Comparison of the effect of conventional and implant-retained overdentures on brain activity and cognition in a geriatric population – A Functional MRI study

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Abstract

**Purpose:** This study aims to evaluate the effect of rehabilitation with complete dentures versus implant-retained overdenture on activity in various parts of the brain cognition in a geriatric edentulous population via Functional MRI (fMRI) studies and the Mini-Mental State Examination (MMSE).

**Methods:** Ten completely edentulous patients were rehabilitated with both complete dentures and two-implant retained overdentures for three months each. fMRI studies were performed for each modality during chewing and recall tasks at three time periods: T0: Completely Edentulous (CE) T1: after three months of wearing Conventional Complete Dentures (CD) and T2: after three months of wearing Implant-retained Overdentures (IOD). The Z scores obtained from the fMRI at these phases of examination were tabulated and correlated with MMSE scores obtained at the corresponding time periods.

**Results:** Z scores obtained during the memory recall tasks at T2 were the greatest (Prefrontal Cortex (p=0.059) and Hippocampus (p=0.036). The MMSE scores obtained were significantly higher for the IODs when compared to the CDs and Baseline values (p < 0.05)

**Conclusion:** IODs may potentially result in superior sensory feedback in edentulous patients and lead to improved cognitive performance when compared to conventional complete dentures.

**Keywords:** Dental prosthesis, Implant-supported, Cognitive dysfunction, Magnetic resonance imaging

1. Introduction

Advances in medicine and an ever-increasing population have led to a drastic demographic shift in several parts of the world, resulting in a larger than ever ‘super-aged’ population[1]. As a result, along with other chronic non-communicable diseases (NCDs), the incidence of complete edentulism has also increased drastically. Complete tooth loss has been included as one of the ten leading causes of Years Lived with Disability[2] Besides resulting in more apparent impairments such as function and esthetics, it is also hypothesized to have a debilitating effect on cognition and memory, hearing, body balance and mental well-being. Cognitive impairment represents any characteristic that acts as a barrier to the cognitive process, that leads to a deficit in global intellectual performance, mental retardation, learning disorders and dyslexia[3]. The influence of the stomatognathic system on cognitive impairment has piqued the interest of dentists and neurologists alike. In 2017, WHO reported the prevalence of 50 million cases of dementia worldwide and predicted an increase to 82 million by 2030[4,5]. Approximately half the individuals with mild cognitive impairment progress to developing dementia within five years of initial diagnosis and tooth loss before the age of 35 is considered one of the major risk factors[3].

To elucidate the sequelae of cognitive decline after tooth loss, Jou defined the term ‘deafferentation’, as the reduction of peripheral afferent neural inputs related to dental and masticatory apparatus. The process of ingesting food was considered a ‘complex harmonization of conscious and unconscious recognition, memory conditioned reflexes and many other functions as multiple neural transmissions, evaluations, decisions and executions happen simultaneously’. Each tooth is like a musician performing in an eating – mastication ‘symphony orchestra’. When one of these ‘musicians’ change their function or are removed, it results in structural and functional deafferentations of the adjacent and opposing teeth. This causes a mistune in the ‘natural melody’ and leads to sustained and even permanent reorganizations of sensory and motor cortices[6]. However, this ability for reorganization dwindles as age progresses, thereby leaving edentulous geriatric patients more susceptible to cognitive dysfunction. More recently, a positive correlation between the inability to chew (rather than tooth loss), and mild cognitive impairment has been established by several cross-sectional studies via a standard battery of tests such as the Mini-Mental State Examination (MMSE).
Completely edentulous patients are conventionally treated with complete dentures, and this ostensby leads to an increase in occlusal force playing an essential role in alleviating stress, improving episodic, working memory, word association and executive function[9]. Although successful in some patients, complete dentures are associated with complications such as rapid bone resorption and patient dissatisfaction, especially due to compromised retention and stability of the mandibular denture. With the advent of osseointegrated titanium implants and the McGill’s consensus[10], rehabilitation of the edentulous mandible with two implant-retained overdentures overcame these complications. They provided greater function and quality of life than conventional complete dentures[11]. Lexomboon et al., speculated that the sensory fibres surrounding the implant improve brain activity[12]. In contrast, Banu et al., suggested that cognitive function improvement is seen only when the osseointegrated implant is loaded with the prosthesis[13]. However, the brain activity brought about by different prosthesis have been compared quantitatively by a few studies, and all of them show that a positive correlation exists between the two[14–16].

To evaluate these changes, molecular level imaging techniques have been undertaken. In this regard, functional MRI (fMRI) is a safe and effective method that detects cerebral blood flow changes, using iron as the paramagnetic contrast and demonstrating regional, time-varying changes in brain metabolism. The blood oxygenation level-dependent (BOLD) signals represent the neural activity, and each voxel of activation corresponds to a few million neurons[17]. As mastication is known to increase cerebral blood flow, we chose to examine and quantify brain activity via fMRI studies.

This fMRI study aimed to assess the effect of conventional complete dentures versus implant-retained overdentures on memory and cognition in the same geriatric completely edentulous cohort. Subsequently, these findings were compared with the scores obtained in the Mini-Mental State Examination Test. It also aimed to visualize and delineate the areas that coincide with chewing and memory recall when rehabilitated with different prostheses.

2. Materials and Methods

Ethical approval was obtained from the Institutional Ethics Committee of Sri Ramachandra Institute of Higher Education and Research Ref No: CSP/18/SEP/73/272 and was undertaken as a preliminary study. The sample size was calculated to be 7. 3 additional patients were recruited to account for dropouts and failures. Ten patients who visited the Department of Prosthodontics between November 2018 – February 2018, 60-85 of age were recruited as per the following eligibility criteria as a pilot sample and were to serve as his/her control. This study was self-funded.

2.1. Inclusion Criteria
1) Completely edentulous maxillary and mandibular ridges
2) History of edentulousness without dentures for at least 1 year
3) Healthy patients with no systemic or mental illness
4) Patients who had adequate mandibular bone volume for implants of dimension 3.5 x 11mm in the interforaminal region

2.2. Exclusion Criteria
1) Preexisting removable denture wearers
2) Patients exhibiting severe ridge resorption and flabby ridges
3) Patients with pacemaker and cochlear implants
4) Patients with foreign metal objects in their back, legs, eyes etc.,
5) Patients who had been diagnosed with Alzheimer’s disease or dementia
6) Patients who had been diagnosed with mental illness
7) Patients who had been diagnosed with claustrophobia

2.3. T0: Completely edentulous (CE) – Day 0
2.3.1. fMRI study

The patients underwent an fMRI study on day 0. fMRI studies were performed using a 3-T Siemens SPECTRA MAGNETOM MR Scanner. Whole-brain T1 Sagittal MPRAge sequences were acquired for anatomical reference images, followed by Whole Brain echoplanar fMRI using a gradient echo pulse sequence (TR/TE 3290/30 ms, flip angle 90, slice thickness 3 mm, 49 axial slices).

A Block design was used for two tasks, with 30 seconds on and 30 seconds off periods. Three sets of on and off blocks were collected for both tasks, with scan time totalling 6 minutes. The images obtained were analyzed using the FSL software suite and BOLD (Blood Oxygenation Level-Dependent) signals were quantified with Z scores. These were used to identify overlapping activation areas and evaluate interval change in signal strength between the different trial phases.

The patients were asked to perform two tasks as follows:

2.3.2. Task 1 (Chewing)

The patients were given a stick of gum that they were instructed to chew during the on-phase, and rest during the off-phase.

2.3.3. Task 2 (Memory recall – Subset of the MMSE)

The patients were assigned three random words (30 minutes prior to the commencement of the imaging procedure). They were instructed to recall the words, one at a time during the on-phase of each block, and rest during the off-phase.

2.3.4. Mini-Mental State Examination Test

The patient’s cognition and recall ability were also tested using the Mini-Mental State Examination Test[10] in the dental operatory. Patients were subjected to questions that tested orientation, attention, memory, language and visual-spatial skills. Patients were given a maximum of 30 points based on their responses.

Prior to the fMRI study, the patients had undergone the standard procedure for the fabrication of conventional complete dentures (Fig. 1). On Day 1, following the Baseline fMRI and MMSE questionnaire, the finished complete dentures were inserted and adjusted, and the patients were allowed to acclimatize to the dentures for one week. Following this (Day 8), two SLA implants of dimensions 3.5 x 11mm (SYNA implant system, Korea) were placed in the canine regions of the mandible. The patients were recalled after a week (Day 15). The intaglio surface of the lower denture directly in contact with the mucoperiosteum was relieved to reduce load transfer to the im-
plants. Patients were asked to wear these dentures for the next three months.

2.4. T2: Conventional Complete Dentures (CD) – Day 106

After three months of wearing conventional complete dentures, a second fMRI study with Task I and II and MMSE (Day 106), in a manner similar to the technique previously mentioned were undertaken by the patients. Subsequently, implants were uncovered (Day 107), and the cover screws were replaced with ball abutments of the appropriate collar height (Fig. 2). (Amelotech Limited, Germany). The intaglio surface of the denture was modified to accommodate a metal housing with a rubber ring. Patients were given post-insertion and maintenance instructions and were asked to wear the implant-retained dentures for another three months.

2.5. T3: Implant-retained overdentures (IOD) – Day 198

The patients undertook the final fMRI study with Task I and II and MMSE after three months as per the previously mentioned protocol.

The time elapsed and the interventions undertaken at each juncture are represented (Fig. 3).

2.6. Statistical Analysis

Brain activity was analysed using the Fsl software obtained as Z scores which are Quantitative measurements of the areas that showed statistically significant activation during the fMRI. The Z scores of all the groups were subjected to the Friedman Test for comparison of repeated measures. Comparison of the Z scores and the MMSE scores between each group was done with the Wilcoxon Signed Rank Test.

3. Results

Ten patients (Age range 62-91, 6 women and 4 men) received 20 implants and were followed up over a period of 6 months. One implant in two patients failed to osseointegrate before loading leading their elimination from the study. fMRI studies were done, and the activation was recorded as Z scores for the remaining patients at Baseline when the patients were completely edentulous (CE), with complete dentures (CD) and implant-retained overdenture (IOD). Additionally, the Mini-Mental State Examination was done to correlate the resultant brain activity with cognitive performance during the three corresponding assessment phases (CE, CD & IOD).

The Z scores thus obtained were non-parametric. The comparison of repeated measures with the Friedman test showed a statistically significant difference between groups (p < 0.05). Only the
regions of interest (ROI) that showed consistent activation were subjected to statistical analysis with the Wilcoxon Signed Rank Test. The other regions showed less or mostly inconsistent activation to be subjected to statistical testing, so we resorted to a qualitative analysis of these observations.

3.1. TASK 1

3.1.1. Analysis of Chewing induced regional brain activity (Quantitative)

The regions with the most significant foci of activation across the patients at all phases of evaluation were: Sensorimotor Cortex, Prefrontal lobe, Hippocampus and Insula. (Fig. 4). There was no consistent pattern of unilateral and bilateral activation, and thus the higher Z score obtained from the region of interest irrespective of lateralization was considered. The least activation with IOD was seen in the Prefrontal Cortex, Hippocampus while the highest was seen in the Insula (Fig. 5). The decrease in brain activity was statistically significant only in the Prefrontal Cortex between CE and IOD and in the Hippocampus between CD and IOD. However, the activation of the insula with IOD was greater than with the CD.

3.1.2. Individual ROI Analysis (Qualitative)

Most of the patients presented with a smaller number of activation areas with IODs than with CDs (62.5%). Sensorimotor activation was evident at all periods in most patients. The thalamus' activation was seen in both CDs and IODs and was distributed non-homogeneously (50%).

3.2. TASK II

3.2.1. Analysis of Recall induced regional brain activity (Quantitative)

Memory recall increased the Z scores in the following regions: Prefrontal Cortex, Hippocampus, Parietal, Sensorimotor cortex, Temporal Lobe, Insula, Cerebellum, Supplementary Motor Area, Occipital, Thalamus and Corpus Callosum regions. The regions with the most significant foci of activation were the Hippocampus and the Prefrontal cortex, with the highest seen with the IODs (Fig. 6). The difference in activation resulting from memory recall between CD and IOD was statistically significant in both Prefrontal Cortex and Hippocampus (Fig. 7).
Fig. 8. MMSE scores obtained with each modality. *The differences between the groups were significant.

3.2.2. Individual ROI Analysis (Qualitative)

Activation of the Hippocampus was seen uniformly in all the subjects with IOD except for one. Activation in the Parietal lobe, Cerebellum and Thalamus was evident only in the recall tasks done with IODs. However, it was not discernible in any of the recall tasks at Baseline or with CD.

3.3. MMSE Results

The MMSE scores obtained with the IOD was the highest, and the difference amongst the groups was statistically significant (p<0.05). Individual group analyses done with Wilcoxon Signed Rank test showed a statistically significant difference between all groups. The distribution of the values obtained is diagrammatically represented using a Box Plot (Fig. 8).

4. Discussion

Cognitive frailty in older adults is one of the greatest threats of the 21st century. The risk factors leading to cognitive deterioration may be modifiable and unmodifiable[18], and since tooth loss is one of former, it needs to be apprehended and treated strategically. Deciphering this complicated relationship has been long underway. It has proven to be cumbersome as the characteristics are so intertwined, with the association between the masticatory in ability and cognitive impairment being bidirectional[18].

The Hippocampus, along with the prefrontal cortex, is considered to play a significant role in encoding, consolidation and retrieval of memories[19]. Elimination of neural signals due to tooth loss, periodontal detachment and TMJ dysfunction, acts as a potential stressor resulting in hyperactivity of the HPA axis and subsequent release of corticosterone, leading to an influx of Ca+ in the neurons, resulting in hippocampal damage[20]. This causes deterioration of neurogenesis in the CA1 and CA3 regions and brings about a reduction in the number of dendritic spines and branching of the dendrites[21–23]. According to Yamazaki et al., nerve growth factors such as BDNF (Brain-derived neurotrophic factor) and tropomyosin receptor kinase B messenger are also depleted, causing a decrease in hippocampal synaptic transmission[24] along with an increase in astrocyte proliferation and astroglial hypertrophy. The latter is an indication of rapid ageing[20].

Mastication improves sensory, and motor feedback to the CNS[25] and alleviates stress by activating NMDA (N-methyl D-aspartate) receptor-mediated long-term potentiation (LTP), which plays a vital role in learning and memory[26]. This potential improvement in cognition with occlusal rehabilitation can be attributed to structural plasticity, which refers to the nerve’s ability to change its physical structure based on learning and change in the environment. New research has also confirmed the occurrence of adult neurogenesis, especially in the Hippocampus[27]. This indicates that neural networks are malleable and introduces the possibility of cognitive improvement upon restoring masticatory efficiency with artificial teeth.

Implant retained denture prosthesis were hypothesized to have a significant influence on the brain function. According to Yan C et al., this effect has been attributed to ‘osseoperception'[28] according to which, kinaesthetic sensation leads to the activation of the chewing related prefrontal cortex without the input of periodontal mechanoreceptors. Kamiya et al., and Narita et al., reported this to be similar to the activation seen in dentate young adults[29,30] Another plausible explanation, according to Shinichiro A et al., was the fact that implant-retained prosthesis increases the occlusal force and contact area resulting in strong occlusal forces allowing the denture wearer to process information in a short period of time[31]. Moreover, the NFP (neurofilament protein) positive nerve fibres in the peri-implant region are said to enhance the sensory input to the brain[32].

Thus, we hypothesized that memory recall tasks with an implant retained overdenture would present with greater brain activation than conventional complete dentures, aiding in improved cognitive functioning.

Ten male and female edentulous patients between the ages of 60-80 were recruited based on the Seattle Longitudinal Study of Adult intelligence which demonstrated that decline in cognitive ability was not reliably observed before the age of 60 but showed significant impairment during the late 70s[33]. Each modality was evaluated after a period of three months as this is minimum time reported for tangible neuroplasticity induced changes[34].

This study’s fMRI block design included 30 seconds on and 30 seconds off periods for mastication followed by memory recall. Chewing gum was selected for Task I was based on precedent set by previous studies. Moreover, it served as a reproducible task which could be performed without compromising image quality. The recall test was a sub-item of the MMSE that required the patients to recall three unrelated objects that they were previously instructed to remember[35]. The order of testing was based on the results of a study that reported that mastication immediately before cognitive task acquisition further increases blood oxygenation levels in the prefrontal cortex and Hippocampus, thereby resulting in enhanced cognitive performance[36]. By randomizing the words, we were able to mitigate patient habituation. Owing to the absence of visual, auditory stimulus and feedback equipment at the centre where this study was conducted, we resorted to tactile cues to indicate resting and activation phases to the patient.

The BOLD signals in the completely edentulous patients during mastication at Baseline showed a haphazard distribution of the areas involved. This was attributed to chewing with the basal tissues. The
areas with consistent, statistically significant activation during chewing were the Sensorimotor cortex and prefrontal cortex. Activation of the Sensorimotor cortex can be attributed to its role in shaping, folding and repositioning the bolus and therefore modulating chewing movements[37]. The activation of the insula, otherwise referred to as the masticatory organ[30] was seen in 3 CDs, and 6 IODs with the difference was statistically significant.

In the present study, the reduction in activation of these regions with IODs, along with robust activation with the CD is consistent with the findings reported by Kimoto et al. This is attributed to the fact that conventional complete dentures are associated with increased mobility leading to a more kinematically irregular and unstable chewing pattern. On the other hand, implant-retained overdentures show smooth and stable functioning of the oral masticatory apparatus, similar to regular dentate patients[38]. Therefore, the reduction of BOLD signals does not necessarily equate to suppression of brain activity.

The areas that showed consistent activation during the recall task were the prefrontal cortex and Hippocampus, with significantly greater activation in the IODs. The prefrontal cortex controls the performance of the other components by allocating a limited capacity of memory resource to each, thereby explaining its activation during the recall task. The activation of the Hippocampus can be explained by its extensively proven association with the retrieval of episodic memories and consolidation. Additionally, recall with IODs showed activation of the cerebellum, parietal lobe and thalamus. A PET study revealed the potential participation of the cerebellum in an interactive cortical cerebellar network that initiates and monitors conscious retrieval of episodic memory[39]. With regards to the parietal lob, although unclear has been associated with learning and memory[40]. According to Wolff M et al., several features of the thalamocortical-circuits are consistent with performing integrative roles in cognition, memory and recall[41]. The number of clusters of activation in the different regions of the brain involved in memory and cognition, was much higher for the IODs than for the CDs, during the recall test. This, upon correlation with the increased MMSE scores, can be considered as enhanced functioning of the regions involved in memory and recall as an effect of IOD treatment. Rhythmic controlled chewing with greater occlusal force could have led to the steady maintenance of sensory and motor feedback to and from the brain, thereby resulting in the formation of new neural pathways.

This study has several limitations:
• The sample size of 8 patients was too small to make any conclusive statements about the patterns of brain activity in the various modalities.
• Many confounding variables such as gender, systemic, and environmental factors may have affected the results.
• We could not account for the lack of consistency in the laterality of brain activation during the tasks. However, brain laterality can be explained by the side of functional preference rather than the efficiency of mastication. Thus, the higher activation value was used in those subjects who presented with bilateral activation[42].
• The activation pattern during chewing at Baseline was too variable across the subjects to draw any conclusive pattern of activation. However, the activation during the recall task for most of the patients was the least at Baseline.

5. Conclusion

Within the limitations of the study, the following conclusions can be derived
• During mastication (Task I), the brain activity brought about by implant-retained overdentures were not as high as the conventional complete dentures as a result of repeated and controlled functioning. This is considered similar to the pattern of mastication seen in natural dentition.
• During memory recall (Task II), the brain activity associated with implant-retained overdentures showed greater activation along with an increase in the number of areas of activation.
• The MMSE scores were significantly greater for the implant-retained overdentures indicating higher brain functioning, and this was consistent with the inference of the fMRI studies.

In conclusion, the implant-retained overdentures are superior for sensory feedback in edentulous patients and have shown an improvement in cognitive performance when compared to conventional complete dentures.

Conflicts of interest

The authors declare that there is no conflict of interest

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