damage to the identified brainstem regions alone may not be sufficient to cause severe impairment of arousal. Finally, it should be acknowledged that our study focused on the state of consciousness (arousal) and not the content of consciousness (awareness), in which the thalamus may still have an important role [1, 13].

In conclusion, our results support the findings by Hindman et al., demonstrating that thalamic damage alone is not sufficient to cause severe impairment of arousal. This finding has clinical implications, supporting active clinical investigations for an alternative cause for patients with coma or stupor following thalamic strokes not extending into the brainstem.

Author Contributions

Elina Jaakkola: writing – original draft, investigation, project administration. **Olli Likitalo:** formal analysis, writing – review and editing, investigation. **Katri Niinivirta-Joutsa:** investigation, writing – review and editing. **Juho Joutsa:** conceptualization, supervision, writing – review and editing, methodology.

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Conflicts of Interest

E.J. has received a grant from the Finnish Medical Foundation; Olli Likitalo has received grants from the Finnish Medical Foundation, Finnish Foundation for Alcohol Studies, University of Turku Foundation, and Turku University Hospital (VTR funds), congress fees covered by Lundbeck and Teva, and own stocks of Osgenic; Juho Joutsa has received conference travel support from Abbvie, Abbott, and Insightec, lecturer honoraria from Addiktum, Nordic Infucare, Lundbeck, and Novartis, and consultation fees from Summaryx, Teva Finland and Adamant Health, and acts as an advisory board member for Teva Finland; and Katri Niinivirta-Joutsa and Juho Joutsa own stocks of NeuroLogic Finland Oy and Suomen Neurolaboratorio Oy.

Data Availability Statement

Research data are not shared.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.