Features of the Sensorimotor Cortex Altered after Tooth Loss and Subsequent Implant Placement in the Maxilla of Rats

Sheng Hao XUE[1#], Jian LI[1#], Jing Wen YANG[1], Zhong Ning LIU[1], Ting JIANG[1]

Objective: *To investigate the synergistic changes of the astrocytes and neurons in the sensorimotor cortex during the process of implant osseointegration after insertion.*
Methods: *A total of 75 rats were allocated into three groups (n = 25): non-operated, extraction and implant. The rats in the latter two groups underwent extraction surgery of three maxillary right molars. One month later, the implant group received one titanium implant in the healed extraction socket. The rats were sacrificed on days 1, 3, 7, 14 and 28 after implantation. The brain sections, including sensory centre S1 and motor centre M1, were selected for further immunofluorescence for measurement of the synergistic morphological and quantitative changes of astrocytes and neurons.*
Results: *In layer IV of S1, the number of astrocytes in the implant group showed a descending trend with time; on days 1, 3, 7 and 14, the number of astrocytes in both the extraction group and the implant group was significantly higher than that in the non-operated group, and there was no difference between the extraction group and the implant group; however, on day 28, the number of astrocytes in the implant group was significantly lower than that in the extraction group. In layer V of M1, on days 7, 14 and 28, the number of astrocytes in the implant group was significantly lower than that in the extraction group; on days 14 and 28, the number of astrocytes in the extraction group was significantly higher than that in the non-operated group. In layer IV of S1 or layer V of M1, the number of neurons showed no significant changes between the three groups.*
Conclusion: *The astrocytes in the face sensorimotor cortex were activated as a reaction to oral environment changes. This kind of neuroplasticity can be reversed by oral rehabilitation with dental implants. The motor cortex may be intimately related to osseointegration and osseoperception.*
Key words: *motor cortex, neuroplasticity, oral implant, osseointegration, sensory cortex*
Chin J Dent Res 2022;25(3):169–177; doi: 10.3290/j.cjdr.b3317969

The sensory signal pathway of natural teeth starts from the Ruffini body in the periodontal ligament. After tooth loss, the transmission of mechanical sensory signals from the periodontal ligament disappears, which affects the deep sensory signals of muscle spindle and temporomandibular joint proprioceptors and interrupts the sensory feedback pathway[1]. Thus, the complete reconstruction of the same shape, structure, function and sensory perception as normal natural teeth is considered the ultimate goal of dental prostheses[2]. Dental implants have innovated traditional restoration methods, offering satisfactory rehabilitation effects approximate to the appearance of natural teeth[3,4]. In clinical application, however, the tactile sensory ability of implant-supported dentures has been found to be far less than that of natural teeth, only 1/50 to 1/10 of the latter[5]. Consequently, there have been clinical cases of unsuc-

1 Department of Prosthodontics, Peking University School and Hospital of Stomatology, National Clinical Research Centre for Oral Diseases, National Engineering Laboratory for Digital and Material Technology of Stomatology, Beijing Key Laboratory of Digital Stomatology, Beijing, China.
# These two authors contributed equally to this work.

Corresponding authors: Dr Jian LI and Dr Ting JIANG, Department of Prosthodontics, Peking University School and Hospital of Stomatology, 22# Zhongguancun South Avenue, HaiDian District, Beijing 100081, P.R. China. Tel: 86-10-8219539. Email: pkujianli@126.com; jt_ketizu@163.com

This work was supported by the National Natural Science Foundation of China (nos. 81100771, 81771045 and 82170928).

cessful implants due to excessive bite force, with failure manifesting itself mainly as mechanical complications and early excessive vertical bone resorption. Thus, the question of how to improve the tactile sensory ability of dental implants has become an urgent issue to be solved in clinical application.

In the 1990s, Brånemark proposed the concept of osseoperception, which was amended gradually before a consensus was reached in academic circles in 2005[6]: the sensation arising from mechanical stimulation of a bone-anchored prosthesis, transduced by mechanoreceptors that may include those located in muscle, joint, mucosal, cutaneous and periosteal tissues, and a change in central neural processing in maintaining sensorimotor function. In other words, the osseoperception of dental implants encompasses not only the information from the peripheral nervous system, but also the perception of the central nervous system, namely the cerebral cortex[7]. However, it has not been fully clarified whether this tactile sensation perceived by implants comes from the establishment of a specific feedback regulatory pathway from the peripheral to the central nervous system. The clarification of this pathway will be of great significance to the strategies and methods to improve osseoperception; however, so far there has been little knowledge about the changes in the microstructure of the sensory conduction pathway at different stages of the implant osseointegration process due to a lack of systematic observation.

Some studies have reported that changes in the oral environment would cause structural and functional neuroplasticity in the central cortex, including the reduction of the number of neurons[8,9], the change of synaptic function[9], the deformation of astrocytes[10] and the reduction in the volume of the brain area controlling the oral and maxillofacial region[11]. Many studies have also shown that when degenerative changes occur in the oral cavity (such as chronic pain, dysfunction, noxious stimulus and cancer)[10-12], they cause proliferation or activation of astrocytes in the corresponding sensory cortex. It has been reported that the number of astrocytes in the hippocampal region of rats increased significantly after tooth loss[10].

At the same time, some studies have suggested that implants could partially reverse the neuroplastic changes of the central nervous system caused by tooth loss. A study using functional magnetic resonance imaging (fMRI) showed that electrical stimulation of implants could activate the cortical somatosensory area corresponding to natural teeth and a wide range of bilateral external areas[13]. Some researchers compared the brain fMRI among three groups of patients who underwent rehabilitation of an implant-supported fixed denture, implant-supported overdenture or mucosal-supported denture, respectively, and found that the blood oxygen–related signals in the primary sensory centre (S1)/motor centre (M1) of patients with implant-supported fixed dentures were significantly higher than those of the other two groups[14]. Another study found that after extraction of the right maxillary molars in rats, the activated area of M1 in the cerebral motor cortex decreased when the anterior abdomen of digastric muscle and genioglossus muscle contracted[15]. After restoration with implants, the changes in M1 were reversed and caused the activation of the wider cortical area, which suggested neuroplastic changes in M1[15]; however, these studies did not investigate the cellular or molecular changes in the cortex or observe the synergic linkage between the osseointegration process and cortical neurons or astrocytes, which would offer the possibility of explaining how osseointegrated implants develop osseoperception.

The oromaxillofacial sensory/motor centre (face-S1/face-M1, hereinafter referred to as S1/M1) plays an important role in coordinating oromaxillofacial sensory/motor function[16]. Many studies have shown that in subprimates and primates, S1 mainly undertakes oral and maxillofacial sensory function and partly participates in the control of oral and maxillofacial movement. M1 mainly outputs motor information to brainstem motor neurons and receives many sensory inputs to assist its role in motor behaviour[17]. Therefore, this study aimed to establish a time-axis animal model to explore the changes in the morphology and number of neurons and astrocytes in S1/M1 region during osseointegration to understand the difference in neuroplastic changes between S1 and M1 and the changes' temporal and spatial linkage with the osseointegration process. This research also aimed to provide indispensable basic data to build up some neurogenic strategies to improve osseointegration and osseoperception of dental implants.

Materials and methods

Experimental animals and groups

The animal experiments were approved by the experimental animal welfare ethics committee of Peking University (license no. LA2013-76). Seventy-five 6-week-old Sprague Dawley male rats weighing 220 ± 15 g were selected and provided by Beijing SPEF Experimental Animal Technology (experimental animal production license: SCXK [Beijing] 2019-001]). All specific path-

ogen free (SPF) rats were fed in the experimental animal room of Peking University Hospital and School of Stomatology. The feeding conditions were temperature 22 ± 1°C, humidity 50% ± 5%, daytime/night 12 hours alternately, and they consumed a mashed chow diet and water ad libitum from the adaptation period.

After the 7-day adaptation period, the rats were randomly divided into three groups: non-operated, extraction and implant (25 rats per group). The rats in the extraction and implant groups underwent extraction of the three right maxillary molars under anaesthesia, and the masticatory function of the left maxillary and mandibular teeth was retained. One month after tooth extraction, the rats in the implant group received one titanium implant in the healed extraction socket of the maxillary right first molar. Since osseointegration of implants in the maxilla of rodents has been confirmed to complete in around 28 days after implantation[18], the rats were sacrificed on days 1, 3, 7, 14 and 28 after implantation (taking the day of implantation as baseline, five rats in each subgroup were sacrificed on day 1, five on day 3, five on day 7, five on day 14 and five on day 28) (Fig 1).

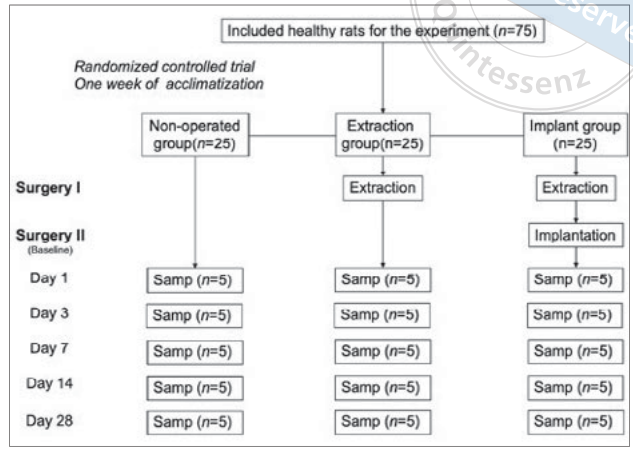

Fig 1 Groups of experimental animals. The implant group (n = 25) underwent both extraction and implant insertion surgery while the extraction group only underwent the former. Baseline was set as the day of implant placement, and the five time points for animal euthanasia and sampling were on days 1, 3, 7, 14 and 28 after implant surgery. Samp, sample.

Surgical protocol

The molar extraction and implant surgery were carried out under aseptic conditions. The gingival tissue around three maxillary right molars was detached with a probe and the teeth were luxated using Ventura forceps (Belevor, Shenzhen, China). One month later, prior to implant surgery, the extraction sites were evaluated through gross examination for adequate soft tissue healing. Then, in the rats in the implant group, the healed edentulous alveolar crest was surgically exposed with a scalpel, then a bone cavity was prepared with a low-speed drill into the healed extraction site of the maxillary right first molar, and a titanium miniscrew implant (MCTBIO, Gyeonggi-do, South Korea; 1.2 mm diameter, 3.0 mm length) was inserted in the cavity (Fig 2). Primary implant stability (a prerequisite for successful bone healing around dental implants) was confirmed manually. The implant head remained non-submerged and was occluded with the mandibular first molar. Bilateral occlusion was checked to verify the existence of occlusal contacts between the implant and the opposing tooth, as well as between the opposing teeth on the contralateral side. Since an increased occlusal load would interfere with bone healing around the implants, maxillomandibular occlusal contact was checked clinically every other day after insertion to ensure no excessive occlusal loading occurred on the implants.

The previous literature pointed out that the mesial root of the maxillary molars in rats was the thickest and was a suitable site for implant placement[19]. The recommended diameter of the drill hole was 1.5 mm and intraosseous length was 2.0 mm[19]. The bone–implant contact rate reached 55.1% ± 8.9% 28 days after implantation, and there was no significant difference in the osseointegration rate between 28 and 56 days[19].

Execution of animals and tissue handling

The rats were sacrificed by intraperitoneal injection of an excess of 1% sodium pentobarbital solution and then placed on an ice table. The head skin was quickly peeled off and the skull was separated. The brain was taken out intact and put in 4% paraformaldehyde to be fixed for 24 hours, then transferred to 30% sucrose solution for at least 2 days. After the specimens sank to the bottom, they were transferred to 0.01 mol/L phosphate-buffered saline (PBS) solution and placed on the prepared freezing table. After the tissue was frozen, serial frozen slices with a thickness of 40 μm were made using Leica CM1950 Cryostats (Leica, Wetzlar, Germany).

Immunofluorescence

Referring to the rat brain stereotactic map[20], the coronal slices at a distance of 2.0 mm from the anterior bregma were selected (Fig 3); the first and second of every three consecutive slices were used for neurons and astrocytes, and the third slice was discarded. Five slices

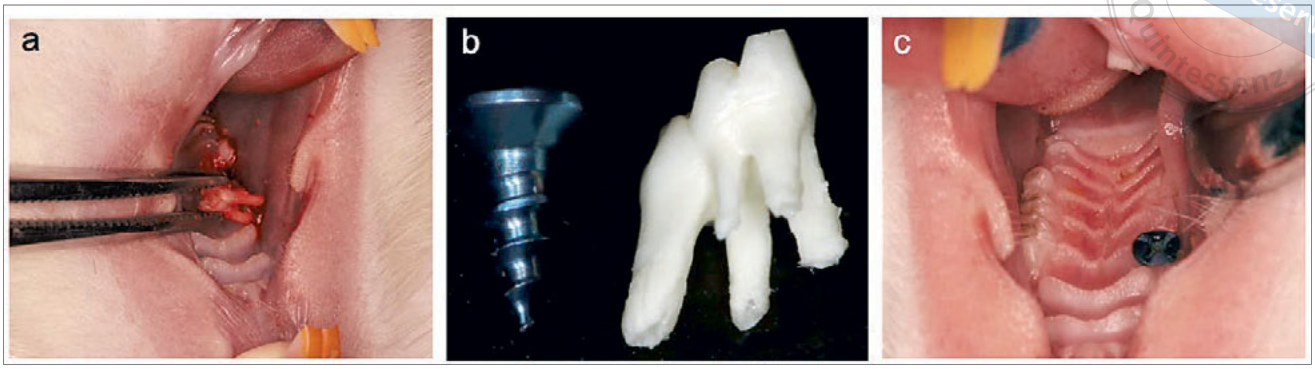

Fig 2 Implantation model in rats' maxilla. **(a and b)** Three maxillary right molars were luxated using a modified dental instrument. **(c)** A titanium miniscrew implant (1.2 mm diameter, 3.0 mm length) was inserted to restore the maxillary right first molar after 1 month of healing from extraction.

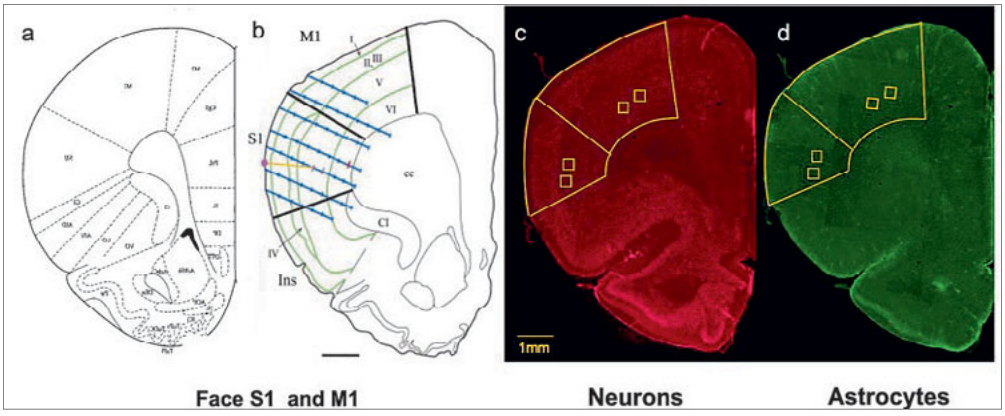

Fig 3 Schematic diagrams of S1/M1 in coronal sections. **(a and b)** S1/M1 in coronal sections of rats' brain. **(c)** Staining of neurons in layer IV of S1 and layer V of M1. **(d)** Staining of astrocytes in layer IV of S1 and layer V of M1.

were obtained for neurons and astrocytes for free-floating immunofluorescence staining. NeuN (1:1000; Proteintech, Rosemont, IL, USA) was used as the marker for neurons and GFAP (1:1000; Proteintech) was the marker for astrocytes. Nonspecific antigens were blocked using goat serum. The sections were placed in the primary antibody and incubated overnight in a refrigerator at 4°C. The fluorescent secondary antibody corresponding to the source species of the primary antibody was diluted with PBS according to the instructions and incubated at room temperature for 3 hours, then the mounting was completed using mounting medium with 4',6-diamidino-2-phenylindole (DAPI) to stain the nucleus. The target proteins were observed with green fluorescence (fluorescein isothiocyanate, FITC) or red fluorescence (tetramethylrhodamine, TRITC) and the nucleus with blue fluorescence (DAPI) (Fig 4).

The neurons and astrocytes could be observed in the same slice at the same time, then two areas of interest (AOI) under the 200-fold lens were selected: one was layer IV of S1 (orofacial sensory centre) and the other was layer V of M1 (orofacial motor centre). After that, two 425 μm × 425 μm square areas for measurement were randomly selected in the AOI. The morphology of neurons and astrocytes was observed, and the number was calculated using Image-Pro Plus software (version 6.0, Media Cybernetics, Rockville, MD, USA).

Tissue staining around the implant

In the implant group, a specimen block containing 3 to 5 mm thick bone around the implant was separated from the maxilla and immersed in 10% formalin at 4°C for 24 hours. It was then immersed in 20% ethylenediaminetetraacetic acid (EDTA) and decalcified at 37°C for 2 months until the implant could be removed easily from the specimen with surgical forceps. Continuous coronal sections with a thickness of 4 μm along the central axis of the implant were prepared after gradient dehydration and paraffin embedding. Masson staining was used to observe the bone remodelling around the implant (Fig 5). The BioQuant Osteo Bone Biology Research System (Biosan, Brussels, Belgium) was used to measure the outline of the screw surface on one side of the

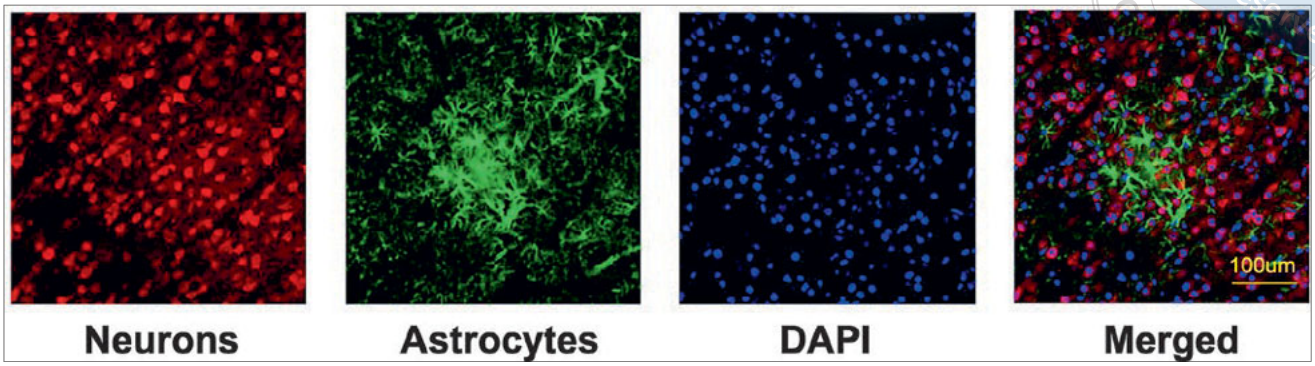

Fig 4 Images of neurons, astrocytes, DAPI and their merger observed using a laser confocal microscope. Neurons were stained as irregular circles, separated from each other (red fluorescence); the astrocytes were star-shaped, with many long and branched protrusions from the cell bodies; DAPI staining showed the nucleus. When neuron staining marked by NeuN and astrocyte staining marked by GFAP were merged, it showed the protrusions of astrocytes were stretched and filled among the cell bodies of neurons and their protrusions.

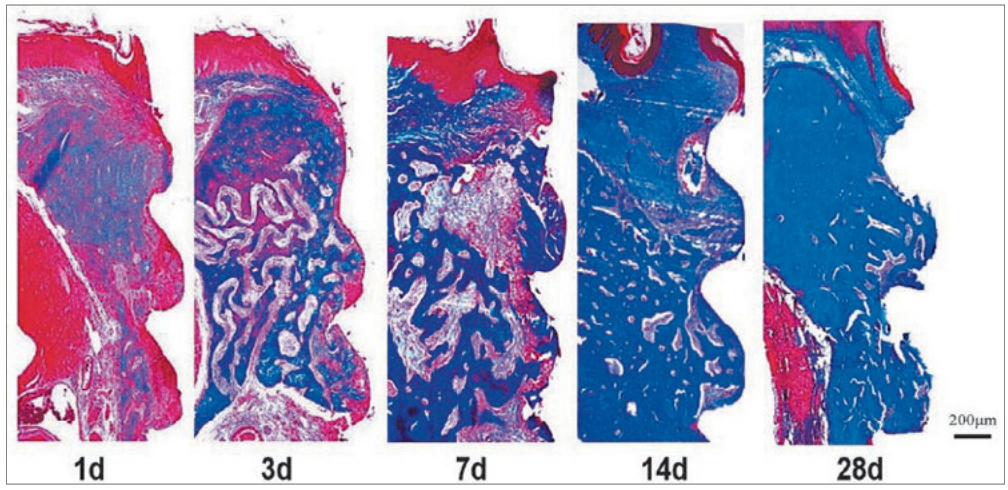

Fig 5 Implant osseointegration on days 1, 3, 7, 14 and 28 by Masson staining.

implant and the length of the contacted bone, then the ratio of the aforementioned two values was calculated and expressed as the percentage of the bone–implant outline contact (BIOC) rate in this experiment.

Statistical analyses

All data were expressed as mean ± standard deviation. The differences in the numbers of neurons and astrocytes were assessed among three groups at the same time point and among different time points within each group. The differences in BIOC were also assessed among different time points in the implant group. First, the homogeneity of variance was tested using a Bartlett test. If the variance was homogeneous, an analysis of variance (ANOVA) was performed using SPSS 27.0 (IBM, Armonk, NY, USA); otherwise, a Kruskal-Wallis (rank-sum) test was employed. The differences in the variables between two time points or two groups were tested using the Student-Neuman-Keuls method. The level of significance was set at $P < 0.05$.

Results

Under red fluorescence, the neurons were quasicircular, separated from each other and had a certain orientation, and protrusions could be seen in the cell bodies. Under green fluorescence, the astrocytes were stellate, emitting long and branched processes from the bodies. In the merged images, the processes of astrocytes extended and filled between the bodies and processes of neurons, separating the latter.

In layer IV of S1, there was no significant difference in the morphology or number of neurons among the implant group, extraction group and non-operated group at five different time points (days 1, 3, 7, 14 and 28). The manifestation of astrocytes was significantly different. Firstly, at the five time points, the morphology

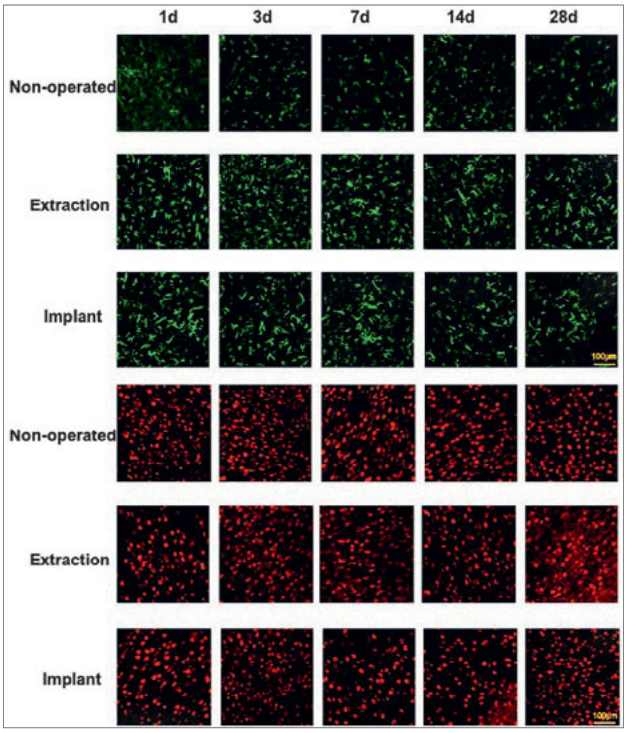

Fig 6 Staining of astrocytes (green fluorescence) and neurons (red fluorescence) in layer IV of S1 on days 1, 3, 7, 14 and 28.

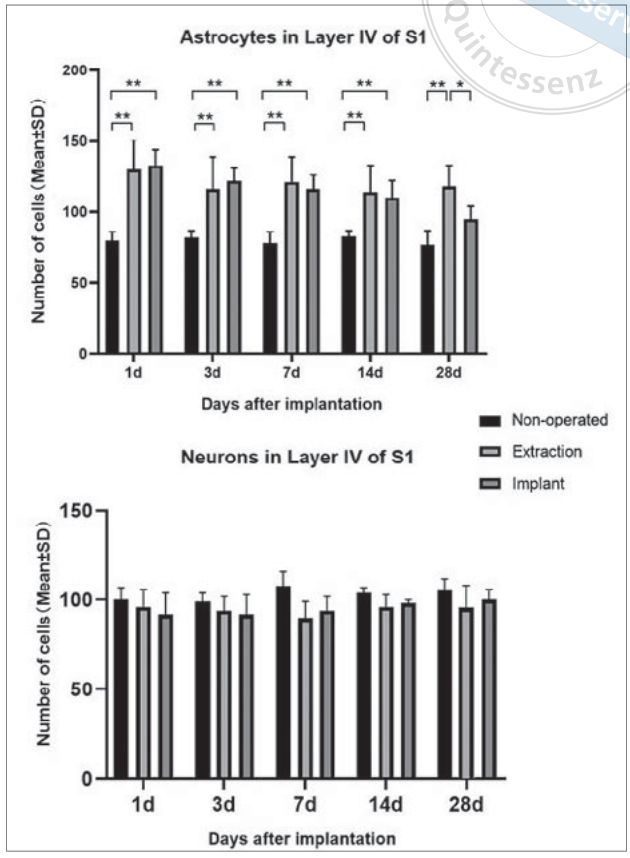

Fig 7 Comparison of the number of astrocytes and neurons in layer IV of S1 among groups. **(a)** On days 1, 3, 7 and 14, the number of astrocytes in both the extraction group and implant group was significantly higher than that in the non-operated group; however, on day 28, the number of astrocytes in the implant group was significantly lower than that in the extraction group. **(b)** There was no significant change in the number of neurons among the three groups. $^{*}P < 0.01$, $^{**}P < 0.05$.

of astrocytes in the extraction group was different from that in the non-operated group, with increased volume, antennae and swelling morphology, and the number was significantly higher too ($P < 0.01$). As for the implant group, the number of astrocytes was also significantly higher than that of the non-operated group on days 1, 3, 7 and 14 ($P < 0.01$), but significantly lower than that of the extraction group on day 28 ($P = 0.03$). No significant difference was found between the implant group and the non-operated group on day 28 ($P > 0.05$); the neurons and astrocytes showed a similar morphology and swelling was significantly reduced compared with the extraction group (Figs 6 and 7).

There was no significant difference in the morphology and number of neurons in layer V of M1 among the three groups at the five time points. The number of astrocytes in the extraction group was significantly higher than that in the non-operated group on days 14 and 28, whereas in the implant group it was significantly lower than that of the extraction group on days 7, 14 and 28. Unlike layer IV of S1, the number of astrocytes in the implant group was even slightly lower than that of the non-operated group on day 28 (Figs 8 and 9).

In layer IV of S1 and layer V of M1, the number of astrocytes in the implant group showed a downward trend with time. In layer IV of S1, the number of astrocytes on day 28 was significantly lower than that on days 1, 3 and 7 (Figs 6 and 7); in layer V of M1, the number of astrocytes on day 28 was significantly lower than that on days 1 and 3 (Figs 8 and 9). However, the BIOC rate showed an obvious upward trend with time, from 36.52% ± 11.17% on day 1 to 85.11% ± 4.02% on day 28. On day 1, the original bone trabeculae were found to have been destroyed due to implant surgery. On days 3 and 7, the early stages of bone remodelling, the inflammatory fibrous tissue began to transform into cartilage callus until the hard callus formed on day 14, and finally the bone remodelling matured further on day 28 (Fig 5). The number of astrocytes in S1 and M1 changed inversely with the BIOC rate (Fig 10).

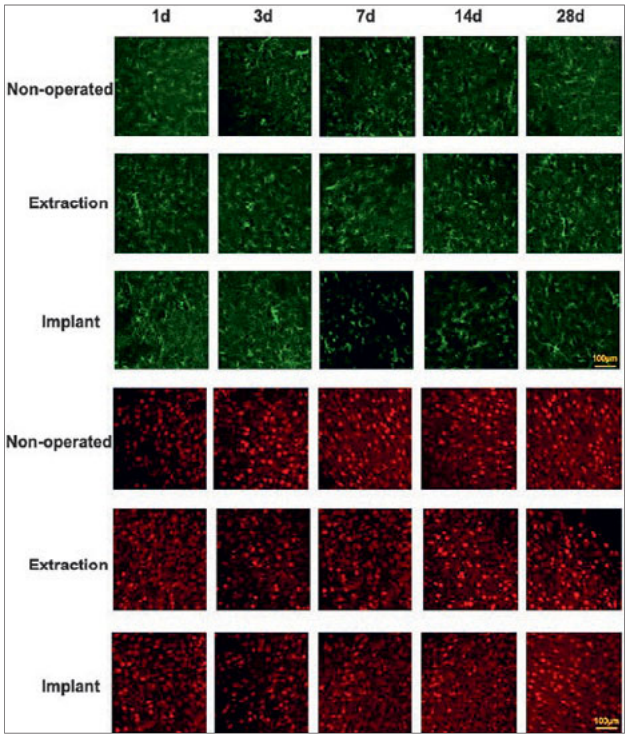

Fig 8 Staining of astrocytes (green fluorescence) and neurons (red fluorescence) in layer V of M1 on days 1, 3, 7, 14 and 28.

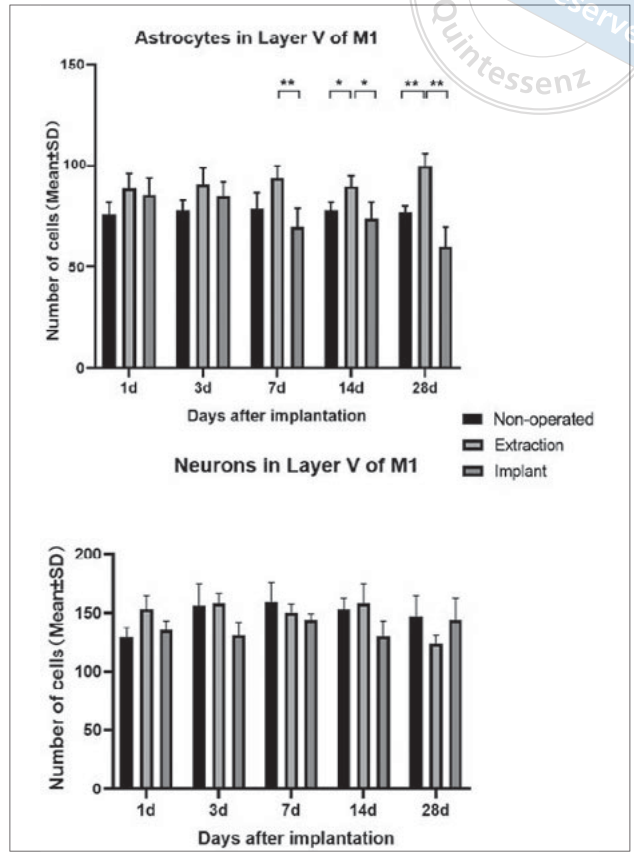

Fig 9 Comparison of the number of astrocytes and neurons in layer V of M1. **(a)** On days 7, 14 and 28, the number of astrocytes in the implant group was significantly lower than that in the extraction group, and on days 14 and 28, the number of astrocytes in the extraction group was significantly higher than in the non-operated group. **(b)** There was a lack of an obvious change in the number of neurons among the three groups. $^{*}P < 0.01$, $^{**}P < 0.05$.

Discussion

In this study, a randomised controlled animal model was established. The synergistic changes of neurons and astrocytes in the sensory motor cortex were observed to explore the cortical neuroplasticity in the process of implant osseointegration. The selected observation areas were S1 and M1, which were responsible for the regulation of oral and maxillofacial sensation and movement. The study drilled further down into specific layers: layer IV of S1, which was the main cortex receiving sensory input from the thalamic somatosensory nucleus and some spherical endothelial layers, and layer V of M1, which was the main output layer, relaying signals to affect the brainstem motor neurons[21]. By analysing the phenomenon of cortical neuroplasticity, this experiment hoped to explore the origin of osseoperception and lay a foundation to promote the tactile sensory ability of implants in future clinical practice. In addition, the basic data obtained in this experiment seeks to have guiding significance for follow-up experiments.

First, the results of this study suggested that tooth loss caused the neuroplastic changes in S1 and M1, which were manifested in the morphological and quantitative changes of astrocytes. In this study, compared with the non-operated group, astrocytes in the extraction group showed "activation"[22] on days 1, 3, 7, 14 and 28 in layer IV of S1 and on days 14 and 28 in layer V of M1. Studies have shown that when degenerative stimuli (such as chronic pain, dysfunction and cancer) were transmitted into the central nervous system, they caused the proliferation and activation of astrocytes in the corresponding sensory cortex, which was regarded as the defensive change of astrocytes[10-12,23,24]. The astrocytes in the hippocampus increased significantly following loss of molar teeth in SAMP8 mice[10]. In the present study, the functional degeneration caused by tooth loss was speculated to be the defensive change of astrocytes to the change of oral environment.

Second, the restoration of masticatory function by osseointegrated implants can partially reverse the plastic changes of S1 and M1 related to tooth loss. On day 28, there was no significant difference in the number

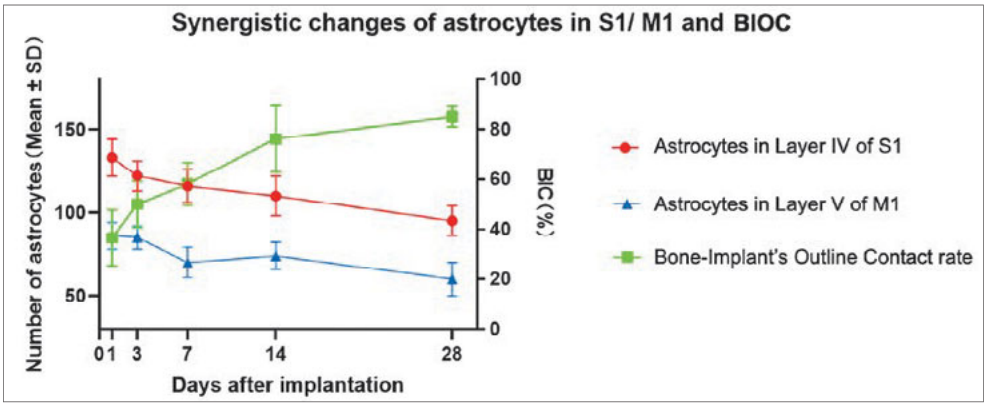

Fig 10 Synergistic changes of the number of astrocytes in S1/ M1 and BIOC rate. The number of astrocytes in layer V of M1 and layer IV of S1 showed a decreasing trend from day 1 to day 28 while the BIOC rate increased from 36.52% ± 11.17% to 85.11% ± 4.02%.

of astrocytes between the implant group and the non-operated group in layer IV of S1, and even in layer V of M1, the number of astrocytes in the implant group was less than that in the non-operated group.

Compared with the extraction group, the number of astrocytes in S1 and M1 in the implant group decreased, and the morphology of cell swelling was reversed. The results also showed that the osseointegration was completed on day 28 after implantation, and the implant in the first maxillary molar area restored the masticatory function to a certain extent.

In addition, there was a slight difference between S1 and M1. Although the number of astrocytes in S1 in the implant group was significantly less than that in the extraction group on day 28 ($P = 0.03$), the P value was not as significant as that of M1 ($P < 0.01$). The number of astrocytes in M1 was even slightly less than that of the non-operated group, which showed more obvious changes in the motor cortex after implantation. It is speculated that M1 has a closer relationship with the establishment of implant osseoperception, but the internal mechanism still needs to be explored further.

Finally, the results suggest that attention should be paid to the metabolic coupling between neurons and astrocytes in the cerebral cortex when exploring osseoperception, which might be related to the establishment and development of the tactile sensibility of dental implants. In this experiment, there was no significant change in the morphology and number of neurons of S1 and M1 among the three groups. It was speculated that more microscopic changes might have taken place in neurons, such as changes in synaptic structure or number, cell branches or cell size, and this needs to be confirmed by further research. Previous studies mentioned that the signal changes in the S1/M1 area of patients' brain after implant restoration could be observed by fMRI[13,14], which means neurons must play an indispensable role in the changes in haemodynamics in this area. This study has proved that neuroplasticity of neurons did not occur in the quantitative level, so it is particularly important to observe the microstructure of neurons further. Astrocytes play a key role in the maintenance of neuronal function. From the developmental regulation of synapse formation to the maintenance of synapses in disease, astrocytes are key participants in the homeostasis of the central nervous system, they can act as a doorkeeper for water, ions (such as potassium and calcium), glutamate and the second messenger through their channels and receptors on the surface. At the same time, they can provide energy for neurons, shuttle lactic acid and amino acids to neurons through and maintain the energy metabolism of neurons[25]. The close supporting relationship between astrocytes and neurons may also partly explain the significant changes of astrocytes and no significant change of neurons in the present study because astrocytes are more sensitive to environmental changes. It is therefore necessary to further clarify the molecular mechanism of energy metabolic coupling between neurons and astrocytes in the establishment of implant osseoperception.

Conclusion

In conclusion, after tooth loss, the astrocytes in the face sensorimotor cortex were activated as a reaction to changes in the oral environment. This kind of neuroplasticity can be reversed to some extent by oral rehabilitation with a dental implant. With regard to the differences in the response altered by implant placement between the sensory cortex and motor cortex, the motor cortex might be more intimately related to osseointegration and osseoperception of dental implants. Further experiments

are required to elucidate the inner mechanism of energy metabolic coupling between neurons and astrocytes in the establishment of implant osseoperception.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Drs Sheng Hao XUE and Jian LI were involved in the conception, design, writing and editing of the manuscript; Drs Jing Wen YANG and Zhong Ning LIU contributed to the data collection and analyses; Dr Ting JIANG was responsible for the conception, design, communication with editors and editing of the manuscript. All authors agreed with the final version.

(Received Sep 30, 2021; accepted Nov 11, 2021)

References

1. Sessle BJ, Yao D, Nishiura H, et al. Properties and plasticity of the primate somatosensory and motor cortex related to orofacial sensorimotor function. Clin Exp Pharmacol Physiol 2005;32:109–114.
2. Negahdari R, Ghavimi M, Ghanizadeh M, Bohlouli S. Active tactile sensibility of three-unit implant-supported FPDs versus natural dentition. J Clin Exp Dent 2019;11:e636–e641.
3. Huang Y, Jacobs R, Van Dessel J, Bornstein MM, Lambrichts I, Politis C. A systematic review on the innervation of peri-implant tissues with special emphasis on the influence of implant placement and loading protocols. Clin Oral Implants Res 2015;26:737–746.
4. Huang Y, Bornstein MM, Lambrichts I, Yu HY, Politis C, Jacobs R. Platelet-rich plasma for regeneration of neural feedback pathways around dental implants: A concise review and outlook on future possibilities. Int J Oral Sci 2017;9:1–9.
5. Enkling N, Nicolay C, Utz KH, Jöhren P, Wahl G, Mericske-Stern R. Tactile sensibility of single-tooth implants and natural teeth. Clin Oral Implants Res 2007;18:231–236.
6. Klineberg I, Calford MB, Dreher B, et al. A consensus statement on osseoperception. Clin Exp Pharmacol Physiol 2005;32:145–146.
7. Mishra SK, Chowdhary R, Chrcanovic BR, Brånemark PI. Osseoperception in dental implants: A systematic review. J Prosthodont 2016;25:185–195.
8. Onozuka M, Watanabe K, Mirbod SM, et al. Reduced mastication stimulates impairment of spatial memory and degeneration of hippocampal neurons in aged SAMP8 mice. Brain Res 1999;826:148–153.
9. Kubo KY, Murabayashi C, Kotachi M, et al. Tooth loss early in life suppresses neurogenesis and synaptophysin expression in the hippocampus and impairs learning in mice. Arch Oral Biol 2017;74:21–27.
10. Onozuka M, Watanabe K, Nagasaki S, et al. Impairment of spatial memory and changes in astroglial responsiveness following loss of molar teeth in aged SAMP8 mice. Behav Brain Res 2000;108:145–155.
11. Avivi-Arber L, Seltzer Z, Friedel M, et al. Widespread volumetric brain changes following tooth loss in female mice. Front Neuroanat 2017;10:121.
12. Zhou B, Zuo YX, Jiang RT. Astrocyte morphology: Diversity, plasticity, and role in neurological diseases. CNS Neurosci Ther 2019;25:665–673.
13. Habre-Hallage P, Dricot L, Jacobs R, van Steenberghe D, Reychler H, Grandin CB. Brain plasticity and cortical correlates of osseoperception revealed by punctate mechanical stimulation of osseointegrated oral implants during fMRI. Eur J Oral Implantol 2012;5:175–190.
14. Yan C, Ye L, Zhen J, Ke L, Gang L. Neuroplasticity of edentulous patients with implant-supported full dentures. Eur J Oral Sci 2008;116:387–393.
15. Avivi-Arber L, Lee JC, Sood M, et al. Long-term neuroplasticity of the face primary motor cortex and adjacent somatosensory cortex induced by tooth loss can be reversed following dental implant replacement in rats. J Comp Neurol 2015;523:2372–2389.
16. Holmes NP, Tamè L, Beeching P, et al. Locating primary somatosensory cortex in human brain stimulation studies: Experimental evidence. J Neurophysiol 2019;121:336–344.
17. Avivi-Arber L, Martin R, Lee JC, Sessle BJ. Face sensorimotor cortex and its neuroplasticity related to orofacial sensorimotor functions. Arch Oral Biol 2011;56:1440–1465.
18. Fujii N, Ohnishi H, Shirakura M, Nomura S, Ohshima H, Maeda T. Regeneration of nerve fibres in the peri-implant epithelium incident to implantation in the rat maxilla as demonstrated by immunocytochemistry for protein gene product 9.5 (PGP9.5) and calcitonin gene-related peptide (CGRP). Clin Oral Implants Res 2003;14:240–247.
19. Du Z, Lee RS, Hamlet S, Doan N, Ivanovski S, Xiao Y. Evaluation of the first maxillary molar post-extraction socket as a model for dental implant osseointegration research. Clin Oral Implants Res 2016;27:1469–1478.
20. Zhuge Qixun. Stereotactic Atlas of Rat Brain, ed 3. Beijing: People's Medical Publishing House, 2005.
21. Tzeng SF, Kahn M, Liva S, De Vellis J. Tumor necrosis factor-alpha regulation of the Id gene family in astrocytes and microglia during CNS inflammatory injury. Glia 1999;26:139–152.
22. Pekny M, Wilhelmsson U, Pekna M. The dual role of astrocyte activation and reactive gliosis. Neurosci Lett 2014;565:30–38.
23. Sofroniew MV. Astrocyte reactivity: Subtypes, states, and functions in CNS innate immunity. Trends Immunol 2020;41:758–770.
24. Pekny M, Pekna M. Reactive gliosis in the pathogenesis of CNS diseases. Biochim Biophys Acta 2016;1862:483–491.
25. Khakh BS, Sofroniew MV. Diversity of astrocyte functions and phenotypes in neural circuits. Nat Neurosci 2015;18:942–952.