Somatotrophic reorganization in the brain after extremity replantation, revascularization and amputations: investigated by SPECT analysis

Ekstremite replantasyon-revaskülarizasyon ve amputasyonlarından sonra beyinde somatotropik reorganizasyon: SPECT analizi ile araştırma

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BACKGROUND

We wanted to investigate the somatotropic reorganization occurring in the motor and somatosensory cortex by using 99mTc-HMPAO SPECT analyses, after the extremity revascularization, replantation or amputation.

METHODS

Twelve patients (11 men, 1 female; mean age 38.9±14.7 years) and controls (5 men, mean age 32.2±7.9 years) were enrolled in this study. After reconstruction, lower, middle and upper orbitomeatal slices with precentral and postcentral slices were obtained. All images were visually and semiquantitatively evaluated. Mann-Whitney U-test was used for statistical analysis.

RESULTS

In the revascularization and replantation patients, postcentral and precentral hypoperfusions were seen at dominant hemisphere. In the amputated patients, postcentral (in 3 of 4 cases) and precentral hypoperfusions were seen at non-dominant hemisphere and postcentral hypoperfusion (in 1 of 4 cases) was seen at dominant hemisphere. In our patients, most significant difference in regional cerebral blood flow was found in posterior parietal cortex (somatic associated area).

CONCLUSION

Changes that take place in precentral and postcentral cortical areas subsequent to the extremity replantation-revascularization of the organ is a good indicator of somatotrophic reorganization.

Key Words: Amputation; motor cortex/physiology; muscle, skeletal/metabolism; phantom limb/physiopathology; replantation; somatosensory cortex/physiology; 99m-Tc-HMPAO.

AMAÇ

Ekstremitelere uygulanan replantasyon, revaskülarizasyon ve amputasyon ameliyatlarından sonra 99mTc-HMPAO SPECT analizi kullanılarak motor ve somatosensoriyel korteksteki somatotropik reorganizasyon açısından araştırıldı.

GEREÇ VE YÖNTEM

Çalışmaya 12 hasta (11 erkek, 1 kadın; ort. yaş 38.9±14.7 yıl) ve 5 sağlıklı erkek (ort. yaş 32.2±7.9 yıl) kontrol grubu olarak alındı. Rekonstrüksiyon sonrası presentral ve postsentral kesitlerle birlikte alt, orta ve üst orbitomeatal kesitlerde ölçümler yapıldı. Tüm görüntüler görsel ve yarı kantitatif olarak değerlendirildi. İstatistiksel analizlerde Mann-Whitney U-testi kullanıldı.

BULGULAR

Revaskülarizasyon ve replantasyon hastalarında dominant hemisferde presentral ve postsentral hipoperfüzyon vardı. Amputasyon hastalarında, nondominant hemisferde presentral hipoperfüzyon ve postsentral hipoperfüzyon (dört olgunun üçünde) bulunurken; dominant hemisferde ise dört olgunun birinde postsentral hipoperfüzyon vardı. Olgularımızda beyin bölgesel kan akımında belirgin fark posterior parietal korteksteki bulundu (somatik ilişkili alan).

SONUÇ

Ekstremite replantasyon-revaskülarizasyon ameliyatları sonrası beyinde presentral ve postsentral kortekste görülen değişiklikler somatotropik reorganizasyonun iyi bir göstergesi olabilir.

Anahtar Sözcükler: Amputasyon; motor korteks/fizyoloji; kas, iskelet/metabolizma; fantom uzuv/fizyopatoloji; replantasyon; somatosensoriyel korteks/fizyoloji; 99m-Tc-HMPAO.

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Sensory perception and its use in assessing motor plans involves large brain areas including primary somatosensory, visual, motor cortices as well as secondary sensory and motor areas. Basal ganglia and thalamic relays significantly contribute to motor planning, sensory perception and sensorimotor integration. Supplementary motor and premotor cortices have a pivotal role in motor preparation and execution and carry out via corticospinal fibers from primary motor cortex. Cerebellar relays constantly monitor the motor output and motor execution.[1]

The sensorial nuclei of thalamus were related to receive and organize sensory impulses originating from the receptors of trunk, face, retina, cochlea and taste. Thalamus is a vital structure in perceiving some sensory types especially pain. Motor nuclei of thalamus transmit the motor information, which was received in cerebellum and globus pallidus to precentral motor cortex.[2]

Concerning the injury of peripheral nervous system such as nerve injury or amputation, animal and human studies emphasized that somatosensory cortex which responded to the deafferented body parts become responsive to neighboring body parts. There is expansion of the motor representation of the stump area following amputation. Ultimately, reorganization of the sensory and motor systems following peripheral injury occurs in multiple levels including the spinal cord, brainstem, thalamus and cortex.[3]

The perception of an existing of whole or a part of the amputated extremity for a while is assumed as phantom. Eventually the perception of this zone gets smaller and finally becomes in a state that patients can not perceive his amputated limb.[4] Phantom limb pain is an intriguing pain syndrome that may result from damage to peripheral nerve tissue but could also involve central amplifying congeners.[5] The pathophysiology and optimal treatment of post-amputation pain states are unclear. Phantom pain is thought be related to cortical reorganization.[6]

Brain perfusion SPECT provides tri-dimensional information on the perfusion and metabolic status of brain tissue. This information is often complementary to the anatomic detail provided by structural neuroimaging techniques such as CT and MRI. However, brain perfusion SPECT has clinical value by itself, because functional impairment in cerebral diseases often precedes structural changes. The ability of SPECT to detect regional cerebral blood flow variations in different conditions has favored the investigation of sensorial, motor, and cognitive activities.[7]

For the planning of future treatment protocols, it is becoming even more important to identify and characterize the "probable" changes in the regional cerebral blood flow that occur after extremity revascularization, replantation or amputation.

In this study, we aimed to investigate the somatotropic reorganization occurring in the motor and somatosensory cortex by regional cerebral blood flow with 99mTc-HMPAO SPECT analyses after limb revascularization, replantation or amputation, and their possible relationship to phantom pain.

PATIENTS AND METHODS

Twelve patients (11 men, 1 female; mean age 38.9±14.7 years; range 22 to 65 years) and controls (5 men, age range 22-44 y, mean 32.2±7.9 years) were enrolled in this study. Three groups were consisted of revascularization-replantation group [5 patients (Median radial and ulnar nerve neurotmezis type injury in three patients; median and ulnar nerve neurotmezis type injury in one; radial nerve neurotmezis type injury and median-ulnar nerve axonotmezis type injury in one)], amputation group (7 patients) and control group (5 patients). Ethics Committee of our institution approved the study protocol and informed consent was obtained from each patient. None of the patients and controls had any major systemic or cerebrovascular disease, head trauma history or overt cognitive dysfunction. None of them were a drug abuser. Ten patients were right-handed and two were left-handed. Four patients were treated with revascularization, one with replantation and seven with amputation and closing stump.

The time between operation and SPECT was 13.1±8.9 mo. Six of them (50%) were affected on the upper and the other six (50%) were affected on the lower extremity. In five patients (42%) dominant extremity was injured. The control group consisted of physically and mentally healthy volunteers. Two amputated patients were not using any prosthesis and five lower extremity amputated patients were using prosthesis.

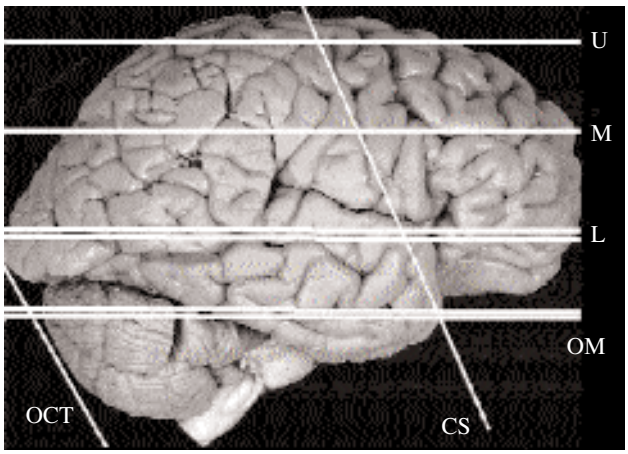

Fig. 1. Occipito-cerebellar tangent (OCT), orbitomeatal (OM) slices, central sulcus slices (CS), upper (U), middle (M) and lower orbitomeatal (L) slice.

(This image was taken with permission from Digital Anatomist Project, Dept. of Biological Structure, University of Washington).

The median phantom pain and stump pain intensity were assessed by visual analogue scaling (VAS) in each patient. The patients could choose a value between `0' (no pain) and `10' (maximal pain) to express the pain strength.

Radiopharmaceutical and SPECT examination: The radiopharmaceutical was prepared strictly according to the manufacturer's instructions. Radiochemical purity exceeded 85% at the time of injection. For brain SPECT perfusion imaging, 740 MBq 99mTc-HMPAO (Frederic Joliot-Curie National Research Institute, Budapest, Hungary) was injected intravenously in tranquil place with eyes closed and ears occluded and dimmed light after about 30 min rest, within 15 min after placement of an intravenous line. Patients were examined in a supine position with a head holder to avoid motion artifact. Imaging was initiated approximately between 20 min and 90 min. after injection. SPECT brain imaging was performed using a two-headed gamma camera (Adac vertex plus V-60) equipped with a high-resolution low energy collimator. The projection data were acquired for 25 s per projection at 60 equal angles of a complete revolution (0-360). Data were obtained from the 140 keV photo peak (20% window) and a 64x64 matrix and zoom factor of 1.85. Reconstruction was performed by filtered back projection using a Gaussian filter (cut off frequency 0.38 cycle/cm, order 20) with attenuation correction by the Chang method. Slices thickness of SPECT samples was 6.3 mm. After reconstruction, orbitomeatal (OM) transaxial, coronal, sagittal and parallel to central gyrus 99mTc-HMPAO SPECT images were obtained.

Two experienced nuclear medicine physicians who were unaware of the patient's diagnosis visually assessed the SPECT slices. Disagreements were resolved by discussion to reach a consensual interpretation.

For semi-quantitative analysis of neuroanatomical region of interest, three OM composite slices and two parallel to central gyrus slices were obtained (Fig. 1). Lower OM transaxial composite slice was obtained by summing up the three well-seen basal ganglia and thalamus slices. Middle and upper OM transaxial composite slices were obtained by summing up the two slices and distance to lower OM transaxial composite slice were 18.9 and 44.1 mm (Fig. 2).

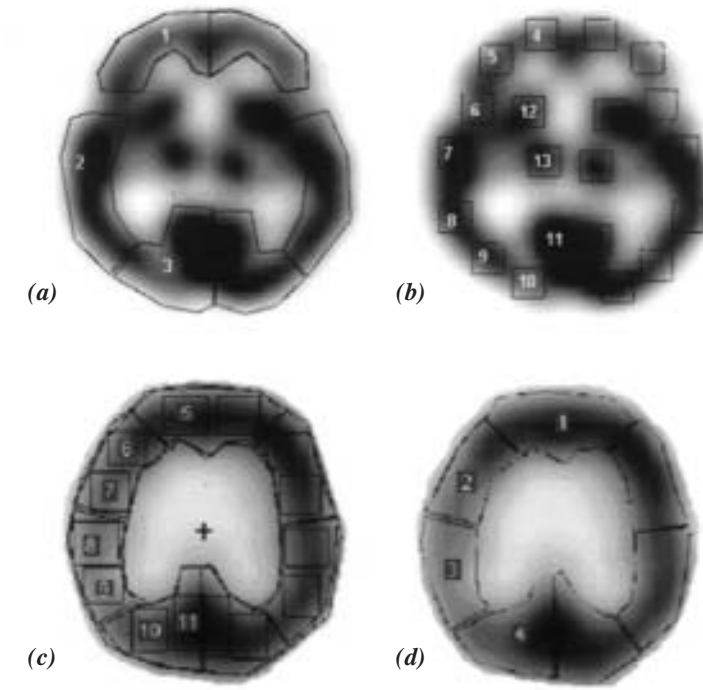

Fig. 2. **(a, b)** Lower OM composite slice: 1 (4,5), frontal; 2 (7,8), temporal; 3 (10,11), occipital; 6, frontotemporal; 9, temporo-occipital. **(c, d)** Middle OM slice: 1 (5) and 2 (6,7) frontal; 3 (8,9) and 6 (10,11) parietal lobe.

Serial parallel images tangent to occipito-cerebellar cortex were performed. Forty percent of the distance from the occipito-cerebellar tangent to the slice involving the frontal tip yielded the central sulcus slice (Fig. 3). For semi-quantitative analysis, precentral and postcentral gyrus slices were considered as two slices front and back of the central gyrus slice.

Region of interest (ROI) of the basal nucleus, thalamus and other cortical areas were drawn manually on the slices. All ROIs were classified by operation site as a contralateral hemisphere's ROIs (ROICH) and ipsilateral hemisphere's ROIs (ROIIH). ROICH mean-count to ROIIL mean-count ratios were obtained and statistically compared. That was the rational for the application of the non-parametric Mann-Whitney U-test to assess the differences among these groups. A p value of <0.05 was considered to be significant.

Visual SPECT analyses: precentral and postcentral areas were evaluated in the parallel to central gyrus images; basal ganglia, thalamus and other cortical areas were evaluated in coronal, sagittal and OM transaxial images.

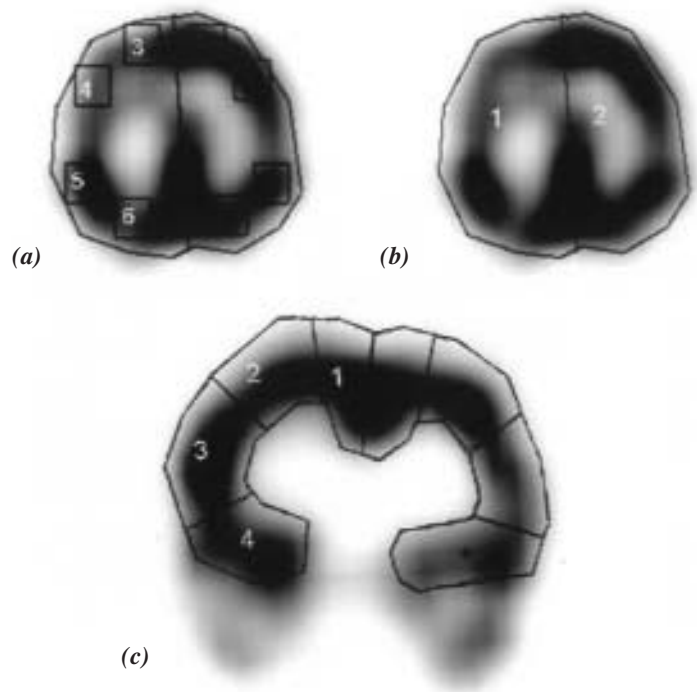

Fig. 3. **(a, b)** Upper OM slice: 1, right hemisphere; 2, left hemisphere; 3,4, frontal lobe; 5,6, parietal lobe. **(c)** Precentral and postcentral slice: 1, upper; 2, superolataral; 3, lateral; 4, inferior.

RESULTS

All patients' characteristics and clinical evaluation, history and visual analysis of SPECT results are illustrated in Table 1.

Phantom pain, according to VAS scale, was found as 4 and 5 in two patient (28.6%) groups of amputation. None of the patients in replantation-revascularization group complained any phantom perception.

In the revascularization-replantation group, precentral hypoperfusion in two patients (40%) and postcentral hypoperfusion in four patients (80%) and right basal ganglia hypoperfusion in one patient (20%) were seen. However, left basal ganglia, thalamus and other cortical areas were not influenced.

In amputation group, precentral hypoperfusion area in one patient (14%); postcentral hypoperfusion in four patients (57%); thalamus hypoperfusion in two patients (28.5%); right basal ganglia hypoperfusion in one patient (14%) and other cortical area hypoperfusion in four patients (57%) was seen. There were phantom pain in two patients (28.5%) and stump pain in one (14%).

The perfusion of left basal ganglia was found as normal in all patients.

In the revascularization-replantation group, precentral hypoperfusion (in 3 cases) and postcentral hypoperfusion (in 4 cases) was seen at dominant hemisphere.

In the amputated patients, precentral hypoperfusion (in 1 case) and postcentral hypoperfusion (in 3 of 4 cases) were seen at non-dominant hemisphere and postcentral hypoperfusion (in 1 of 4 cases) was seen at dominant hemisphere.

It is interesting that the case, which had a SPECT at the fourth week following surgery, had a postcentral hypoperfusion in the dominant hemisphere. Thalamic hypoperfusion were found more evident in amputation group.

Other cortical hypoperfusion were seen in left anterolateral and posterolateral

Table 1. Characteristics of patients and results

Treatment	Lesion side	Extremity location	Age	Gender	Nerve injury	PCA	PoCA	LBN	RBN	Thalamus	OCA	Dominant side	Phantom pain	Other pain
RV	Right	Upper	61	M	M+U+R	N	LS	N	N	N	N	R	None	None
			27	M	M+U	LS	LS	N	+	N	N	R	None	None
			38	M	M+U+R	LS	N	N	N	N	N	R	None	None
	Left	Upper	32	M	R, MU ax	N	CLS	N	N	N	N	R	None	None
A	Right	Lower	48	M		N	N	N	N	+	LPT	R	None	+
			22	M		N	LS	N	N	N	LF postlat	L	None	None
			38	M		LS	N	N	N	N	N	L	+	None
	Left	Upper	65	F		N	LS	N	N	N	N	R	+	None
		Lower	46	M		N	LS	N	+	N	LF antelat	R	None	None
			20	M		N	CLS	N	N	+	N	R	None	None
			25	M		N	N	N	N	N	LT	R	None	None
R	Right	Upper	45	M	M+U+R	N	LS	N	N	N	N	R	None	None

RV: Revascularization; A: Amputation; RP: Replantation; M: Median nerve neurotmezis type injury; U: Ulnar nerve neurotmezis type injury; R: Radial nerve neurotmezis type injury; N: Nerve neurotmezis type injury; MUax: Median-Ulnar nerve axonotmezis type injury; OCA: Other cortical areas; PCA: Precentral area; PoCA: Postcentral area; LBN: Left basal nucleus; RBN: Right basal nucleus; LS: Lesion side; CLS: Contralateral lesion side; LPT: Left parietotemporal area; LF postlat: Left frontal lobe posterolateral area; LF antelat: Left frontal lobe anterolateral area; LT: Left temporal lobe.

areas of frontal lobe, left temporal lobe and left parietotemporal region in four patients (57%) of the amputation group.

When replantation-revascularization and amputation groups were compared to control group, there were statistically significant differences in the anterolateral region of frontal lobe, temporo-occipital region, posteromedial region of occipital lobe and basal ganglia (Fig. 2a-b) on lower OM slice and at posteromedial region of parietal lobe and posterior region of parietal lobe (Fig. 2c-d) on middle OM slice and superior region on precentral slice and lateral region on postcentral slice (Table 2).

Statistically significant differences were found in the frontoparietal cortex and posterior region of frontal lobe (Fig. 2c-d) areas on middle OM slice between replantation-revascularization and amputation groups (Table 2).

DISCUSSION

In this study, we investigated the changes of regional cerebral blood flow in the brain hemispheres of patients who were operated for revascularization, replantation or amputation and their probable relationships with somatotropic reorganization and phantom pain. In a study with monkeys, Qi et al.[8] showed the consequences of long-standing limb amputation and amputation at different ages provided us regardless of the injury age, the deprived cortex does not remain nonfunctional and this cortex takes on new roles and triggers movements in new target muscles. Furthermore, Roricht et al.[9] found the reorganization changes of the motor cortex contralateral to a replanted hand using focal transcranial magnetic stimulation in 10 cases to which successful replantations were applied following complete traumatic amputation. They found that in seven of eight cases with forearm amputation, the area representing biceps muscle, which is stimulated in the cortex after amputation, is larger. Irlbacher et al.[10] revealed the spatial changes of the motor cortical representation of the biceps brachii muscle (stump muscle) in ten patients with long-standing amputations at the level of the forearm using focal transcranial magnetic stimulation and found that the extension of the stump muscle motor maps was increased.

Nevertheless, Merzencih et al.[11] was demonstrated that cortical area in the 3b and 1 regions representing the skin surface enlarged and completely occupied new areas in monkeys with median nerves cut. Moreover, in some animal experiments, it was shown that these plastic changes occur rapidly, within minutes to hours after peripheral deafferentation.[12]

Many studies about neural plasticity had focused on cortical reorganizations.[13-18] On the other hand, the investigations on somatotopic organization of the brainstem and thalamic areas

revealed plastic changes occurred there too.[19-26] In this study, there was an increased incidence of postcentral hypoperfusion on the 3.1 and 2 areas of parietal lob which are primary sensory areas in all groups. These areas receive their fibers from the ventral posterolateral and ventral posteromedial nuclei of thalamus. We thought that the changes of taking place in precentral and postcentral areas

Table 2. All groups Mann-Whitney U-test statistical analysis results

		ROI no	A X±SD	RR X±SD	C X±SD	A-RR	A-C	RR-C
Lower OM composite slices	R-frontal	1	0.92±0.051	0.969±0.049	1.037±0.060	NS	S	NS
	R-L temp	2	1.001±0.129	0.938±0.065	1.129±0.032	NS	NS	S
	R-L occipital	3	1.019±0.143	1.087±0.110	0.908±0.032	NS	NS	S
	Anterior frontal	4	1.049±0.093	1.013±0.095	1.050±0.067	NS	NS	NS
	Anterolateral frontal	5	0.979±0.057	0.935±0.072	1.100±0.111	NS	S	S
	Frontotemporal	6	1.027±0.105	0.983±0.067	1.070±0.073	NS	NS	NS
	Anterior temporal	7	0.944±0.090	0.980±0.091	1.087±0.050	NS	S	NS
	Posterior temporal	8	0.976±0.088	0.973±0.140	1.125±0.073	NS	S	NS
	Temporo-occipital	9	0.947±0.074	0.969±0.052	1.094±0.089	NS	S	S
	Lateral occipital	10	1.003±0.134	1.004±0.089	1.084±0.025	NS	NS	NS
	Medial occipital	11	0.908±0.084	0.953±0.008	1.057±0.010	NS	S	S
	Basal ganglia	12	1.174±0.147	1.060±0.064	0.889±0.032	NS	S	S
	Thalamus/total	13	0.952±0.147	1.017±0.069	1.021±0.105	NS	NS	NS
Middle OM composite slices	Anterior frontal/total	1	1.049±0.124	0.983±0.081	1.128±0.058	NS	NS	S
	Posterior frontal	2	0.958±0.075	1.058±0.055	1.038±0.060	S	NS	NS
	Anterior parietal	3	1.017±0.081	0.938±0.057	1.037±0.033	NS	NS	S
	Posterior parietal	4	1.016±0.035	1.031±0.076	1.102±0.028	NS	S	NS
	Anterior frontal	5	1.021±0.083	0.990±0.101	1.017±0.032	NS	NS	NS
	Posterior frontal (front)	6	1.004±0.029	1.053±0.054	1.015±0.062	S	NS	NS
	Posterior frontal (back)	7	1.025±0.071	0.998±0.117	1.027±0.079	NS	NS	NS
	Anterior parietal (front)	8	1.011±0.030	1.039±0.064	1.043±0.022	NS	NS	NS
	Anterior parietal (back)	9	0.913±0.102	0.922±0.080	1.037±0.048	NS	S	NS
	Posterior parietal (lateral)	10	1.089±0.096	1.039±0.064	1.174±0.057	NS	NS	S
	Posterior parietal (medial)	11	0.894±0.086	0.949±0.049	1.108±0.039	NS	S	S
	R/L	1 / 2	1.049±0.042	1.043±0.060	1.053±0.012	NS	NS	NS
Upper OM slices	Anterior frontal	3	0.978±0.022	0.963±0.055	0.971±0.048	NS	NS	NS
	Anterolateral frontal	4	0.644±0.361	0.911±0.324	1.026±0.052	NS	NS	NS
	Posterolateral parietal	5	0.997±0.070	0.951±0.048	1.074±0.070	NS	NS	S
	Posterior parietal	6	0.981±0.087	1.040±0.063	1.028±0.059	NS	NS	NS
Precentral gyrus	Superior	1	0.985±0.096	0.958±0.051	1.039±0.035	NS	NS	S
	Superolateral	2	1.002±0.077	1.032±0.074	1.018±0.016	NS	NS	NS
	Lateral	3	1.053±0.083	0.987±0.094	1.094±0.112	NS	NS	NS
	Inferior	4	0.981±0.050	1.020±0.093	1.029±0.052	NS	NS	NS
Postcentral gyrus	Superior	1	1.052±0.127	1.030±0.183	1.047±0.040	NS	NS	NS
	Superolateral	2	1.013±0.035	1.036±0.068	1.042±0.039	NS	NS	NS
	Lateral	3	1.000±0.044	0.952±0.049	1.081±0.065	NS	S	S
	Inferior	4	0.997±0.063	1.034±0.071	1.039±0.038	NS	NS	NS

A: Amputation; RR: Revascularization + Replantation; C: Control; N: Significant; NS: Non-significant.

after replantation of extremities can be attributed to the good indicator of somatotopic reorganization.

Phantom pain was thought to be associated with cortical activation involving the frontal, temporal, or parietal cortex, and it may imply the possibility of the existence of an ascending polysynaptic pathway that conveys the uncomfortable phantom limb sensation to the cerebral cortex. These findings may also indicate that reorganization of the cortical blood flow occurs in amputees. However, it is still difficult to conclude that the changes in regional cerebral blood flow were attributable directly to pain.[13,27] Ramachandran[28] concluded about the less incidence of phantom in children as perhaps there has not yet been enough time for the body image to consolidate. Works on phantom phenomenon, with new connections emerging in the adult brain, revealed the way how the information different sensory modalities interacts and how the brain continuously updates its model of reality in response to novel sensory inputs.[7] Almost everyone (30-98%) who has an amputated limb will immediately experience a phantom, an impression that the extremity is not only still present but in some cases painful too.[28-37] An increased regional cerebral blood flow in right parietal was demonstrated by Hung et al.[13] in a patient with left above-elbow amputation. However Liaw et al.[27] showed in the changes of regional cerebral blood flow using 99mTc-HMPAO SPECT in three patients with amputation and these changes were disappeared after severe phantom limb discomfort subsided. It is interesting that in our study we did not find any increased regional cerebral blood flow in none of the cases. There was precentral or postcentral hypoperfusion in two patients with phantom pain. These findings can be interpreted in favor of relationship between the phantom limb pain and brain's cortical reorganization. As a difference from the literature in our study, there was not a statistically significant difference in regional cerebral blood flow between the groups with and without phantom limb pain. There was precentral or postcentral hypoperfusion in two patients with phantom pain. These findings can be interpreted in favor of relationship between the phantom limb pain and brain cortical reorganization. In our amputation group, phantom pain was present in 2 of 7 cases (28.6%) and this result was found slightly low when compared to the literature.

Thus, there is not a standardized method at drawing of ROIs during semi quantitative evaluations shape of taken slices in brain perfusion scintigraphy. In our study, a more acceptable method with a higher rate of objectivity and more discriminative qualities was aimed. On ROI drawing, although the ROIs, which we applied to OM transaxial slices, were similar to many authors' method or synthesis, our method of precentral and postcentral slice formation was unique. Especially on visual evaluation, correlation between areas with lesion and area of operation yielded the thought that these slices could be used.

The most significant differences were found at parietooccipital cortex (somatic associated area) in both revascularization-replantation and amputation groups.

As a result, even if revascularization-replantation was applied to extremity there may be changes in cortical levels and postcentral hypoperfusion can be seen in motor cortex. Changes taking place in precentral and postcentral areas despite the replantation of the organ may be a good indicator of somatotopic reorganization.

Acknowledgments

The authors thank Assoc. Prof. Saim Yologlu for statistical assistance.

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