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RESEARCH ARTICLE

Evaluation of temporomandibular joint, masticatory muscle, and brain cortex activity in patients treated by removable functional appliances: a prospective fMRI study

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Objectives: The aim of this study is to evaluate the effects of functional orthodontic appliances on the masticatory muscles, temporomandibular joint (TMJ), and brain to determine whether using functional appliances full-time or only at night yields different results.
Methods: 16 patients with Class II malocclusion were included in this study. Eight patients were instructed to wear their appliances (monoblock/twinblock) full-time and the other eight patients were instructed to wear them at night while sleeping. An additional 10 patients with Class II malocclusion were later included as a pre-treatment control group. Signal intensity ratios (SIR) of TMJ structures and morphological evaluations of the masticatory muscles were done for all patients. Functional MRI (fMRI) data were also obtained from the patients while performing chewing and biting movements.
Results: ANB angle was reduced significantly in both the full-time and night wear groups, by values of 1.17° and 1.35°, respectively ($p < 0.05$). MRI showed that SIRs were significantly increased in both groups in the masticatory muscles, retrodiscal pad, condylar process, and articular disc ($p < 0.05$). Both resting and task-based fMRI evaluation revealed significant increases in blood oxygen level dependent signals in several regions of the brain in both groups ($p < 0.05$).
Conclusions: The cephalometric and MRI findings of this study indicate that the treatment effects were similar for both wear schedules. Functional appliances should be regarded not as simple devices that treat Class II malocclusion through skeletal and dental correction alone, but as exercise devices that lead to neuromuscular changes by facilitating muscle adaptation and activating various brain regions.
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Keywords: functional orthodontic appliances; fMRI, masticatory muscle; cortex activity; TMJ

Introduction

Removable functional appliances have been used for many years to treat Class II malocclusions of mandibular origin by modifying the condyle–fossa relationship and the activity of neuromuscular structures. Although condylar cartilage proliferation and increased mandibular length have been demonstrated with the use of appliances in animal studies, there is still no consensus on their mechanism of action.[1,2]

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Functional jaw orthopedics provides not only dental and skeletal corrections, but is also said to bring about morphological changes by training the patient in a new mode of function by actively engaging the central nervous system via stimulation of nerve receptors in the teeth, periodontium, muscles, and joints while the appliance is in the mouth.[3] In terms of changes in facial form, not only physiological muscle function or dysfunction, but also the basal tone of opposing muscle groups is important. In order to assess the effects of muscle function on dentofacial development in a biologically accurate way, they must be considered in conjunction with the central nervous system, which regulates and controls muscle function.[4]

Petrovic and Stutzmann,[5] stated that effective appliance wear time varied based on their design and argued that appliances like hyperpropulsors, twin-blocks, and the Frankel Functional Regulator must be worn full-time (FT). According to a study by Oudet and Petrovic,[6] investigating the effects of postural hyperpropulsors on rats for 4 weeks, removing the appliances from the mouth resulted in signal interruption, reduced lateral pterygoid muscle activity, and a subsequent decrease in condylar cartilage growth rate. Therefore, FT wear is recommended to ensure that the achieved effect is not interrupted. According to a more recent study by Frankel and Frankel,[4] the muscle training and reprogramming necessary for neuromuscular adaptation is not possible when functional appliances are worn only at night.

MRI is a diagnostic method that uses a magnetic field and radio wave energy to visualize internal organs and body structures. MRI has become a widely used modality for imaging soft tissues in particular because the patient is not exposed to ionizing radiation and it enables high-sensitivity visualization of different tissue densities.[7] Functional MRI (fMRI) is used to measure changes in brain activity based on blood flow.[8] According to this technique, cerebral blood flow is associated with neural activity. It is also predicted that blood flow will increase in an area of the brain that is activated.[9] The measure of this phenomenon is called the BOLD (blood oxygen level dependent) signal.

Despite the many advantages of MRI (*e.g.* high contrast sensitivity, lack of ionizing radiation, demonstration of changes in activity within tissues, ability to measure and create three-dimensional reconstructions of soft tissues, and utility in neurological examination), research on its use in the field of orthodontics has generally been limited to the evaluation of condyle/disc position in the temporomandibular joint (TMJ) after functional orthopedic treatment.[10–12]

The results of our previous study examining the effects of functional maxillary orthopedics on joints and muscles demonstrated that even in the early period, wearing these appliances on both FT and part-time (PT, night only) basis could lead to changes in masticatory muscle size.[13] This made us wonder what long-term changes might occur in the cerebral cortex and in what regions with different wear schedules.

Therefore, our objective in the present study was to examine the cephalometric results of functional orthopedic appliance use as well as its effects on the masticatory muscles, TMJ, and cerebral cortex in growing individuals with Class II malocclusion using MRI in order to determine whether FT and PT wear yield different outcomes.

Methods and materials

The study was approved by the Ankara University Faculty of Dentistry ethics committee (IRB approval number: 36290600/27). The patients' first-degree relatives were informed about the study and provided written informed consent.

This study was conducted on a total of 64 radiographic images (32 cephalometric radiographs and 32 hand-wrist X-rays) as well as anatomical and functional MR images from 16 patients (8 males, 8 females) with Class II division one malocclusion obtained before using appliances (T0) and at the end of treatment (T1). The patients were randomly divided into two groups: patients in Group 1 were instructed to wear their appliances FT (full-day except during meals), while patients in Group 2 were instructed to wear their appliances PT (only at night while sleeping). Initially, the study included a total of 16 patients, 8 with FT wear and 8 with PT wear, and post-treatment data were collected at a mean of 14.8 months.

Due to inconsistencies in fMRI sequence acquisition at the beginning of the study, pre-treatment fMRI data obtained from the treatment groups could not be used. For this reason, a control group of 10 individuals with Class II malocclusion were included in the study and pre-treatment fMRI scans from these individuals were used for comparison. Mean age and sex distribution of the treatment groups and this control group are given in Table 1.

Inclusion criteria were as follows:

(1) Having skeletal and dental Class II malocclusion due to mandibular retrusion;
(2) Having an unaesthetic and inharmonious soft tissue

Table 1 Chronological and skeletal ages of subjects at start of treatment and distribution of appliances by sex in Group 1, Group 2, and the control group

		Group 1	*Group 2*	*CONTROL*
CHRONOLOGICAL AGE		11,54	11,35	11,98
SKELETAL AGE		11,40	11,65	11,72
MALE	*Monoblock*	2	2	2
	Twin block	2	2	3
FEMALE	*Monoblock*	2	2	3
	Twin block	2	2	2

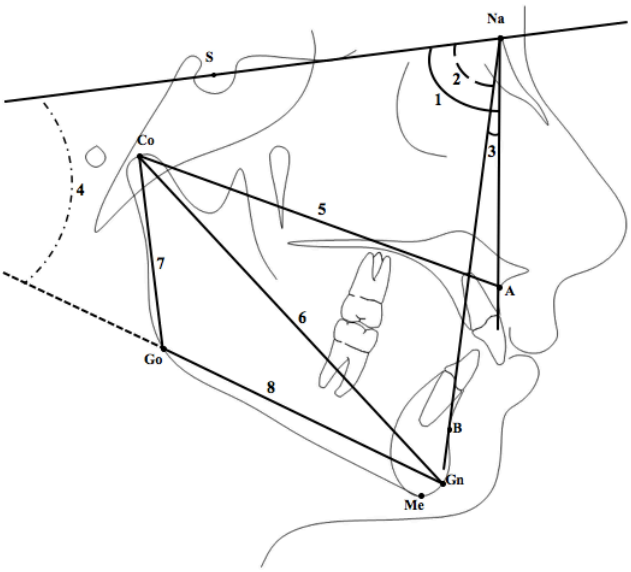

Figure 1 Cephalometric measurements. *Skeletal angular measurements (°):* 1. SNA (the posteroinferior angle between anterior cranial base and nasion-point A line), 2. SNB (the posteroinferior angle between anterior cranial base and nasion-point B line), 3. ANB (the angle between nasion-point A and nasion-point B lines), 4. GoGn/SN (the angle between anterior cranial base and the mandibular plane); *Skeletal linear measurements (mm):* 5. Co-A (the distance between condylion and point A; total maxillary length), 6. Co–Gn (the distance between condylion and gnathion; total mandibular length), 7. Co–Go (the distance between condylion and gonion; ramus length), 8. Go–Gn (the distance between condylion and gonion; corpus length).

profile;
(3) Being in or near the period of maximum pubertal growth according to hand-wrist radiographs;[14,15]
(4) Not requiring gradual mandibular activation for profile correction (<6–7 mm); and
(5) Having late mixed or permanent dentition.

All patients received a monoblock or twin-block appliance, with the twin-block preferred for patients requiring expansion of the maxillary dental arch and monoblock preferred for the other patients. The activators were constructed to achieve a Class I relationship between the molars and the canines. The vertical activation of the devices was adjusted to 3–4 mm above resting position. In the twin-block appliance, the upper and lower acrylic plates interlocked at a 70° angle.[16]

Cephalometric evaluation

Profile distance X-rays were obtained using a Sirona Orthophos XG 5 DS/Ceph X-ray device under standard conditions with the patients' heads positioned so that the Frankfurt horizontal plane was parallel to the ground. Dolphin Imaging Software 9.0 (Los Angeles, CA) was used to obtain and evaluate the data. Eight measurements, four linear and four angular, were made from the cephalometric films (Figure 1).

MRI evaluation

All MRI examinations were conducted at the National Magnetic Resonance Research Center (UMRAM) and the same protocol was used for all patients included in the study. Patients were not wearing their appliances at the time of MRI acquisition. Follow-up MRI (T1) was performed at a mean of 14.88 months. Patients are positioned in the supine position during the MRI procedures. Heads of the patients were fixed with cushions to minimize movement artifacts and disposable ear plugs were used to reduce the volume between sequences.

MRI was performed using a 3.0 T Magnetom Trio device (Siemens Medical, Germany) with a 32-channel head coil. Anatomic structures were visualized in T_1 weighted high-resolution images using the following acquisition parameters: TR (repetition time)=2000 ms, TE (echo delay time)=35 ms, slice thickness = 0.84 mm, flip angle = 12°, field of view (FOV) = 215 cm.

In this study, evaluations were based on two parameters, signal intensity ratio (SIR) and muscle volume. Signal intensity refers to the intensity of BOLD signal associated with change in the activity or vascularity of a certain tissue, and is used to evaluate activity level in the tissue being examined. To measure volume, anatomic borders of the target muscle were marked in each region where it was visible and the areas within these borders were marked. The designated muscle regions were processed and reconstructed in a separate three-dimensional image using Synapse 3D software (Fuji, Japan).

fMRI evaluation

Acquisition parameters for fMRI scans were as follows: TR = 3000 ms, TE = 30 ms, voxel size = 9 mm^3, number of slices = 35, flip angle = 75°, FOV = 192 × 192 mm, matrix size = 64 × 64, and slice thickness = 3 mm. During the task-based fMRI procedure, chewing and biting sessions were performed using codes that were previously written in the MATLAB software. In the chewing session, an instruction reading "Make a chewing motion while moving your head as little as possible" was displayed for 20 s, followed by the instruction "Remain motionless" for 12 s. In the biting session, the instruction on the screen read "Make a biting motion without moving your head" for 20 s and was followed by the command "Remain motionless" displayed for 12 s. These sets of commands were repeated 12 times in each session.

Images in DICOM 3.0 format were transferred to Freesurfer (v. 6.0.0, MGH, Boston, MA) software for morphometric analysis. After recon-all or pre-processing procedures (normalization, smoothing motion correction, cortical parcellation) were completed, volume, thickness, and surface area values were obtained for the right and left hemispheres of the brain. Group comparisons were made with the qdec function of the Freesurfer program. Based on the results of these comparisons, the groups' dominant regions, names, and coordinate values were determined. (Figure 2).

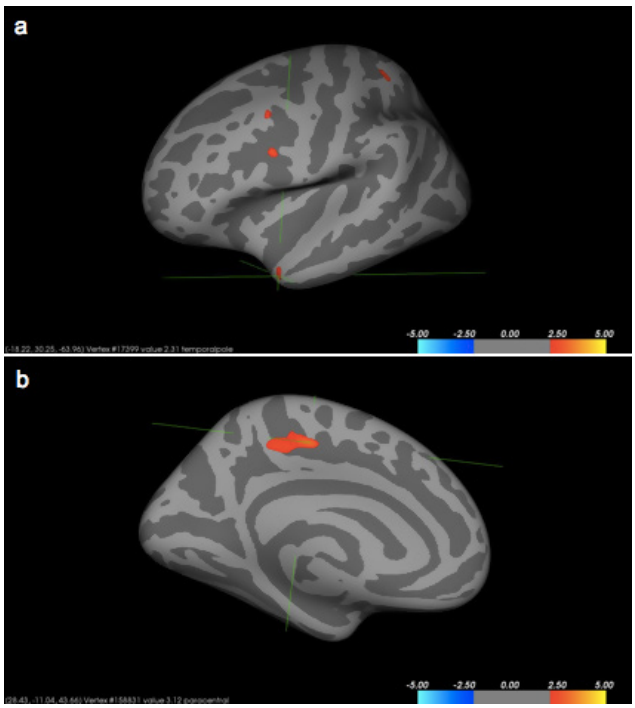

Figure 2 Determination of brain regions showing activation in the Freesurfer program.

All fMRI images were evaluated together by two experienced analysts blinded to the patients' clinical status and a consensus was reached on the results. The signal intensity values in the images were calculated and compared statistically. Volume, thickness, and surface area values of the right and left hemispheres of the brain were obtained. Morphometric analyses were performed in the Freesurfer program (Freesurfer version 6.0.0, MGH, Boston, MA). Task-based fMRI images were analyzed in the FSL program (FMRIB Software Library 5.0, Analysis Group, Oxford, UK).

For task-based analysis, first-level analysis was run on each individual, followed by higher-level analysis. The cluster sizes, coordinates, and the relevant brain regions were determined for observed activations (Figure 3).

Resting fMRI data were analyzed using 2D-BOLD (EPI) sequence data in DICOM format. After pre-processing the data in the SPM 12 program (SPM12, Wellcome Department of Cognitive Neurology, London, UK), a general linear model (GLM) was first applied. This was followed by MELODIC analysis and dual regression, and based on the results, the cluster size, co-ordinates, and *z*-values of the spatial brain components that best matched were determined. The names of the brain regions corresponding to these co-ordinates were obtained using FSLview (v 3.1).

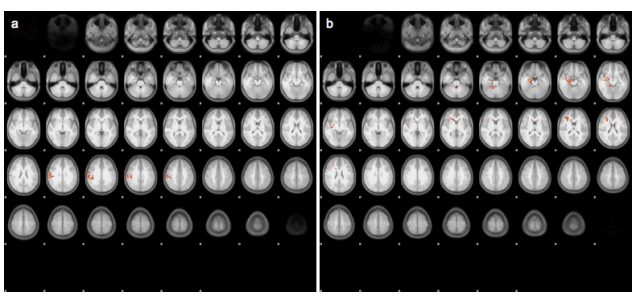

Figure 3 (a) Brain regions with activity on fMRI during the biting task (Group 2 *vs* control group), (b) Brain regions with activity on fMRI during the chewing task (Group 1 *vs* control group).

Statistical analysis

In order to determine the tracing and measurement error levels of the cephalometric measurements, they were repeated for each individual in each of the three groups after 4 weeks to assess repeatability of the measurements. Signal intensity and muscle volume measurements were made by the same oral/maxillofacial radiologist twice in order to evaluate reproducibility.

Statistical analyses were performed using the IBM SPSS Statistics 20 software package. A paired samples *t*-test was used to determine whether or not the differences in the evaluated parameters between T0 and T1 were statistically significant. Student's t-test was used to compare T0–T1 changes in the evaluated parameters between the groups. Variance analysis was used for descriptive statistics at T0 and morphometric analyses of T1 between the treatment groups and the control group.

Results

Cephalometric measurements

Cephalometric measurements showed high reliability, with correlation coefficients ranging between 0.9912 and 0.9984. All measurements were also found to be highly reproducible, with no significant difference between the two measurements of the observer ($p > 0.05$).

When the cephalometric measurements of Groups 1 and 2 at the start of treatment were compared, Co-A and Co-Gn values were significantly higher in Group 1 ($p < 0.05$). Separate examination of treatment-induced changes in the groups showed that the increase in SNB angle was significant in Group 1 ($p < 0.001$), while the decrease in ANB angle ($p < 0.05$) and increases in Co-A, Co-Gn, and Co-Go lengths were significant in both groups. Comparison of post-treatment changes between Group 1 and Group 2 revealed similar effects in both groups (Table 2).

MRI measurements

Cephalometric measurements showed high reliability, with correlation coefficients ranging between 0.8915 and 0.9878. All measurements were also found to be highly reproducible, with no significant difference between the two measurements of the observer ($p < 0.05$).

Evaluation of MRI measurements at the start of treatment showed borderline significant differences

Table 2 Descriptive statistics and comparison of the mean values of cephalometric parameters at the start of treatment (T0) between Groups 1 and 2 (variance analysis), evaluation of cephalometric changes from pre- to post-treatment (T0–T1) within groups (paired samples t test) and comparison of these changes between groups (Student's *t*-test).

	Pre-treatment (T0)						*Post-treatment (T1)– Pre-treatment (T0)*							
	Group 1		*Group 2*		*Group 1–Group 2*		*Group 1*			*Group 2*			*Group 1-Group 2*	
	X	S_x	*X*	S_x	*P*	*Test*	D	P	Test	D	P	Test	P	Test
Chronological age	11,48	1,49	11,28	1,24	0.595									
Skeletal age	11,38	0,83	11,56	0,78	0.649									
Skeletal angular measurements (°)														
SNA	82,05	2,50	79,44	1,5	0.117		0,53	0.168		0,34	0.529		0.768	
SNB	75,51	2,96	73,88	1,48	0.492		1,70	**0.001**	***	1,67	0.065		0.977	
ANB	6,54	2,18	5,56	1,49	0.256		−1,17	**0.04**	*	−1,35	**0.042**	*	0.809	
GoGn/SN	32,16	4,06	32,90	4,36	0.132		0,67	0.469		0,36	0.668		0.800	
Skeletal linear measurements (mm)														
Co-A	81,84	4,31	78,95	3,79	**0.026***		6,37	**0.001**	***	5,14	**0.004**	**	0.449	
Co-Gn	98,79	4,77	98,00	2,01	**0.038***		9,44	**0.001**	***	7,71	**0.001**	***	0.430	
Co-Go	46,04	2,24	47,26	3,30	0.682		5,63	**0.007**	*	5,54	**0.000**	**.	0.964	
Go-Gn	71,09	4,67	68,28	4,28	0.124		3,86	0.056		1,00	0526		0.224	

D: mean change between T0 and T1; S_x: error of the mean;X: mean.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

between Group one and Group two in signal intensities of the posterior articular disc (right) and posterior condylar process (left) and in lateral pterygoid muscle volume (left) ($p < 0.05$). Analysis of post-treatment changes revealed significant increases in the SIR values of all masticatory muscles and both anterior and posterior aspects of the articular disc and retrodiscal tissue in both study groups ($p < 0.05$ for all except left anterior condylar process in Group 2). When these changes were compared between the study groups, the only significant difference was in the signal intensity of the posterior articular disc (left) ($p < 0.05$) (Table 3).

fMRI measurements

Table 4 shows some significant changes identified in comparisons of BOLD data obtained from post-treatment resting fMRI of Groups 1 and 2 and pre-treatment fMRI in the control group.

In the chewing task, Group 1 showed significant post-treatment differences compared to pre-treatment values in the control group in the hippocampal cornu ammonis (right) ($p < 0.001$), inferior frontal gyrus ($p < 0.001$), pars triangularis (right) ($p < 0.001$), temporal occipital fusiform cortex (left) ($p < 0.001$), paracingulate gyrus (left) ($p < 0.001$), inferior temporal gyrus (right) ($p = 0.001$), lingual gyrus (right) ($p < 0.01$), middle temporal gyrus (right) ($p = 0.01$) regions. In the biting task, Group 2 showed significant differences compared to control pre-treatment values in the central opercular cortex (right) ($p < 0.01$), central opercular cortex (left) ($p < 0.001$), and supramarginal gyrus (right) ($p < 0.001$) regions (Table 5).

The brain regions showing significant differences in morphological parameters such as curvature, area, volume, and thickness in analyses of post-treatment data in the FT wear (Group 1) and PT wear (Group 2) groups compared to pretreatment data from the control group are shown in Table 6.

Discussion

Discrepancies in reported outcomes with functional appliances are related to factors such as duration of wear, appliance design, and timing of treatment initiation. Sander[17] has argued that FT wear of functional orthopedic appliances facilitates neuromuscular adaptation because the appliance is used more consciously and with more functional movements. Due to the higher frequency of functional activities during the day, the masticatory muscles adapt more readily to their new positions, and the appliance acts as a myofunctional exercise device to create a new engram in the brain.[4] Therefore, in this study we aimed to compare the effects of FT and PT wear of functional orthopedic appliances.

Studies on functional orthopedic treatment have demonstrated its effect on the size and position of the mandible.[2,18] Researchers have reported a strong

Table 3 Comparison of the mean values of MRI parameters at the start of treatment (T0) between Groups 1 and 2 (Student's *t*-test), evaluation of cephalometric changes from pre- to post-treatment (T0–T1) within groups (paired samples t test) and comparison of these changes between groups (Student's *t*-test).

	Pre-treatment (T0)		***Post-treatment (T1)–Pre-treatment (T0)***					
	Group 1–Group 2		***Group 1***		***Group 2***		***Group 1-Group 2***	
	P	***Test***	***D***	***Test***	***D***	***Test***	***P***	***Test***
SIR								
M. pterygoideus lateralis pars inf. (right)	0.202		0.9393	***	0.6786	**	0.167	
M. pterygoideus lateralis pars inf. (left)	0.157		0.8631	***	0.8083	***	0.801	
M. pterygoideus lateralis pars sup. (right)	0.284		0.9305	***	0.6405	**	0.213	
M. pterygoideus lateralis pars sup. (left)	0.324		0.9804	**	0.6659	***	0.206	
M. pterygoideus medialis (right)	0.116		0.8732	***	0.7275	**	0.405	
M. pterygoideus medialis (left)	0.649		0.8463	***	0.7472	**	0.627	
M. massetericus (right)	0.335		1.0475	***	0.8935	***	0.421	
M. massetericus (left)	0.069		0.9338	***	0.8279	***	0.646	
M. temporalis (right)	0.276		0.9922	***	0.7140	**	0.255	
M. temporal (left)	0.412		0.9752	***	0.6786	**	0.169	
Anterior discus articularis (right)	0.094		1.1089	***	0.7925	**	0.242	
Anterior discus articularis (left)	0.266		1.0225	**	0.9164	**	0.747	
Posterior discus articularis (right)	**0.033**	*	1.1696	***	0.8450	**	0.189	
Posterior discus articularis (left)	0.114		1.3537	***	0.8300	***	**0.046**	*
Anterior proc. condilaris (right)	0.465		0.5436	*	0.3948	**	0.466	
Anterior proc. condilaris (left)	0.197		0.4448	*	0.2960		0.548	
Posterior proc. condilaris (right)	0.143		0.4938	*	0.3810	***	0.567	
Posterior proc. condilaris (left)	0.352		0.4887	*	0.3189	*	0.393	
Retrodiscal tissue (right)	**0.034**	*	0.8297	**	0.7090	**	0.669	
Retrodiscal tissue (left)	0.085		1.0159	***	0.7058	***	0.181	

(Continued)

Table 3 (Continued)

	Pre-treatment (T0)		*Post-treatment (T1)–Pre-treatment (T0)*					
	Group 1–Group 2		*Group 1*		*Group 2*		*Group 1-Group 2*	
	P	*Test*	*D*	*Test*	*D*	*Test*	*P*	*Test*
Muscle volume measurements (cm^2)								
M. pterygoideus lateralis volume (right)	0.051		1.017	***	0.924	*	0.788	
M. pterygoideus lateralis volume (left)	**0.022**	*	1.147	***	0.786	**	0.232	
M. pterygoideus medialis volume (right)	0.879		1.073	**	1.227	***	0.671	
M. pterygoideus medialis volume (left)	0.410		0.644		1.175	*	0.368	
M. massetericus volume (right)	0.533		1.499		1.763	*	0.783	
M. massetericus volume (left)	0.652		1.705	**	1.604	**	0.861	

SIR, signal intensity ratio.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

association between change in mandibular length and increased condylar growth.[2,19] Our evaluation of the effect of functional appliances on mandibular parameters in the present study revealed a significant increase in SNB angle with FT wear while ANB angle decreased in both groups after treatment, consistent with the results of previous studies. In addition, total maxillary length (Co-A), total mandibular length (Co-Gn), and ramus length (Co-Go) increased in both treatment groups. The results obtained from both treatment groups demonstrated that an increase in mandibular length caused the reduction in ANB angle.

MRI is the modality that yields the most detailed information when imaging soft tissues such as the TMJ and joint disc. Aksoy and Orhan[20] reported that joint anatomy could be visualized particularly well with T_1 weighted images. We also acquired T_1 weighted images due to their diagnostic capacity in the joint region. When changes in signal intensity were examined separately in each group, there were increases of varying magnitudes in the masticatory muscles, joint disc, condyle, and retrodiscal tissue in both groups.

Hinton and McNamara[21] demonstrated in an animal study that adaptive changes occur not only in the condylar region but also in the glenoid fossa. The authors suggested that periosteal tension transmitted through the posterior fibers of the articular disc may cause the osteogenic response in the glenoid fossa. Studies have indicated that cellular activity in the posterosuperior aspect of the condylar process in particular is increased by positioning the condyle inferior to the glenoid fossa.[2,22] The increase in signal intensity in the posterosuperior aspect of the condyle observed in our study corroborates previous studies and indicates that functional orthopedic treatment stimulates condylar growth in the superior and posterior directions and that there may also be adaptive changes in the disc and retrodiscal tissue. We believe that in addition to growth, the volume increase and changes in signal intensity observed in the masticatory muscles may be attributable to vascularization and increased perfusion of the muscle as a result of increased muscle activity, together with muscular adaptation and hypertrophy due to long-term treatment.

Frankel intended to treat Class II patients by creating a new closure model in the brain with the Frankel two appliance, which he designed as an exercise appliance. This appliance moves the mandible anteriorly during wear and causes pressure and pain in the alveolar protrusions when the mandible attempts to return to a retrusive position. These sensations activate the proprioceptors in the gingiva and periosteum of the gums and stimulate the protrusive muscles to eliminate the discomfort, resulting in mandibular protrusion. This persistent discomfort is recognized by the central nervous system and creates negative feedback through which the brain can learn that the correct position of the lower jaw, *i.e.* the most comfortable position that avoids sensations of pressure, is Class I closure.[23] Based on these concepts, we

Table 4 Evaluation of parameters measured in resting-state functional magnetic resonance imaging (fMRI) in the full-time wear group after treatment (T1) compared to the control group at the start of treatment (T0) and in the part-time (night) wear group after treatment (T1) compared to the control group at the start of treatment (T0) according to BOLD (blood-oxygen-level-dependent) signals (Student's *t*-test).

Group 1 (T1)–Control group (T0)						***Group 2 (T1)–Control group (T0)***					
Region	*Cluster size*	*x*	*y*	*z*	*p*	***Region***	***Cluster size***	***x***	***y***	***z***	*p*
Central opercular cortex	33	50	-2	8	0.001***	*Central opercular cortex*	5	50	−18	16	0.008 **
Frontal operculum cortex	13	−38	10	8	0.002**	*Central opercular cortex*	14	−54	-2	8	0.001***
Frontal operculum cortex	6	46	26	0	0.001***	*Central opercular cortex*	89	50	-2	4	0.001***
Superior frontal gyrus	5	-6	18	64	0.001***	*Frontal operculum cortex*	11	50	14	-4	0.004 **
Superior frontal gyrus	7	−22	18	56	0.004**	*Superior frontal gyrus*	19	−10	34	48	0.001***
Middle frontal gyrus	12	−42	26	44	0.004 **	*Superior frontal gyrus*	10	22	34	44	0.001***
Middle frontal gyrus	31	26	2	40	0.001***	*Superior frontal gyrus*	9	-2	54	40	0.002 **
Inferior frontal gyrus	7	42	14	16	0.003 **	*Middle frontal gyrus*	9	50	18	44	0.002 **
Inferior frontal gyrus	10	−54	14	8	0.001***	*Middle frontal gyrus*	10	−38	14	52	0.004 **
Supramarginal gyrus	6	−50	−34	32	0.001***	*Inferior frontal gyrus*	22	42	22	20	0.001***
Supramarginal gyrus	13	−54	−42	24	0.002 **	*Inferior frontal gyrus*	7	58	22	-4	0.003 **
Supramarginal gyrus	29	34	−38	32	0.001***	*Supramarginal gyrus*	52	−62	−26	32	0.001***
Angular gyrus	4	−50	−54	40	0.003 **	*Supramarginal gyrus*	6	−58	−50	32	0.005 **
Angular gyrus	7	54	−50	44	0.001***	*Supramarginal gyrus*	26	66	−38	44	0.001***
Angular gyrus	7	−38	−54	44	0.002 **	*Angular gyrus*	10	58	−50	36	0.001***
Cingulate gyrus	10	10	−38	44	0.001***	*Cingulate gyrus*	8	-2	−38	32	0.003 **
Cingulate gyrus	16	2	−26	28	0.001***	*Cingulate gyrus*	5	6	22	28	0.003 **
Cingulate gyrus	32	6	−26	40	0.001***	*Cingulate gyrus*	42	-6	−38	44	0.00***
Paracingulate gyrus	5	6	34	32	0.002 **	*Paracingulate gyrus*	7	-6	54	12	0.003 **
Precentral gyrus	29	−58	-6	36	0.001***	*Paracingulate gyrus*	5	−10	38	24	0.005 **
Precentral gyrus	7	−38	−14	36	0.001***	*Precentral gyrus*	25	−58	-6	40	0.001***
Precentral gyrus	8	46	−10	52	0.008**	*Precentral gyrus*	5	−42	−18	56	0.002 **
Postcentral gyrus	7	−54	−22	52	0.002**	*Precentral gyrus*	6	6	−22	52	0.010 **
Postcentral gyrus	5	−42	−26	32	0.009**	*Postcentral gyrus*	22	62	−18	36	0.001***
Postcentral gyrus	7	46	−14	32	0.001***	*Postcentral gyrus*	16	−42	−30	52	0.001***
Juxtapositional cortex	7	−10	−14	56	0.004**	*Precentral gyrus*	33	38	−10	44	0.001***
Precuneus cortex	6	−26	−50	8	0.001***	*Juxtapositional cortex*	10	2	2	64	0.001***
Superior temporal gyrus	20	58	−34	8	0.001***	*Precuneous cortex*	10	−30	−66	12	0.001***
Superior temporal gyrus	7	−50	−26	0	0.001***	*Middle temporal gyrus*	8	−58	−34	−16	0.001***
Middle temporal gyrus	22	−42	−46	0	0.001***	*Middle temporal gyrus*	5	−54	−50	4	0.003 **
Inferior temporal gyrus	17	46	−46	-8	0.001***	*Middle temporal gyrus*	15	58	−58	8	0.002 **
Lingual gyrus	4	2	−90	-8	0.002 **	*Inferior temporal gyrus*	10	−50	−54	−16	0.001***
Lingual gyrus	4	-2	−90	−12	0.009 **	*Lingual gyrus*	114	−26	−50	4	0.001***
Parahippocampal gyrus	6	−26	−34	-8	0.003 **	*Lingual gyrus*	45	-2	−70	-4	0.001***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

analyzed and compared the neurological effects of the appliance with FT and PT wear by examining changes in the brain with fMRI after functional treatment.

According to our resting fMRI data, both FT wear and PT wear resulted in statistically significant differences in several parameters after treatment compared to baseline data from the control group. Regions exhibiting significant changes included the primary and supplementary motor areas, primary sensory cortex, supplementary sensory cortex, areas responsible for motor movements like the supramarginal gyrus, vision-related areas, motor mirror neuron system, areas responsible for the coordination of skeletal muscles, and sensory areas that process sensory data from movements such as speech, chewing, and biting. When we looked into the known functions of these regions, we noted that the supramarginal gyrus is involved in interpreting tactile sensory data (*e.g.* from dental sensory receptors and muscle spindles) and proprioception, in addition to perceiving and processing language. This activity was observed in the supramarginal gyrus with both FT and PT wear and seems to confirm the negative feedback mechanism proposed by Frankel and Frankel.[23] The mandible, which adopts Class I closure through avoidance of the discomfort created by the appliance, may be responsible for activation of the supramarginal gyrus. It

Table 5 Evaluation of parameters measured during the chewing task in fMRI in the full-time wear group after treatment (T1) compared to the control group at the start of treatment (T0) and in the part-time (night) wear group after treatment (T1) compared to the control group at the start of treatment (T0) according to BOLD (blood-oxygen-level-dependent) signals (Student's *t*-test).

	Region	*Cluster size*	*x*	*y*	*z*	*z-score*	*p*
Chewing Group 1 (T1)– Control (T0)	*Hippocampus cornu ammonis (right)*	575	22	−12	−22	3.57	0.001***
	Inferior frontal gyrus, pars triangularis (right)	396	28	26	18	3.24	0.001***
	Temporal occipital fusiform cortex (left)	341	−20	−52	−18	3.22	0.001***
	Paracingulate gyrus (left)	269	−14	20	34	3.33	0.001***
	Inferior temporal gyrus (right)	108	46	−20	−22	3.30	0.001***
	Lingual gyrus (right)	50	32	−38	-6	2.93	0.003 **
	Middle temporal gyrus (right)	47	46	−24	-6	3.09	0.002 **
Biting Group 2 (T1)– Control (T0)	*Central opercular cortex (right)*	168	42	6	16	3.05	0.002 **
	Central opercular cortex (left)	73	−44	2	6	3.21	0.001***
	Supramarginal gyrus (right)	66	44	−30	34	3.33	0.001***

fMRI, functional MRI.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

is reported in the literature that the supramarginal gyrus plays a major role in motor control, including rapid alternation of motor functions.[24]

The middle frontal gyrus and left inferior frontal gyrus are known as the language region.[25,26] In this study, we observed significant activation in the middle frontal gyrus in the treatment group compared to the control group. Another region that was significant in our study is the angular gyrus. The angular gyrus is a region involved in language, particularly understanding the meaning of metaphorical statements, in mathematical ability, and in distinguishing between the left and right directions.[27] Chen et al[28] reported that the angular gyrus enhanced adaptation to three-dimensional environments. The precuneus cortex is a region involved in our self-awareness, recollection of previously experienced tasks, and response to details regarding these, as well as our ability to focus when planning, visualizing, or directly performing a task, and to carry out conscious movements.[29,30] Ashizuka et al[31] reported selective activation of the precuneus cortex during polite speech in their fMRI study. The activation of these regions in our study suggests that functional treatment in developing patients can improve command of language and increase the ability to form sentences that conform to spelling and grammar rules. For example, the activators initially used for Pierre Robin sequence can improve patients' language command and social adaptation.

Furthermore, Ohnmeiss et al[32] reported that mandibular advancement after treatment with Andresen activator compensated for lumbar hyperlordosis. Thus, it is conceivable that patients' motor coordination may be improved through functional orthopedic treatment with activators that cause activation of the supplementary motor area (juxtapositional motor cortex), which is allegedly responsible for maintaining body balance, and postural corrections.

Task-based fMRI images revealed increased activation in certain regions of the brain in the FT group during chewing compared to the control group. The right aspect of the inferior frontal gyrus controls movements that are maintained until a command arrives.[33] This region also controls the avoidance of risky movements. The activation we observed in this region may represent a "stop" command to the mandible to prevent retraction and maintain an anterior position to avoid discomfort while the appliance was in the mouth during waking hours. The inferior temporal gyrus, another significant region in this study, is involved in object, face, and pattern recognition.[34] In addition to its function of recognizing complex objects, the lingual gyrus is also particularly influential in seeing and recognizing letters.

Of the brain regions that showed statistical significance during the biting task in the PT wear group after treatment compared to the control group, we noted increased activation in the opercular cortex and supramarginal gyrus. The insular cortex located in the opercular cortex is responsible for motor movements involving hand–eye co-ordination and activities such as swallowing, speech, and learning.[35]

Morphometric analyses involved volume, area, thickness, and curvature measurements in the brain after treatment. Consistent with the results of fMRI, both the FT and PT wear groups exhibited statistical significant morphometric changes compared to the control group in regions similar to those in both the resting and task-based results. The regions that yielded morphometrically significant results were generally the previously mentioned regions, such as those involved in sight, self-awareness, objects recognition, language, and mathematical skills. However, since the results of morphometric analysis mostly reflect physical changes in the brain, more extensive and detailed studies are needed to assert the superiority of either of the wear regimens based on these regions.

One of the main objectives underlying our decision to compare PT and FT wear in this study was to determine whether conscious appliance use had different effects on the brain than wear during sleep alone in functional orthopedic treatment. We expected the

Table 6 Analysis of post-treatment results in the full-time and part-time (night) wear groups compared to pre-treatment results in the control group in terms of the morphological features of the brain such as curvature, area, volume, and thickness and regions that presented significance (variance analysis).

	REGION	*Group 2 t value*	*Control p value*	*Group 2 t value*	*Group 1 p value*	*Group 1 t value*	*Control p value*
AREA	*rh-Post-central*	−3.35	**0.004**	/	**/**	−2.46	**0.026**
	rh-Pre-central	−3.28	**0.005**	/	**/**	−3.26	**0.005**
	rh-Middle temporal	−2.62	**0.019**	/	**/**	−2.35	**0.032**
	rh-G post-central	−2.34	**0.033**	/	**/**	−2.36	**0.031**
	rh-G temporal middle	−2.16	**0.046**	/	**/**	−2.31	**0.035**
CURVATURE	*lh-Lateral occipital*	−3.27	**0.005**	/	**/**	−2.51	**0.023**
	lh-Superior frontal	−3.04	**0.008**	2.31	**0.032**	2.41	**0.028**
	lh-Lateral occipital	2.92	**0.010**	/	**/**	3.15	**0.006**
	lh-Lateral orbitofrontal	2.87	**0.011**	2.43	**0.03**	−2.44	**0.027**
	lh-Caudal middle frontal	2.85	**0.012**	2.58	**0.022**	2.71	**0.015**
	lh-Precuneus	2.74	**0.016**	/	**/**	2.55	**0.021**
	lh-Inferior temporal	−2.55	**0.020**	2.45	**0.028**	2.58	**0.02**
	lh-Superior frontal	−2.53	**0.022**	−2.93	**0.011**	4.4	**<0**
	lh-Rostral middle frontal	−2.51	**0.023**	/	**/**	−2.27	**0.037**
	lh-Superior frontal	2.39	**0.030**	−3.36	**0.005**	2.41	**0.028**
	lh-Lingual	−2.35	**0.032**	/	**/**	2.54	**0.022**
	lh-Medial orbitofrontal	2.33	**0.033**	/	**/**	2.59	**0.019**
	lh-Supramarginal	2.22	**0.041**	/	**/**	−2.39	**0.03**
	lh-Infeior parietal	−2.19	**0.043**	-3	**0.01**	2.2	**0.043**
	rh-Rostral middle frontal	3.05	**0.008**	/	**/**	−2.32	**0.034**
	rh-Lateral occipital	−2.64	**0.018**	2.92	**0.011**	2.3	**0.035**
	rh-Lateral orbito frontal	−2.63	**0.018**	/	**/**	2.21	**0.042**
	rh-Precentral	2.31	**0.035**	−2.52	**0.025**	3.13	**0.006**
	rh-Inferior parietal	−2.22	**0.041**	−2.24	**0.041**	−2.65	**0.017**
THICKNESS	*lh-Superior frontal*	5.48	**<0**	/	**/**	4.35	**<0**
	lh-Lateral occipital	2.71	**0.015**	2.63	**0.02**	3.48	**0.003**
	lh-Entorhinal	2.34	**0.033**	/	**/**	2.3	**0.035**
	lh-Pericalcerine	−2.21	**0.042**	2.98	**0.01**	2.29	**0.036**
	rh-Postcentral	2.74	**0.015**	/	**/**	3.33	**0.004**
	rh-Precentral	2.3	**0.035**	/	**/**	3.12	**0.007**
	lh-pole temporal	2.54	**0.022**	/	**/**	2.26	**0.038**
VOLUME	*lh-Precentral*	2.46	**0.026**	−3.21	**0.006**	−2.47	**0.025**
	lh-Supramarginal	−2.44	**0.027**	/	**/**	−2.24	**0.04**
	lh-Supramarginal	−2.36	**0.031**	/	**/**	−2.13	**0.049**
	lh-Superior frontal	−2.16	**0.046**	−3.06	**0.008**	−2.19	**0.044**
	rh-Precentral	−2.50	**0.024**	/	**/**	−2.75	**0.014**
	rh-Lateral occipital	−2.30	**0.035**	/	**/**	−2.61	**0.019**
	rh-Caudal middle	−2.29	**0.036**	/	**/**	−2.25	**0.039**
	rh-G parietal superior	3.03	**0.008**	/	**/**	−2.39	**0.03**

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

benefit of wearing the appliance at night to be limited to dental and skeletal corrections, without formation of a new model of closure in the brain. However, the fMRI results in both the FT and PT wear groups led to a different conclusion. Night wear of the appliance also resulted in significant changes in the brain according to several parameters.

Limitations

The biggest limitation of our study is that the fMRI images acquired from both the FT and PT wear groups before treatment became unusable due to modifications in fMRI methodology at later stages of the study. For this reason, we selected a control group of 10 individuals with similar anomalies and characteristics. Changes

in the brains of patients in the FT and PT wear groups after treatment were determined based on comparisons with data obtained from the control group prior to treatment. Therefore, more accurate results could be obtained by conducting a new study with larger study groups, utilizing pre- and post-treatment fMRI images from the same patients.

Another limitation for this study is the lack of treatment-free control group. The main reason for the lack of treatment-free control group is that all of our patients were at or near the period of maximum pubertal growth. Optimal treatment timing for functional appliances is at the period of maximal pubertal growth. So, having a treatment-free control group for this study would mean that skeletal ages of patients could be delayed for ideal treatment results. Therefore, both ethical considerations and the difficulties of obtaining MRIs from children prevented us from including treatment-free control subjects in this study. Nevertheless, this study offers a new perspective on the long-debated topic of the neuromuscular effects of functional orthopedic treatment.

Conclusion

The effects of FT and night-only use of functional orthopedic appliances were similar according to cephalometric, MRI, and fMRI evaluation. Functional appliances not only correct morphology, but also bring about structural alterations of the masticatory muscles. Instead of regarding these appliances as simple devices that only provide skeletal and dental correction of Class II malocclusion, it would be more accurate to think of them as exercise tools that lead to neuromuscular changes by facilitating muscle adaptation and activating various brain regions.

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Patient consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study.

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