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Original Article

Relationship Between Olfactory Disturbance After Acute Ischemic Stroke and Latent Thalamic Hypoperfusion

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Abstract

Odor detection, recognition, and identification were assessed in 19 acute ischemic stroke patients who had no magnetic resonance imaging-detectable thalamic lesions but in whom technetium-99m ethyl cysteinate dimer single photon emission tomography revealed thalamic hypoperfusion. Although these patients were unaware of reduced olfactory function, they exhibited significantly lower scores in tests for odor identification and recognition threshold as compared with 9 ischemic stroke controls that had normal thalamic hypoperfusion. However, absolute odor detection thresholds were similar in the 2 groups. These results demonstrate the usefulness of cerebral perfusion scintigraphy in assessing sensory loss after ischemic stroke and provide further evidence for the role of the thalamus in olfaction.

Keywords: brain injury, cerebral perfusion, human brain, olfaction, thalamus

Introduction

The role of the thalamus in olfaction remains unclear (Courtiol and Wilson 2015). Animal models have shown that thalamic lesions and aberrant connections between the piriform cortex and the thalamus do not affect smell detection, but impair smell recognition and learning ability (Slotnick and Kaneko 1981; Slotnick and Risser 1990; Courtiol et al. 2019). Research on humans showed that subjects with unilateral thalamic lesions have normal odor detection thresholds but exhibit increased odor recognition thresholds and reduced ability to determine pleasantness of odor (Sela et al. 2009). This dissociation between odor detection threshold (detection threshold) and odor recognition threshold (identification threshold) is characteristic of olfactory dysfunction caused by a thalamic lesion (Tham et al. 2011). Functional magnetic resonance imaging (fMRI) studies have reported that the thalamus likely plays an important role in olfactory attention (Plailly et al. 2008), suggesting the involvement of the thalamus in higher-order processing of olfactory information.

The thalamus constitutes an important hub for neural connections due to its involvement in thalamocortical and corticothalamic pathways (Briggs and Usrey 2008). Although the thalamus is primarily perfused by the perforating branch of the posterior cerebral artery (PCA), an ipsilateral infarct of the middle cerebral artery (MCA) has been associated with a decline in thalamic metabolism and perfusion, even when blood supply to the PCA is maintained (Feeney et al. 1986; Sakashita et al. 1993; De Reuck et al. 1995; Reidler et al. 2018). A latent decline in metabolism and perfusion in the thalamic area distant to any lesion is known as ipsilateral

thalamic diaschisis (De Reuck et al. 1995). Additionally, secondary neurodegeneration of the thalamus has been reported in the chronic phase of MCA-area infarct (Tamura et al. 1991; Koliatsos et al. 2004; Kuchcinski et al. 2017). Although it has been hypothesized that latent hypoperfusion may cause dysfunction of the central olfactory pathway (including the mediodorsal thalamic nucleus), few studies have investigated this phenomenon.

In general, central olfactory dysfunction is diagnosed using computed tomography (CT) or magnetic resonance imaging (MRI) (Li et al. 1994; Mueller et al. 2006; Decker et al. 2013). However, as in ipsilateral thalamic diaschisis, it is difficult to detect olfactory center pathologies that result from reduced metabolism and perfusion of areas of the brain that do not undergo distinct histological changes. Cerebral perfusion scintigraphy may assist with the pathologic diagnosis of central olfactory dysfunction, as this modality has been shown to be useful in the diagnoses of cerebral dysfunction that are undetectable by other modalities and are unaccompanied by histological changes (Masdeu and Brass 1995; Clauss and Nel 2004; Heiss 2014). If cerebral perfusion scintigraphy indicates the presence of central olfactory dysfunction in the absence of histological change, we may gain further insight into the causes of olfactory impairment that are currently thought to be of unknown etiology (Decker et al. 2013).

The objective of this study was to clarify the relationship between latent thalamic hypoperfusion and olfaction, and the usefulness of cerebral perfusion scintigraphy in the pathological diagnosis of central olfactory dysfunction. To this end, we used technetium-99m ethyl cysteinate dimer (^{99m}Tc–ECD) (Tsuchida et al. 1994) single photon emission computed tomography (SPECT) to investigate the presence of latent thalamic hypoperfusion in patients with acute ischemic stroke. We then correlated these findings with a functional evaluation of the patients' olfactory ability.

Materials and methods

Data availability

The data support the findings of this study are available from the corresponding author on reasonable request.

Subjects

Our subjects were 28 Japanese first-time stroke patients (18 male, 10 female, mean age 69.8 ± 1.0 years) admitted to Kanazawa Medical University Hospital between April 2017 and April 2018 in whom MRI scans did not reveal any abnormality on either side of the thalamus. Patients who had PCA stenosis or occlusion were excluded from the study. All of subjects were determined to be right-handed via the Edinburgh Handedness Inventory (Oldfield 1971). All subjects scored ≥25 on the Mini-Mental State Examination (MMSE), ensuring that none of the subjects had any cognitive impairment (Folstein et al. 1975). A speech language therapist interviewed all subjects and confirmed that there were no problems with the language, communication, and underlying semantic memory. Patients had no history of olfactory dysfunction, respiratory infections, or allergies at evaluation. Subjects' smoking habits were evaluated using the Brinkman index (Brinkman and Coates 1963).

Ethical considerations

This study was conducted in accordance with the guidelines set forth in the Declaration of Helsinki. The protocol was approved by the Clinical Research Ethics Committee of the Kanazawa Medical University Hospital (acceptance number: H152). All subjects provided written informed consent before participating.

^{99m}Tc–ECD SPECT imaging

^{99m}Tc–ECD SPECT images were taken within 5 days of MRI imaging. We used a triple-head gamma camera (PRISM IRIX, Phillips Corp.) equipped with a low-energy, high-resolution parallel beam collimator (LEHR-PAR). Image processing was done using Odyssey LX (Shimadzu Corporation). SPECT collection was done using a 128 × 128 matrix and 3.31 × 3.31 mm pixels at 120 frames per second. Quantitative brain measurements were made using the Patlak Plot method (Matsuda et al. 1995). SPECT images of hypoperfused areas of the brain were comprehensively judged, by both visual inspection by a radiologist, and analysis using the brain function statistical analysis software easy *Z*-score Imaging System (eZIS) ver.3 (Mizumura and Kumita 2006). In the eZIS method, the SPECT template was used to anatomically standardize each subject's cerebral perfusion SPECT image with the Talairach and Tournoux standard brain, followed by smoothing. Data were compared with mean + standard deviation (SD) images from a database of healthy brains (the Musashi normal database installed in eZIS), and the obtained differences were depicted on a *Z*-score map. *Z*-scores were calculated using the following formula: (normal group mean voxel value – patient voxel value)/(normal group SD); hypoperfused areas have positive *Z*-scores and hyperperfused areas have negative *Z*-scores. Voxel with a *Z*-score of 2 or greater was considered abnormally hypoperfused. Furthermore, the anatomical hypoperfusion site was identified by projecting the standardized SPECT image on the MRI model.

Subjects were divided into 3 groups based on the analysis: the right thalamus group (hypoperfusion in the right thalamic area including the mediodorsal nucleus), the left thalamus group (hypoperfusion in the left thalamic area including the mediodorsal nucleus), and the control group (no hypoperfusion in the thalamus).

Olfactory function testing

Standard olfactory testing using the T&T olfactometer (Daiichi Yakuhin Sangyo Inc., Tokyo, Japan) and olfactory identification testing using the Open Essence (OE) (FUJIFILM Wako Pure Chemical Inc., Osaka, Japan) were performed for all subjects. Additionally, a self-administered odor questionnaire (SAOQ) was given to all subjects to subjectively evaluate olfactory ability. All tests were administered by clinical technicians blinded to the subjects' lesions. The T&T olfactometer contains serial dilutions of the following 5 odors: β-phenylethanol, cyclotene, isovaleric acid, γ-undecalactone, and skatole. Each odor increases 10-fold in concentration several times over the course of the test, with 4 of them increasing from –2 to 5 (8 stages), and 1 increasing from –2 to 4 (7 stages). Subjects begin by sniffing each odor at its most dilute concentration. The stage at which they are first able to detect the odor is the odor detection threshold, and the stage at which they are first able to recognize the odor is the odor recognition threshold. When odor detection threshold or odor recognition threshold was not reached even at the highest concentration, the highest concentration plus a value of 1 was considered the threshold value. For each patient, the average odor detection threshold and average odor recognition threshold range were graded from –2 to 5.8, as well as the severity of olfactory dysfunction ranging from normal olfaction to anosmia (Table 1). In young adults, an average odor recognition threshold of ≤1 indicates normal olfaction, and a value of 5.6 indicates anosmia (Takagi 1987; Miwa et al. 2019). The OE consists of 12 odors with which Japanese people are likely to be familiar (perfume, rose, condensed

Table 1. The severity of olfactory dysfunction determined by average odor recognition thresholds for the 5 odors of the T&T olfactometer

Recognition threshold	Severity of olfactory dysfunction
≤1.0	Normal
1.1–2.5	Mild hyposmia
2.6–4.0	Moderate hyposmia
4.1–5.5	Severe hyposmia
≥5.6	Anosmia

milk, Japanese orange, curry, roasted garlic, sweaty clothes, cooking gas, menthol, India ink, wood, and Japanese cypress). Each card is spray-printed with ~15-μm microcapsules of each odorant, then folded in half. Subjects unfold their cards, releasing the odorant into the air, and select which odor they recognize (Fujio et al. 2012; Okutani et al. 2013; Shiga et al. 2014). The SAOQ allows quantification of the participants' subjective opinion of their olfactory ability. Subjects are given 20 odors with which Japanese people are likely to be familiar (boiled rice, miso, nori seaweed, soy sauce, baked bread, butter, curry, roasted garlic, Japanese orange, strawberry, green tea, coffee, chocolate, cooking gas, kitchen waste, wood, feces, sweat, flowers, and perfume), and are asked to answer in 1 of 4 ways: "can identify" (2 points), "can sometimes identify" (1 point), "cannot identify" (0 points), or "have not smelled it recently/have never smelled it before." Scores are expressed as a percentage of the maximum possible total for all items, excluding those for which they answered that they "have not smelled it recently/have never smelled it before." An SAOQ percentage of 70% or lower indicates possible olfactory dysfunction (Takebayashi et al. 2011).

Statistical analysis

Differences in average odor detection threshold, average odor recognition threshold, odor detection threshold, and odor recognition threshold obtained from standardized tests of olfactory ability were compared using 2-way analysis of variance (ANOVA) and Bonferroni's method, with SPECT grouping and olfactory stimulus laterality (ipsilateral or contralateral to hypoperfusion) as factors. The number of correct answers for each group from the OE and scores on the SAOQ were compared using 1-way ANOVA and Bonferroni's method. Further, groups in which thalamic hypoperfusion was observed were further divided into 1) subjects in whom the difference between their odor recognition threshold and odor detection threshold (hereafter referred to as threshold dissociation) was 1.5 or greater, and 2) those in whom such a dissociation was not observed. Then, the likelihood ratio of a threshold dissociation was determined for each of the 12 items of the OE. Finally, we used the Mann–Whitney *U*-test to examine which combinations of items correlated most with a dissociation between the odor detection threshold and the odor recognition threshold. Data were analyzed using the SPSS Windows (v.18.0; SPSS, Chicago, IL, USA) software package. Threshold for significance was $P = 0.05$. A power analysis was carried out using the G*Power (v.3.1; HHU, Düsseldorf, NRW, DEU) software package (Faul et al. 2009).

Results

Subject groupings

SPECT imaging revealed hypoperfusion in the right thalami of 9 subjects and in the left thalami of 10 subjects (termed right and left thalamus groups, respectively) (Figure 1). Hypoperfusion in the thalamic area was not observed in 9 subjects (control group). In nearly all subjects, no abnormality was observed in the olfactory pathway outside of the thalamus; however, ipsilateral hypoperfusion in the orbitofrontal cortex was observed in 1 subject in each of the right and left thalamus groups. No significant difference in age, number of days since stroke onset, MMSE score, or Brinkman index was observed between groups. For all groups, SAOQ scores were greater than 70%, and no significant differences were observed between groups (Table 2). The lesions and the subtype of ischemic stroke in all subjects are shown in Supplementary Table 1.

Odor detection and recognition threshold test results

The results of the 2-way ANOVA conducted with group classification (right thalamus, left thalamus, and control) and olfactory stimulus laterality (ipsilateral or contralateral) as factors are as follows. For the average odor detection threshold, no interaction or primary effect was observed. However, for the average odor recognition threshold, a primary effect of group classification was observed ($F(2,50) = 15.39$, $P < 0.001$, *effect size* (η^2) = 0.375). Bonferroni multiple comparisons tests for average odor recognition threshold revealed significant differences between the right thalamus and control groups ($P < 0.001$, *effect size* (r) = 0.57) and between the left thalamus and control groups ($P < 0.001$, *effect size* (r) = 0.63). No significant difference was observed between right and left thalamus groups for the average odor recognition threshold (Figure 2). A threshold dissociation between the odor detection threshold and odor recognition threshold was observed in 7 subjects in the right thalamus group (77%), 9 subjects in the left thalamus group (90%), and no subjects in the control group (0%). Regarding the dissociation between the odor detection threshold and odor recognition threshold (termed ΔD-R), a primary effect for group classification was observed ($F(2,50) = 12.78$, $P < 0.001$, *effect size* (η^2) = 0.328). Bonferroni multiple comparisons tests for ΔD-R revealed significant differences between the right thalamus and control groups ($P < 0.001$ *effect size* (r) = 0.63) and between the left thalamus and control groups ($P < 0.001$, *effect size* (r) = 0.62). No significant difference was observed between right and left thalamus groups for ΔD-R (Figure 3).

Odor identification threshold test results

One-way ANOVA revealed a significant difference between groups in the number of correct answers ($F(1,18) = 4.612$, $P = 0.019$, *effect size* (η^2) = 0.27). Bonferroni multiple comparisons tests revealed a significant difference between the right thalamus and control groups ($P = 0.032$, *effect size* (r) = 0.61) (Figure 4). The likelihood ratios of the 12 OE items in relation to the threshold dissociation are shown in Table 3. After comparing the numbers of correct answers for the set of 3 items on the OE with likelihood ratios greater than 3 (India ink, menthol, and curry), we found that subjects who exhibited threshold dissociation had significantly reduced number of correct answers for these items ($P = 0.008$, *effect size* (r) = 0.504) (Figure 5).

Discussion

In this study, we investigated the role of the thalamus, a part of the olfactory pathway, and examined whether olfactory function is affected in patients without MRI-detectable thalamic lesions but in whom SPECT revealed thalamic hypoperfusion. The T&T olfactometer revealed no significant differences in our subjects' odor detection threshold;

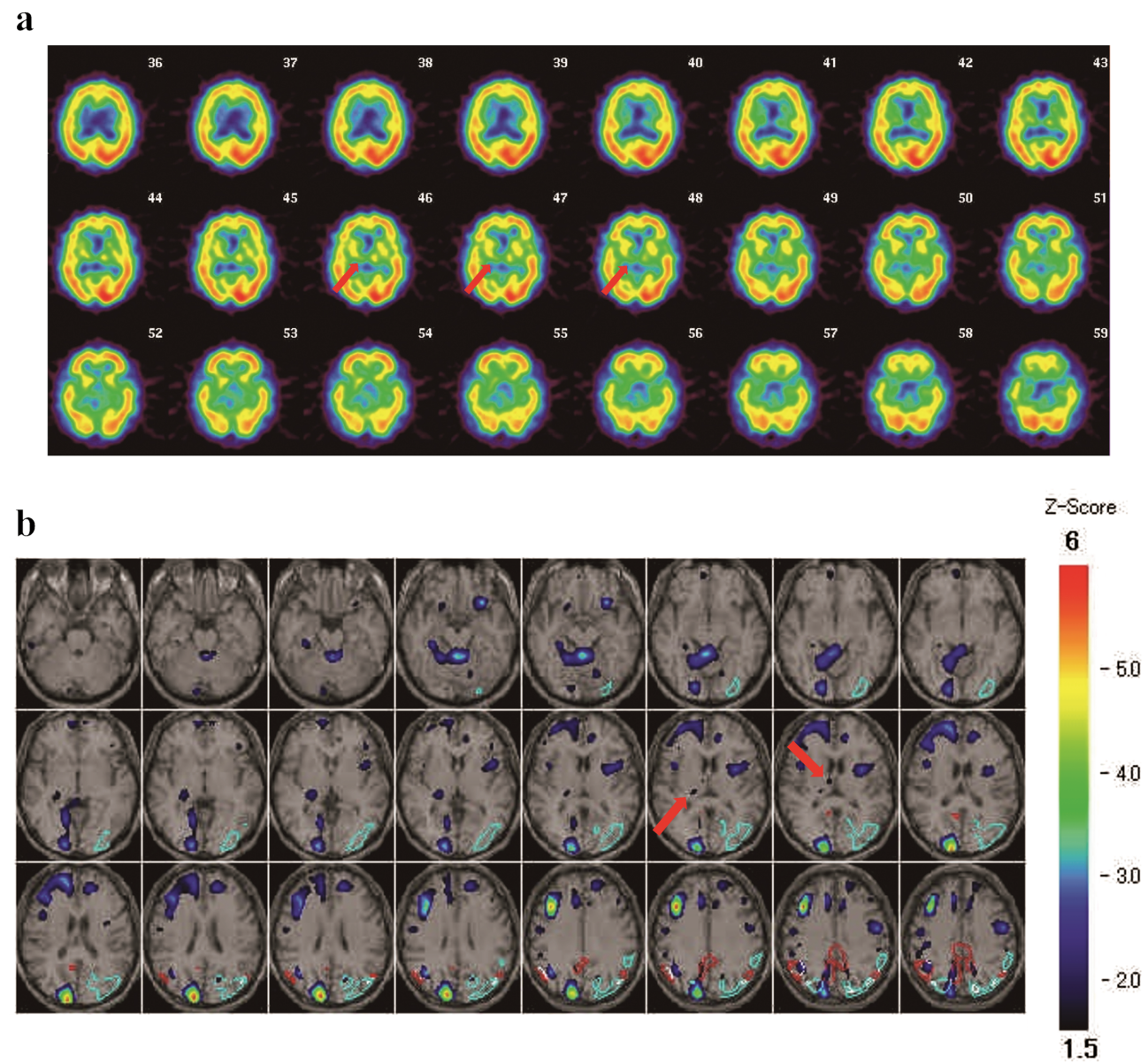

Figure 1. Diagnosis of hypothalamic blood flow by SPECT. SPECT image of patient in the right thalamus group (**a**), eZIS image of the same patient. (**b**) Red arrow indicates relative hypoperfusion site.

Table 2. Patient background

	Lt. thalamus $n = 10$	Rt. thalamus $n = 9$	Control $n = 9$	*P* value
Age (mean ± SD)	72.2 ± 5.84	70.3 ± 4.45	66.8 ± 4.65	0.08
Sex (F/M)	6/4	8/1	4/5	0.16
Days after cerebral infarction (mean ± SD)	16.7 ± 7.82	20.9 ± 7.74	18.7 ± 11.3	0.61
MMSE (mean ± SD)	27.6 ± 2.27	27.0 ± 2.50	28.2 ± 1.20	0.47
Brinkman index (mean ± SD)	236 ± 272	165 ± 239	210 ± 290	0.85
SAOQ (mean ± SD)	91.7 ± 15.3	82.8 ± 26.0	91.9 ± 10.4	0.48

Lt. thalamus = left thalamus group, Rt. thalamus = right thalamus group, Control = no thalamus lesion group.

however, odor recognition threshold and ΔD-R were both significantly elevated in groups with thalamic hypoperfusion. Significant score decrements were also observed in olfactory identification tests administered to subjects with thalamic hypoperfusion using the OE.

Although an olfactory pathway involving the mediodorsal thalamic nucleus and its subsequent projection to the prefrontal cortex has been clearly documented in anatomical studies the function of this pathway remains unclear. Recent research has suggested that

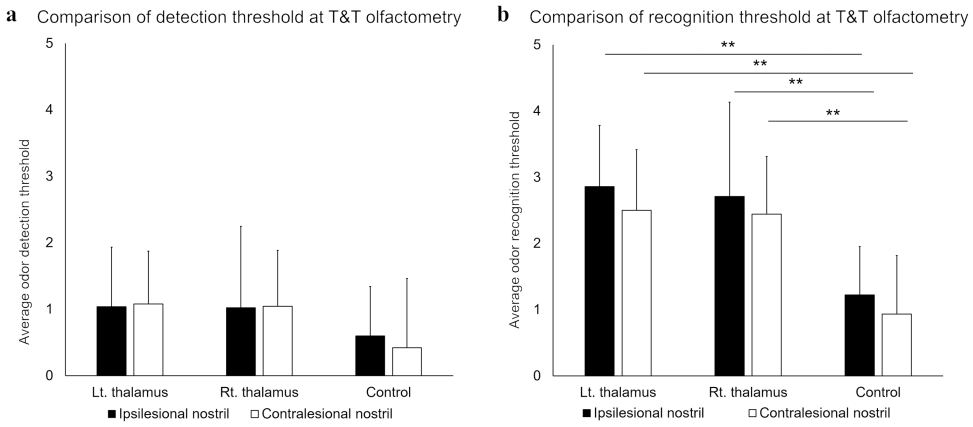

Figure 2. Comparison of odor detection threshold for each group (**a**). Comparison of odor recognition threshold for each group (**b**). Each bar represents the ipsilesional nostril (black bar) and contralesional nostril (white bar). Error bars represent SD. Lt. thalamus = left thalamus group, Rt. thalamus = right thalamus group, Control = no thalamus lesion group. $^{**}P < 0.001$.

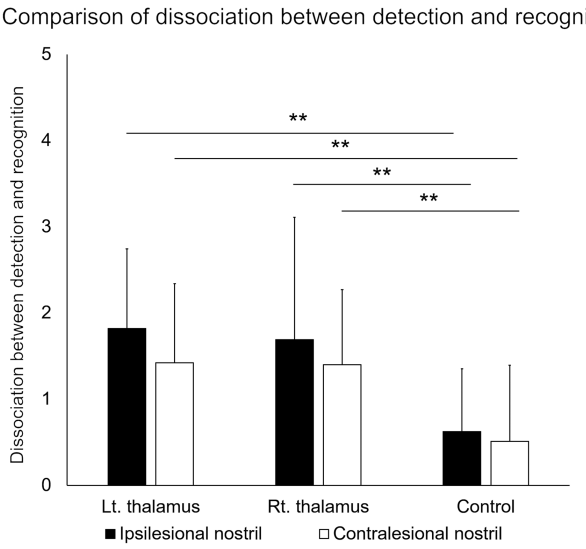

Figure 3. Comparison of dissociation between odor detection threshold and odor recognition threshold for each group. Each bar represents the ipsilesional nostril (black bar) and contralesional nostril (white bar). Error bars represent SD. Lt. thalamus = left thalamus group, Rt. thalamus = right thalamus group, Control = no thalamus lesion group. $^{**}P < 0.001$.

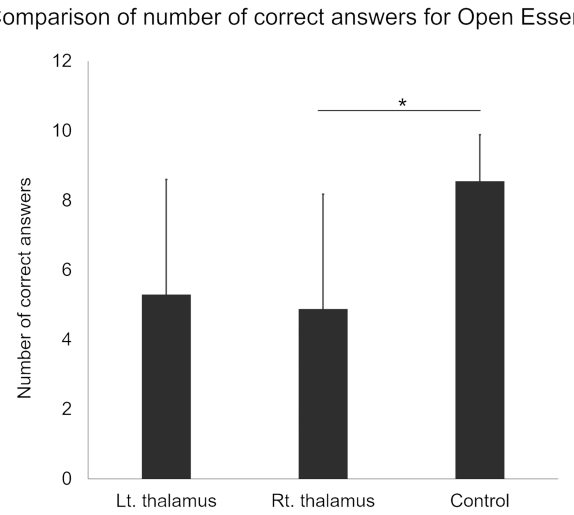

Figure 4. Comparison of number of correct answers for Open Essence. Error bars represent SD. Lt. thalamus = left thalamus group, Rt. thalamus = right thalamus group, Control = no thalamus lesion group. $^{*}P < 0.05$.

this area may be involved in odor attention and learning, as well as judgment of pleasantness/unpleasantness (Zelano et al. 2007; Plailly et al 2008; Small et al. 2008; Sela et al. 2009; Tham et al. 2009). Additionally, Sela et al. found that unilateral thalamic lesions do not affect the olfactory odor detection threshold but do cause cognitive deficits (Sela et al. 2009). Our results are consistent with these findings in that thalamic abnormalities reduce olfactory cognitive ability. Further, because our study targeted subjects without direct damage to the thalamus, there is evidence to suggest that latent thalamic hypoperfusion after acute ischemic stroke affects olfactory cognitive ability.

One unexpected outcome of this study is that unilateral thalamic hypoperfusion not only causes ipsilateral, but also contralateral decrement in olfaction when 1 nostril is tested at a time. The T&T olfactometer revealed that not only the ipsilateral, but also the contralateral in odor recognition threshold was significantly elevated in groups with thalamic hypoperfusion. Decrements in bilaterally tested olfaction were also observed, in the OE results. Olfactory stimuli are known to be transmitted ipsilaterally to the primary olfactory cortex. Further, when 1 breathes through both nostrils, even if olfaction on 1 side is peripherally inhibited, there is no observable effect on olfactory function. However, anatomical reviews of the olfactory center and research reports in rodents and in humans suggest the existence of both ipsilateral and contralateral connections between the nostrils and the olfactory center (Price et al. 1983; Shipley and Ennis 1996; McBride and Slotnick 1997; Wilson 1997; Savic and Gulyas 2000; Porter et al. 2005; Uva and de Curtis 2005, Cross et al. 2006). Thus, we can conclude that in the processing of olfactory stimuli that enter through either the right or left nostril, information can be carried contralaterally from the thalamus to the orbitofrontal cortex. It is apparent that both sides of the thalamus contribute cooperatively to the cognitive processing of olfactory input.

It is not uncommon for the elderly to experience asymptomatic MCA stroke (Kobayashi et al. 1991), which may remotely affect the olfactory pathway (thalamic) hypoperfusion, impairing olfactory function. Ipsilateral thalamic diaschisis occurs in 43–86% of cases

Table 3. Screening with single odorant of the Open Essence in participants with hypoperfusion in the thalamus

Odorant	Positive likelihood ratio	Sensitivity (%)	Specificity (%)
India ink	3.38	56.2	83.3
Wood	2.00	50.0	75.0
Perfume	1.88	62.5	66.7
Menthol	5.25	43.7	91.7
Japanese orange	1.22	81.3	33.3
Curry	3.75	31.3	91.7
Cooking gas	1.50	62.5	58.3
Rose	1.75	87.5	50.0
Japanese cypress	2.75	68.7	75.0
Sweaty smelling clothes	1.50	37.5	75.0
Condensed milk	1.88	62.5	66.7
Roasted garlic	1.63	50.0	81.3

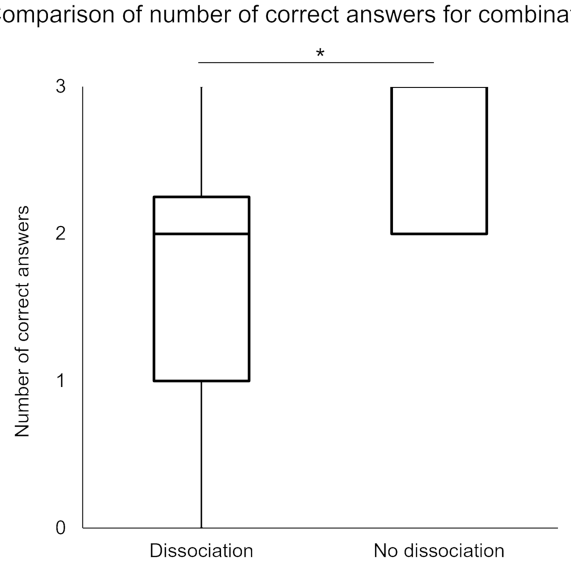

Figure 5. Average number of correct answers for odor combination (India ink, Menthol, Curry) in dissociation group and no dissociation group. Error bars represent SD. $*P < 0.05$.

between subacute and chronic phases of MCA stroke (Feeney et al. 1986; Sakashita et al. 1993; De Reuck et al. 1995), implying that patients often develop olfactory dysfunction following cerebral infarction. Nevertheless, many patients have little awareness of this condition. The results of this study demonstrated that patients with abnormally enhanced odor recognition thresholds as a result of thalamic hypoperfusion still subjectively rated their olfactory performance as 70% or higher on the SAOQ; they were unaware of their impaired olfaction. Age-related olfactory decline, olfactory dysfunction associated with neurodegenerative diseases like Alzheimer's, and other olfactory disorders that progress gradually are almost never detected by the patients themselves. Olfactory dysfunction may cause dysgeusia, loss of appetite, unexplainable weight loss, anorexia, and an increased risk of potentially life-threatening circumstances, as they individuals are less capable of detecting rotting food, gas leaks, and smoke (Miwa et al. 2001). Latent olfactory dysfunction has also been linked to sarcopenia and frailty (Harita et al. 2019). Consequently, the evaluation of the olfactory function in stroke patients is important not only for accurate localization of lesion but also for improving patient quality of life and activities of daily living. Thus, it is important for medical professionals to evaluate olfactory sensation during medical checkups for elderly individuals. Conversely, it is also common for patients with olfactory dysfunction who visit otorhinolaryngologists to remain undiagnosed. The present study showed that some cases of olfactory dysfunction are due to latent hypoperfusion in the olfactory pathway. Cerebral perfusion scintigraphy may help physicians elucidate etiologies for currently undiagnosable cases of olfactory dysfunction.

Cerebral perfusion scintigraphy is more time-consuming than either CT or MRI, and expensive for the patients. It is therefore difficult to incorporate cerebral perfusion scintigraphy into the routine diagnostic procedure for olfactory dysfunction. In addition, the number of facilities in Japan that can perform T&T olfactometry is limited. In our study, the 3 odorants in the OE that were most likely to detect threshold dissociation were India ink, menthol, and curry. Shiga et al. have reported that the most useful OE odorants for the diagnosis of olfactory dysfunction are India ink and Japanese cypress (Shiga et al. 2014), and Harita et al. have reported that Japanese cypress, wood, and roasted garlic odorants most effectively diagnose sarcopenia in elderly individuals although India ink, menthol, curry, and Japanese orange odorants most effectively diagnose frailty (Harita et al. 2019). Thus, instead of screening for all 12 OE odorants, an abridged screen using odorants of India ink, menthol, curry, and Japanese cypress would help efficiently diagnose olfactory decline although also screening for latent stroke, sarcopenia, and frailty.

This study was not without limitations. First, although our subject population of 19 is the largest of any human study of thalamic lesions to our knowledge, this sample size is far smaller than that seen in rodent studies. The small sample size may have prevented the observation of a significant difference in the number of correct responses on the OE scores between the left thalamus and control groups. Two patients, 1 each in the left and right thalamus groups, also exhibited ipsilateral orbitofrontal cortical hypoperfusion. It is possible that this condition exerted some degree of influence on their olfactory tests. Future studies with a larger sample size and stricter guidelines for candidate lesions are warranted. Second, it is unclear whether the results obtained are specific to olfaction or rather are a reflection of other cognitive impairment or sensory deficits unrelated to olfaction. From the interview response and MMSE assessment, we concluded that subjects did not have cognitive impairment that would affect olfaction. Although non-olfactory cognitive tested was not performed in this study such evaluation should be used in future work. The third limitation is the fact that SPECT lesion diagnosis and olfactory function testing were not performed at the same time. Differential recovery may have occurred in the interim period between these tests, which may have affected the results. However, no significant difference in the number of days since stroke onset was observed between groups. Further, because SPECT lesion diagnosis was carried out by individuals blinded to the patients' olfactory ability, it is unlikely that this process gave rise to Type I errors.

Conclusion

Our results suggest that central olfactory dysfunction after acute ischemic stroke may be caused by latent thalamic hypoperfusion. Cerebral perfusion scintigraphy may play a vital role in the image-based diagnosis of central olfactory dysfunction and help medical professionals reach etiological diagnoses in cases of olfactory dysfunction previously diagnosed as due to unknown causes. Further,

the OE has been shown to be useful for detecting olfactory dysfunction as well as latent stroke. Further investigations of the mechanism by which the thalamus affects olfactory identification as well as an improved understanding of the lateralization of the effects demonstrated here are necessary.

Supplementary material

Supplementary data are available at *Chemical Senses* online.

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Conflict of interest

There are no conflicts of interest.

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