Behavioural Brain Research 329 (2017) 172–179

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Semantic memory deficits are associated with pica in individuals with acquired brain injury

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ARTICLE INFO

Keywords:
Pica
Hyperorality
Temporal lobe
Semantic memory deficits
Frontal release signs

ABSTRACT

Although pica is one of the most prominent signs in individuals with severe cognitive impairment, the mechanisms and neural basis for pica have not been well elucidated. To address this issue, patients with acquired brain injury who showed pica and hyperorality were investigated. Eleven patients with pica, i.e., individuals who eat non-food items, and eight patients with hyperorality but who never eat non-food items were recruited. The cognitive and behavioral assessments and neural substrates of the two groups were compared. For basic cognitive and behavioral functions, two kinds of mental state examination—the mini-mental state examination and the new clinical scale for rating of mental states of the elderly—were administered. For pica-related behavioral features, frontal release signs, semantic memory deficits, and changes in eating behaviors were compared. Compared with the hyperorality group, the pica group had more severe semantic memory deficits and fewer frontal release signs, whereas there was no significant difference in changes in eating behaviors. Individuals in the pica group always had a lesion in the posterior part of the middle temporal gyrus. These findings suggest that semantic memory deficits following temporal lobe damage are associated with pica.

1. Introduction

Pica is a persistent eating of non-nutritive, nonfood substances (DSM-5, American Psychiatric Association, 2013 [1]). It may lead to dangerous consequences, such as malnutrition, intoxication, suffocation, and ileus or intestinal perforation, which sometimes require emergency medical treatment [2]. Descriptions of pica as a syndrome are found in antiquity [3–6], but the mechanisms underlying pica have not been well elucidated except for a nutritional hypothesis for ice eating, which may result from iron deficiency anemia [6]. Definitions of pica vary among investigators. Most researchers apply the term pica to a pathological craving both for food and non-food items [2–7], whereas Walker et al. [8] defined it as the eating of non-food items. The mixing of both food and non-food items within the definition of pica might be responsible for difficulties in investigating the mechanisms underlying pica. In this article, we applied Walker's definition, in which pica is defined as the eating of non-food items, to better study the mechanisms and neural basis of this behavior.

Hyperorality, which was first reported in Klüver–Bucy syndrome [9,10], has symptoms that are similar to those of pica. The symptoms of hyperorality have been described in terms of their neurological basis more thoroughly than those of pica and might provide a clue to the mechanisms underlying pica. Despite their similarities, there is a notable difference between pica and hyperorality as described in Klüver–Bucy syndrome [9,10]. Whereas monkeys with hyperorality never eat non-food items but instead discard them after examining them by mouth, patients with pica do eat non-food items. This clear distinction is not always maintained, as some individuals who were reported to have Klüver–Bucy syndrome did eat non-food items [11–14], whereas others had only a tendency to stuff or place food items in their mouths [15,16]. Our goal is to clarify the mechanisms that separate these two conditions.

In human studies, hyperorality has often been linked to frontotemporal dementia rather than Alzheimer's disease [14,17]. Although hyperorality in Klüver–Bucy syndrome is associated with temporal lobe deficits, human hyperorality has also been described in patients with focal frontal lobe lesions and in the context of frontal release signs [18,19]; it also has a remarkable dependency on external stimuli, e.g., utilization behavior [20]. Kertesz et al. [21] pointed out that hyperorality is one of the signs of frontal behavior abnormalities. These studies

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http://dx.doi.org/10.1016/j.bbr.2017.04.054
Received 1 March 2017; Received in revised form 21 April 2017; Accepted 26 April 2017
Available online 29 April 2017
0166-4328/

thus suggest that hyperorality might be related to frontal lobe damage and relevant frontal release signs and/or temporal lobe damage.

Although pica has been found in individuals with schizophrenia, intellectual disability, and pervasive development disorder, as well as in normal children and a pregnant woman [4], there have been several previous case reports of pica in individuals with degenerative disease and acquired brain injury. Cummings and Duchen [11] described a degenerative patient with pica who showed marked atrophy in the left anterior temporal region. Likewise, Lilly et al. [12] described a pica patient with anterior temporal atrophy. In the same report, they described a patient with pica that occurred after a traumatic brain disease in which neural damage was observed in the inferior portions of the bilateral temporal lobes. Hodges et al. [22] also reported a semantic dementia patient who ate non-food items such as cigarette ends during later stages of the disease. Mendez and Foti [23] reported a patient with focal left temporoparietal damage who underwent respiratory arrest after stuffing his mouth with surgical gauze. Funayama et al. [24] described three patients with pica-associated severe semantic memory deficits whose initial symptom was logopenic variant of primary progressive aphasia with focal left temporoparietal cortical atrophy. Funayama and Nakajima [25] also described a patient with temporoparietal cortical atrophy who had progressive transcortical sensory aphasia and progressive ideational apraxia at the onset and pica at later stages. From clinical observations, Morris et al. [26] suggested that a failure to recognize objects might account for the eating of inedible objects. Ikeda [27] also suggested that pica might be related to semantic memory deficits. These reports suggest that pica might be associated with temporal lobe damage and relevant semantic memory deficits.

To study pica and hyperorality, changes in eating such as appetite and food preference among dementia patients should be taken into account. Morris et al. [26] suggested that changes in eating, including pica, could result from a change in the sense of taste and of smell. Changes in the sense of taste [29] and smell [29,30] and in eating behaviors [27] are common in dementia, especially in frontotemporal lobar degeneration.

These earlier findings prompted us to explore the mechanisms behind pica and hyperorality by recruiting patients with acquired brain injury who developed pica and hyperorality and using systematic cognitive and behavioral examinations that focused on frontal release signs, semantic memory deficits, and changes in eating behaviors. We focused on patients with acquired brain injury rather than degenerative diseases, as they have relatively focal brain damage in contrast to patients with degenerative diseases, and analyzed their lesions to determine common and disease-specific regions.

2. Materials and methods

2.1. Participants

Ethical aspects of this study were reviewed and approved by the Ashikaga Red Cross Hospital Human Research Ethics Committee. Because the subjects were incapable of giving consent because of their severe cognitive impairment resulting from acquired brain injury, this study was performed after obtaining informed consent from all caregivers who had legal custody of the subjects. As we defined pica as the eating of non-food items, the compulsive eating of food items, e.g., ice eating because of iron deficiency anemia, was not counted as pica. As it is difficult to clearly assess hyperorality, we defined hyperorality as having to remove substances from the mouth because of an excessive eating of nutritive substances [14] or because of a strong tendency to examine non-food items by mouth [9,10]. Thus, patients who do eat non-food items in the context of hyperorality were classified into the pica group, not the hyperorality group.

The study participants were recruited from the Cognitive Dysfunction Clinic associated with Ashikaga Red Cross Hospital, Tochigi, Japan, during the period from January 2007 to December 2016 and were limited to those with acquired brain injury. Patients who had neuropsychiatric, developmental, or degenerative diseases before the onset of acquired brain injury were excluded. No children or pregnant women were included in this study. Also excluded were those with acute or subacute confusional state. All the participants were screened to rule out iron deficiency anemia.

2.2. Methods

Background demographic information about the patients included their etiologies, the age of pica or hyperorality onset, gender, and level of education. The following assessments were carried out at the time of onset of pica or hyperorality.

2.2.1. Basic cognitive and behavioral assessments

We used the Japanese version of the Mini Mental State Examination (MMSE-J) [31] and the new clinical scale for the rating of mental states of the elderly (NM scale) [32], which assesses cognitive functions for everyday life, i.e., the ability to do housework and to communicate, along with measures of speech, memory, and orientation, with a maximum of 50 points. Both tests have high validity and reliability [31,32]. For episodic/autobiographic memory performance, we used the subscale for episodic memory performance in the MMSE-J, which includes an orientation task and a delayed recall task.

We also assessed symptoms of Klüver-Bucy syndrome. The five symptoms of Klüver–Bucy syndrome [9,10] are psychic blindness (i.e., multi-modal agnosia or semantic memory deficits), hyperorality, hypermetamorphosis, changes in emotional behavior, and changes in sexual behavior. Assessments for the first two symptoms are described in detail below. Hypermetamorphosis, a strong tendency to attend and react to every visual stimulus, can be considered as a utilization behavior in humans, the assessment of which is described below. The remaining two symptoms, changes in emotional behavior (i.e., the complete absence of all emotional reactions) and changes in sexual behavior (i.e., an increase in sexual activity), were assessed from clinical observations.

2.2.2. Frontal release signs

Typical frontal release signs/symptoms include primitive reflexes [33,34], utilization behavior [20], imitation behavior [35], and environmental dependency syndrome [36]. Among those, primitive reflexes are the most basic signs and are usually involved in the other symptoms. In this context, we first examined the grasp reflex and sucking reflex as frontal release signs for which their neural substrates lie in the frontal lobe, in particular, in the medial frontal lobe [37,38]. For the grasp reflex, we followed Seyffarth's method [33], in which the grasp reflex is assessed as the finger flexion with thumb adduction that occurs in response to a distally moving pressure applied to the palm before traction of the finger flexors occurs, while the shoulder, arm, and forearm are held in a fixed position. In this study, the examiner used the pressure of his/her finger on each of the patients' palms to trigger the reflex. For the sucking reflex, we followed the definition of Schott and Rossor [39], which defines the sucking reflex as instinctive sucking in response to tactile stimulation in the oral region. The examiner assessed this reflex by tapping each subject's upper lip lightly with his finger.

Second, we used the scale of utilization behavior from the Japanese version of the Frontal Behavioral Inventory [21,40–42] to further assess frontal release signs. In this scale, utilization behavior is defined as follows: “Does he/she seem to need to touch, feel, examine, or pick-up objects within reach and sight?” The question was answered by a caregiver familiar with the patient's everyday life. In the inventory, the frequency of utilization behavior is scored as follows: 0, “never”; 1, “occasionally”; 2, “moderately often”; and 3, “most of the time”, and the severity is scored as follows: 0, “none”; 1, “mild”; 2, “moderate”; 3, “severe”. A total score is expressed as the product of the frequency score multiplied by the severity score.

2.2.3. Semantic memory deficits

Because of the severe cognitive impairment among these patients, detailed semantic memory tests (e.g., Pyramid and Palm Trees Test [43]) could not be carried out. However, we could more clearly assess the presence of severe semantic memory deficits in the clinical setting. According to Bier and Macoir [44], semantic memory is necessary to support everyday actions and single-object use. Hodges et al. [45] showed that everyday object use was markedly impaired in patients with semantic dementia and was heavily dependent upon object-specific conceptual knowledge. Likewise, a deficit in person knowledge is regarded as a feature of semantic dementia [46,47]. In this context, we assessed basic semantic memory (e.g., single-object use, recognition of people, and knowledge about family and friends) among these individuals using the following methods: the manipulation of everyday objects use, an interview consisting of three questions regarding semantic memory deficits from the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [48], and a semi-structured interview for semantic memory errors in everyday life. Considering the potential concurrence of aphasia among these patients, all semantic memory assessments that we used in this study were able to be carried out nonverbally.

First, we examined the ability of each patient to use 10 everyday objects: scissors, a comb, a toothbrush, a fork, a spoon, a hammer, a knife, a cup, nail clippers, and a magnifying glass. Subjects were handed one of the above-mentioned tools and were instructed to use it. Any type of semantic parapraxis, e.g., misuse of a toothbrush to comb one's hair, as well as amorphous responses or no response, was counted as a semantic error. In contrast, clumsy reactions, correcting attempts of "conduit d'approche", and spatial errors, which are found in ideomotor apraxia, were not considered semantic errors. One point was earned for the semantic parapraxis of each tool, with a maximum score of 10.

Second, we used the Japanese version of the IQCODE (http://cmhr.anu.edu.au/ageing/Iqcode/). This is a brief questionnaire that uses information provided by a caregiver familiar with the patient's everyday life to assess a person's change in cognitive functioning over the previous 10 years. Of the 26 questions, three questions cover semantic memory, including recognizing the faces of family and friends (Q1), remembering things about family and friends (Q2), and knowing how to work familiar machines around the house (Q3). In short, Q1 and Q2 focus on personal semantics and Q3 on tools. IQCODE requires each question to be rated on a 5-point scale from 1, "much improved" to 5, "much worse", as compared with the premorbid state. A total score was counted from the three questions with a maximum score of 15.

Third, we used a semi-structured interview to assess clinically evident semantic memory errors in everyday life. Semantic memory errors clearly represent semantic memory deficits. Questions regarding the semantic misuse of tools and foods were asked of a caregiver who is familiar with the patient's everyday life. The question related to tool use (S1) was "Does he or she sometimes try to use tools for inappropriate purposes, for example, trying to use a toothbrush for a comb, shaving cream for a toothbrush, or a watering can for a dustpan?" Errors related to pica, i.e., the eating of non-food substances, were excluded. The question for foods (S2) was "Does he or she sometimes try to eat foods or drink in an unusual way, for example, trying to eat spaghetti with a straw or putting yogurt in a microwave?" Again, errors related to pica were excluded. The caregivers were asked to give a 'yes' or 'no' answer to each question. When a patient had a 'yes' for each question, he or she was counted as having semantic memory errors.

2.2.4. Changes in eating behaviors

Changes in eating behaviors were assessed with the Japanese version of the Swallowing/Appetite/Eating Habits Questionnaire [28,49]. We used two of the five domains covered in the questionnaire, change in appetite and change in food preference, which are both likely to be involved in pica. Information was gathered from a caregiver familiar with the patient's eating habits. There were nine questions regarding a change in appetite, which mainly focus on increased appetite. The eight questions regarding a change in food preference include questions about sweet food preferences and adding more seasoning to their food. In the inventory, the frequency of utilization behavior is scaled as follows: 0, "never"; 1, "rarely"; 2, "occasionally"; 3, "frequently"; and 4, "most of the time", and the severity as: 0, "none"; 1, "mild"; 2, "moderate"; and 3, "severe". A total score for both a change in appetite and a change in food preference is separately calculated. Scores for the individual nine and eight questions were expressed as the product of frequency score multiplied by the severity score. A total score for a change in appetite and a change in food preference was calculated by adding these scores with maximum scores of 108 and 96, respectively.

2.2.5. Neuroanatomical analysis

Because it was extremely difficult to obtain magnetic resonance images of two pica patients owing to their severe cognitive impairments and behavioral symptoms, we applied a manual tracing technique using morphological imaging with magnetic resonance imaging for nine pica patients and eight hyperorality patients and computed tomography for the remaining two pica patients. Traumatic brain injury, which was considered as having relatively focal brain damage in this study, often also involves diffuse axonal injuries. Likewise, lesions related to encephalitis or brain tumors might be more extensive than the areas detected by structural scans. However, in general, diffuse axonal injuries alone or undetectable lesions are not considered to cause pica.

Images of overlapping lesion areas based on the clinical structural scans, magnetic resonance imaging, and computed tomography, were generated using MRIcro software (http://www.sph.sc.edu/comd/rorden/mricro.html). This method is essentially a direct-to-digital variant of template-based spatial normalization that has been the standard approach in group-lesion studies and remains the gold standard for delineation of chronic brain lesions with intraclass correlation coefficients of 0.86–0.95 [50]. A medical doctor (A.K.) who is experienced in this form of lesion analysis performed the analysis without knowing whether the patients had pica or hyperorality or how the patients had performed on the neuropsychological and behavioral assessments. Lesions of individual participants were traced from clinical magnetic resonance images (all patients except two individuals with traumatic brain injury) or computed tomography (for those two patients with traumatic brain injury) at the time of pica/hyperorality onset. The mixing of magnetic resonance imaging and computed tomography, which have different levels of sensitivity, would be a major methodological concern. Thus, as described below, we also compared the two groups using only the incidence of cerebrovascular disease, which was determined in all patients by magnetic resonance imaging.

The method to transpose lesions was as follows. The operator positioned the lesions onto a template brain by visual inspection. All major sulci in the lesions were identified via T1 resonance imaging or computed tomography. Each lesion boundary was identified and manually transferred onto the template brain, taking into account the relation of the lesion boundary to the identified sulci. After transferring all lesion images, the areas from each group of patients were overlapped to explore their regions of mutual involvement on a voxel-by-voxel basis using the MRIcro regions of interest menu commands. Then, subtraction of the hyperorality overlapped lesion from the pica overlapped lesion was performed by using the MRIcro subtraction regions of interest commands to clearly differentiate the neural basis for pica. After the most densely overlapped lesion for each group was found, the number of patients who had this lesion was compared between the two groups.

2.2.6. Statistical analysis

The Mann–Whitney U-test was used to analyze the age of onset, level of education, MMSE-J data, the NM scale, utilization behavior, everyday objects use, semantic memory deficits, and changes in eating behaviors. The Fisher's exact test was used to analyze gender, the number of patients with primitive reflexes, and the number of patients with semantic memory errors, as well as to make lesion comparisons.

3. Results

3.1. Neuropsychological and behavioral comparisons between pica and hyperorality patients

Eleven patients with pica and eight patients with hyperorality were compared. As all cases had a lesion in the left hemisphere language areas, these patients all had mild to moderate aphasia. The proportion of sensory aphasia, i.e., both transcortical sensory aphasia and Wernicke's aphasia, was higher in the pica group at 81.8% as compared with the hyperorality group at 25% ($P = 0.02$, Fisher's exact test). In contrast, motor aphasia, i.e., both Broca's aphasia and transcortical motor aphasia, was observed more frequently in the hyperorality group (50%) as compared with the pica group (9.1%), although the difference was not statistically significant ($P = 0.10$, Fisher's exact test).

Items related to daily necessities were the most common objects involved in pica, such as toothpaste, soap, sponge, shampoo, face lotion, laundry detergent, bathing powder, antiseptic solution, aromatic air freshener, cotton, paper, toilet paper, and diapers. Background demographic information and cognitive and behavioral assessments between the two groups are presented in Table 1. Gender (Fisher's exact test, $P = 1.0$), average age (Mann–Whitney U-test, $P = 0.97$), and level of education (Mann–Whitney U-test, $P = 0.7$) did not differ between the two groups. Clinical etiologies of the 11 individuals with pica included seven individuals with cerebrovascular disease (63.6%), two with traumatic brain injury (18.2%), one with a brain tumor (9.1%), and one with encephalitis (9.1%). For the individuals with hyperorality, etiologies included six patients with cerebrovascular disease (75.0%), one with a brain tumor (12.5%), and one with encephalitis (12.5%). The unequal sex distribution might reflect a higher incidence of both cerebrovascular diseases and traumatic brain diseases in men than in women [51,52]. For basic cognitive and behavioral assessments, scores for the MMSE-J, episodic memory performance, and NM scale did not differ significantly between the two groups.

Regarding frontal release signs, although the number of patients who exhibited a sucking reflex and the score for utilization behaviors did not differ significantly between the two groups, a grasp reflex was observed more frequently in the hyperorality group than the pica group (Fisher's exact test, $P < 0.01$). For semantic memory, although the scores for IQCODE did not differ significantly between the two groups, the scores for semantic parapraxis for everyday object use were higher in the pica group when compared with the hyperorality group (Mann–Whitney U-test, $P < 0.05$). There were more patients who had semantic memory errors for tool use in the pica group than in the hyperorality group (Fisher's exact test, $P < 0.01$), whereas no difference was found in the number of patients who had semantic memory errors for foods. For changes in eating behaviors, there was no significant difference in the scores for either changes in appetite or changes in food preferences between the two groups. To sum up, semantic memory deficits were observed more often in the pica group, whereas the frontal release signs were noted more in the hyperorality group.

Regarding the other symptoms of Klüver–Bucy syndrome, changes in emotional behavior were observed in 3 of 11 pica patients (27.2%) and 2 of 8 hyperorality patients (25%). With respect to changes in sexual behavior, only one pica patient showed an increase in sexual activity. In contrast, most pica and hyperorality patients present with a decrease in sexual activity. In summary, symptoms of Klüver–Bucy syndrome were often present in these study groups, except for an increase in sexual activity.

3.2. Neuroanatomical analysis

3.2.1. Neuroanatomical comparisons between pica and hyperorality patients

There were more patients who had a lesion in either side of the posterior middle temporal gyrus in the pica group (100%) than in the hyperorality group (37.5%) (Fisher's exact test, $P < 0.01$). In contrast, there was a tendency toward having a lesion in either side of the medial frontal lobe in the hyperorality group (75.0%) relative to the pica group (27.2%) (Fisher's exact test, $P = 0.070$). The affected brain areas of the patients with pica are shown as overlaid images in Fig. 1A; the main affected area is confined to the temporal gyrus, with a maximal focus in the posterior part of the left middle temporal gyrus and its underlying white matter. Those of hyperorality patients are shown in Fig. 1B; the main affected areas were found in the medial frontal lobe, bilaterally. Fig. 1C shows subtraction of the hyperorality overlapped lesion from the pica overlapped lesion. The main pica-specific areas were found in the posterior part of the left middle and inferior temporal gyri and their underlying white matter.

Table 1
Demographic factors and cognitive and behavioral assessments between individuals with pica and hyperorality.

Item	Characteristic or assessment	Pica ($n = 11$)	Hyperorality ($n = 8$)	P-value
Demographics	Gender (males)	10 (90.9%)	7 (87.5%)	1.0
	Average age, years (range)	61.5 (16–80)	63.3 (44–88)	0.97
	Education, years (range)	11.8 (10–12)	12.1 (9–16)	0.70
Cognitive assessment	MMSE-J (0, worst; 30, best)	2.7 ± 2.6	6.8 ± 7.0	0.48
Episodic memory	Orientation and delayed recall in MMSE-J (0, worst; 13, best)	0.3 ± 0.6	1.4 ± 2.1	0.13
Behavioral assessment	NM scale (0, worst; 50, best)	5.3 ± 6.8	9.4 ± 9.5	0.67
Frontal release sings	Sucking reflex	8.8%	50.0%	0.11
	Grasp reflex	0%	50.0%	< 0.01
	Utilization behaviors (9, frequent; 0, absent)	0.6 ± 1.3	1.8 ± 3.1	0.31
Semantic memory	Semantic parapraxis for everyday object use (10, worst; 0, best)	6.9 ± 2.9	3.6 ± 3.3	< 0.05
	Semantic memory deficits on IQCODE (15, worst; 10, best)	14.3 ± 0.9	13.4 ± 1.5	0.17
	Interview on semantic memory errors for tool use (Percentage of individuals having semantic memory errors)	90.9%	33.3%	< 0.01
	Interview on semantic memory errors for foods (Percentage of individuals having semantic memory errors)	45.5%	12.5%	0.18
Change in eating behaviors	Change in appetite (108, extreme; 0, no change)	1.6 ± 4.3	1.8 ± 3.3	0.73
	Change in food preferences (96, extreme; 0, no change)	0.3 ± 0.9	0.3 ± 0.7	0.88

IQCODE, the Informant Questionnaire on Cognitive Decline in the Elderly; MMSE-J, the Japanese version of the Mini Mental State Examination; NM scale, the new clinical scale for rating of mental states of the elderly.

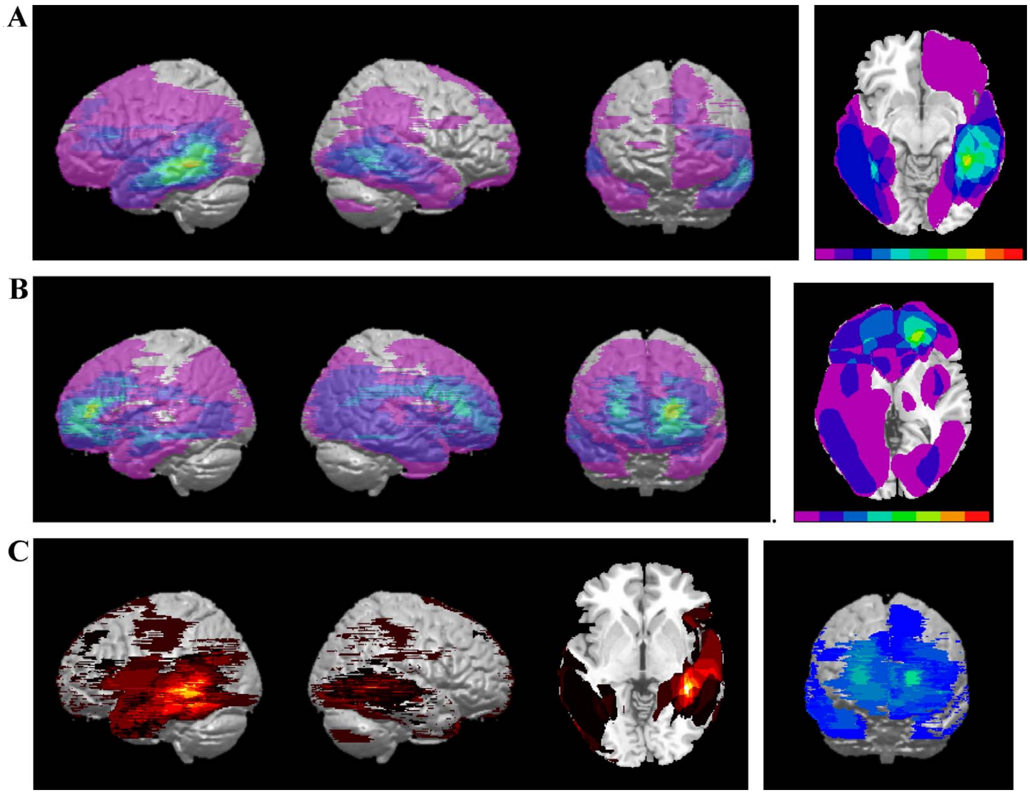

Fig. 1. Lesion areas among pica and hyperorality patients. (A) Overlap of lesion areas among pica patients. Yellow represents regions of maximum overlap, and purple represents regions of minimal overlap. From left to right, the images show the left hemisphere, the right hemisphere, the frontal lobes, and a horizontal slice at the level of the midbrain. The affected areas mainly overlapped in the posterior part of the left middle temporal gyrus and its underlying white matter. (B) Overlap of lesion areas among hyperorality patients. Yellow represents regions of maximum overlap, and purple represents regions of minimal overlap. From left to right, the images show the left hemisphere, the right hemisphere, the frontal lobes, and a horizontal slice at the level of the lateral ventricle. The affected areas mainly overlapped in the bilateral medial frontal lobe. (C) Subtraction of the hyperorality overlapped lesion from the pica overlapped lesion. Warmer colors represent pica-specific lesions and cooler colors represent hyperorality-specific lesions. From left to right, the images show the left hemisphere, the right hemisphere, a horizontal slice at the level of the midbrain, and the frontal lobes. Subtraction analysis showed that the main areas of the pica-specific lesions lie in the posterior part of the left middle and inferior temporal gyri and their underlying white matter. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

As magnetic resonance images provide better contrast resolution than computed tomography, the extent of the lesions of the two patients with traumatic brain injury, who were evaluated by computed tomography, might have been underestimated. However, both of these patients had a lesion in the left posterior middle temporal gyrus. Thus, the differences in the neuroimaging techniques did not substantially affect the localization findings of the results.

3.2.2. Neuroanatomical comparisons between pica and hyperorality patients with cerebrovascular disease

All seven pica patients with cerebrovascular disease (100%) had a lesion in either side of the posterior middle temporal gyrus lesion, whereas two of six hyperorality patients with cerebrovascular disease (33.3%) had a middle temporal gyrus lesion (Fisher's exact test, $P < 0.05$). In contrast, four of six hyperorality patients (66.7%) had a lesion in either side of the medial frontal lobe lesion, whereas two of seven pica patients (28.6%) had a medial frontal lobe lesion (Fisher's exact test, $P = 0.29$). The results were similar with the above-mentioned comparison between both groups of pica and hyperorality individuals. The affected brain areas of the pica patients with cerebrovascular disease are shown as overlaid images in Fig. 2A. The affected areas mainly overlapped in the left temporal lobe, with the maximal focus in the posterior part of the left middle temporal gyrus and its underlying white matter. The overlapped lesions for hyperorality patients with cerebrovascular disease are shown in Fig. 2B, with the main affected areas in the medial frontal lobe, bilaterally. Fig. 2C shows a subtraction of the hyperorality overlapped lesion from the pica overlapped lesion. The main pica-specific area was in the posterior part of the left middle temporal gyrus and its underlying white matter.

4. Discussion

The present study yielded two findings. First, compared with individuals with hyperorality, individuals with pica had greater semantic memory deficits and fewer frontal release signs, whereas there was no significant difference in eating behaviors between the two groups. Second, neuroanatomical analysis showed that the neural basis for pica might involve the posterior part of the left middle temporal gyrus. Although we assessed frontal release signs, other frontal lobe signs were unable to be analyzed because of severe cognitive dysfunction, e.g., executive dysfunction, working memory deficits, and impulsiveness. However, those other frontal lobe dysfunctions, such as executive dysfunction, working memory deficits, and impulsiveness, are unlikely to produce pica symptoms because almost all patients with executive dysfunction, working memory deficits, or impulsiveness do not show symptoms of pica. To sum up, our findings suggest that semantic memory deficits following temporal lobe damage are associated with pica, rather than frontal release signs or changes in eating behaviors.

The overlapping lesions of the temporal lobe in the present individuals with semantic memory deficits are in agreement with mounting convergent evidence for the importance of the temporal lobe in semantic memory, which is based on patients with temporal lobe damage, functional neuroimaging, and repetitive transcranial magnetic stimulation studies [53]. However, it is interesting to note that the maximal overlap of the lesions occurred in the posterior part, not the anterior part, of the left middle temporal lobe in the present pica cases.

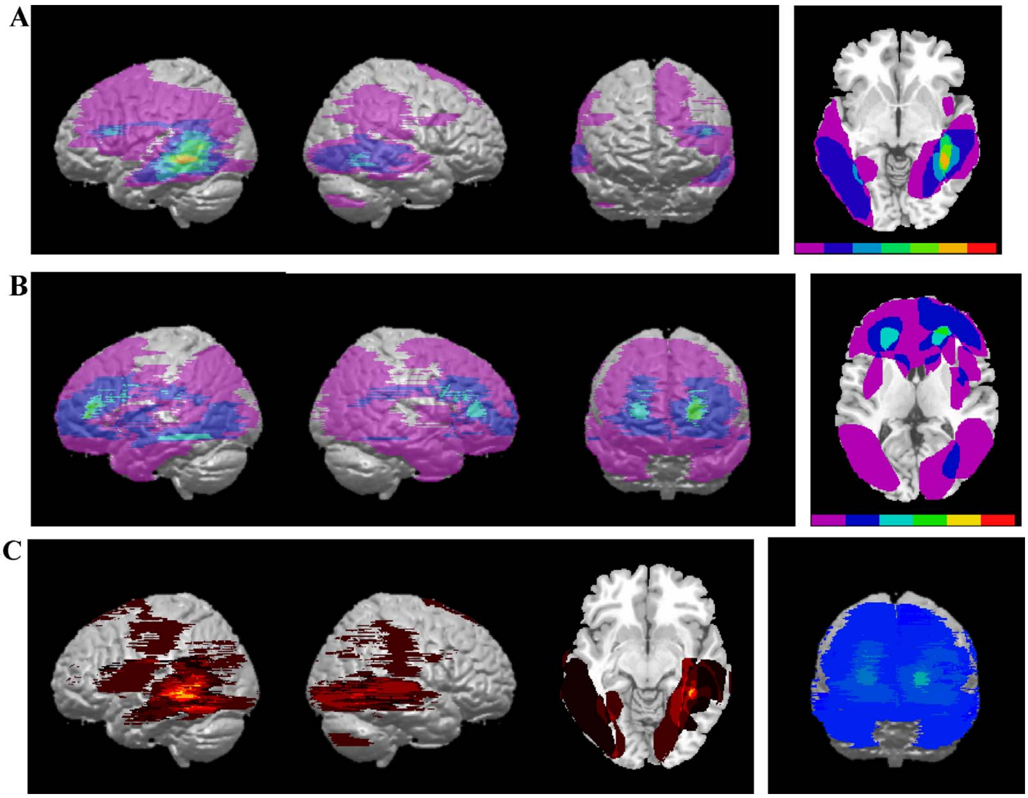

Fig. 2. Lesion areas among pica and hyperorality patients with cerebrovascular disease. (A) Overlap of lesion areas in pica patients with cerebrovascular disease. Red represents regions of maximum overlap and purple represents regions of minimal overlap. From left to right, the images show the left hemisphere, the right hemisphere, the frontal lobes, and a horizontal slice at the level of the midbrain. The affected areas mainly overlapped in the posterior part of the left middle temporal gyrus and its underlying white matter. (B) Overlap of lesion areas in hyperorality patients with cerebrovascular disease. Green represents regions of maximum overlap and purple represents regions of minimal overlap. From left to right, the images show the left hemisphere, the right hemisphere, the frontal lobes, and a horizontal slice at the level of the lateral ventricle. The affected areas mainly overlapped in the posterior part of the bilateral medial frontal lobe. (C) Subtraction of the hyperorality overlapped lesion from the pica overlapped lesion. Warmer colors represent the pica-specific lesions, and cooler colors represent the hyperorality-specific lesions. From left to right, the images show the left hemisphere, the right hemisphere, a horizontal slice at the level of the hypothalamus, and the frontal lobes. The main areas of the pica-specific lesions lie in the posterior part of the left middle and inferior temporal gyrus and their underlying white matter. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

Recent studies have demonstrated that not only the anterior temporal area [54] but also the middle temporal gyrus are crucial for semantic memory [55,56]. These different neural substrates for semantic memory may reflect category-specific semantic systems. Based on a lesion study for lexical retrieval, whereas words for living things are associated with the left anterior temporal lobe, those for tools are associated with the left posterior temporal lobe [57]. Likewise, based on a voxel-based morphometric study of neurodegenerative diseases, Brambati et al. [58] showed that lexical retrieval for living things correlates with the right anterior temporal pole, whereas that for non-living items correlates with the posterior part of the left middle temporal gyrus. Neuroimaging studies have also demonstrated that the left posterior middle temporal gyrus is particularly important for perceiving and knowing about tools and their functions [59,60]. Regarding hemispheric lateralization, Gainotti [61] indicated in his review of lesion studies on category-specific disorders that whereas a bilateral injury to the antero-mesial and inferior parts of the temporal lobes was found in patients with a category-specific semantic impairment for living things, an extensive lesion of the areas lying on the dorso-lateral convexity of the left hemisphere was found in patients with a category-specific semantic impairment for man-made objects.

These previous reports suggest that the neural basis for semantics related to non-living things involves the posterior part of the middle temporal gyrus, but not the temporal pole, in the left hemisphere. As the most common items for pica were items that were used for daily necessities and that were man-made objects, our findings on the relationship between pica and the posterior part of the left middle temporal gyrus are compatible with the previous reports.

These findings suggest that the inability to recognize objects is associated with symptoms of pica rather than frontal release signs or changes in eating behaviors. It is still unknown why semantic memory deficits lead to the eating of non-food items. One clue to this neurological progression may come from observations of infants, who are not yet able to understand whether substances are edible or inedible. They examine unrecognizable substances with their hands and mouths and sometimes end up swallowing them, in the same way that patients with pica and dementia do. We human beings might be inclined to eat unrecognizable substances when we are unable to understand their meanings through any sensory modalities.

Our study has several limitations that should be considered when interpreting the results. First of all, because of the severe cognitive impairment of these individuals, detailed neuropsychological tasks could not be carried out. For example, semantic memory deficits are frequently measured with the Pyramid and Palm Trees Test [44], but we could not use this assessment tool because of the severe cognitive impairment of these patients. Second, the manual technique we used in the neuroanatomical analysis might be a methodological concern. However, the results are most likely to be similar even without the overlapping lesion analysis using MRIcro because all pica patients (100%) had a lesion in the posterior middle temporal gyrus, whereas only three of 10 (27.2%) had the medial frontal lobe lesion. Likewise, whereas six of eight hyperorality patients (75.0%) showed the medial frontal lobe lesion, only three (37.5%) had the middle temporal gyrus lesion. Third, we could not directly assess olfactory impairment in these dementia patients [29] because of their severe cognitive impairment. However, Luzzi et al. [29] showed that olfactory impairment in patients with semantic dementia reflects the semantic deficits of those individuals and not their perceptual impairment. Piwnica-Worms et al. [30] also proposed that semantic dementia produces deficits of flavor knowledge and that those deficits might lead to abnormal eating behavior and altered food preferences, which we assessed in this study. These reports indicate that olfactory impairment might be attributed to semantic memory deficits. Fourth, the number of pica and hyperorality patients was small. However, these symptoms are rarely found in patients with acquired brain injury, which precludes studying a large cohort, and thus our study likely represents the best possible assessment of a cohort of pica and hyperorality patients. To our knowledge, there has been no systematic cohort study related to this issue.

5. Conclusions

Despite these limitations, our study sheds some light on the mechanism and the neural basis for pica. Our findings suggest that semantic memory deficits as a result of temporal lobe damage are associated with pica.

Author contributions

M.F. conceived the project, analyzed the data, and wrote the paper. A.K. performed lesion analysis. T.M., A.K., M.K., M.M., and Y.N. supervised the study. All authors contributed to the final written product.

Acknowledgments

We wish to thank the patients and their caregivers who participated in these studies.

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