INTRACORTICAL MICROSTIMULATION ANALYSIS OF RAT MOTOR CORTEX FOLLOWING MAXILLARY MOLAR EXTRACTION

DEEPAK NALLASWAMY VEERAIYAN

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Graduate Department of (Prosthodontics)
University of Toronto

Intracortical microstimulation analysis of rat motor cortex following maxillary molar extraction.

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Deepak Nallaswamy Veeraiyan,
Graduate Department of (Prosthodontics), University of Toronto.

Abstract

The neuroplastic changes in the motor representations within the face primary motor cortex (Face-M1) due to jaw and tongue motor alterations following the unilateral extraction of maxillary molars teeth have not been explored. The present study used intracortical microstimulation (ICMS) and recordings of evoked electromyographic responses to compare jaw (anterior digastric) and tongue (genioglossus) motor representations within the histologically defined Face-M1 one week post intervention across naive rats (n=6), rats that underwent anesthesia, right maxillary molar extraction after soft tissue manipulation (n=6) and rats that underwent anesthesia and soft tissue manipulation without extraction (n = 7). A small but significant anterior increase in the representation of the jaw and tongue motor representations was observed (oneway ANOVA $p < 0.01$, Bonferroni $p < 0.01$) in the contralateral Face-M1 one week following unilateral extraction of maxillary molars in rats.

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List of Special Terms and Acronyms

AMPAR	- Aminohydroxy Methylisoxazole Propionic Acid Receptor
AP	- Anteroposterior
CG	- Centre of Gravity
CMA	- Cotrical Masticatory Area
CPG	- Central Pattern Generator
CT	- Computed Tomography
EEG	- Electroencephalolography
fMRI	- functional Magnetic Resonance Imaging
GG	- Genioglossus
ICMS	- Intracortical Microstimulation
LAD	- Left Anterior Digastric
LTD	- Long-term Depression
LTP	- Long-term Potentiation
M1	- Primary Motor Cortex
MEG	- Magnetoencephalography
MEPs	- Motor Evoked Potentials
ML	- Mediolateral
NCS	- Neuronal Calcium Sensor
NMDA	- N-Methyl D-Aspartate
PET	- Positron Emission Tomography
PTP	- Post Tetanic Potentiation
PV	- Parietal Ventral cortex
RAD	- Right Anterior Digastric
S1	- Primary Somatosensory Cortex

SEP - Somatosensory Evoked Potential

SMA - Supplementary Motor Area

S2 - Secondary Somatosensory Cortex

TMS - Transcranial Magnetic Stimulation

V nerve - Trigeminal Nerve

Glossary of Terms

Neuroplasticity:

Neuroplasticity refers to the ability of the central nervous system or its component parts to change and adapt in response to changes in the environment, experience and behaviour to learning and to injury and disease.

ICMS Positive Site:

ICMS positive site refers to the site from which an electromyographic (EMG) response could be evoked within 40ms of stimulation in at least 3 of 5 stimulation trains and with an amplitude greater than two standard deviations of the background EMG level in one of the recorded muscles.

ICMS Positive Track:

ICMS positive track refers to a microelectrode track that contains at least one ICMS positive site in its path.

Onset Latency:

Onset Latency is the time interval between the onset of the ICMS current and the onset of a ICMS-evoked response in the EMG activity of a muscle.

Threshold:

Threshold refers to the lowest intensity of ICMS current required at a positive ICMS site to elicit a positive EMG response in the recorded muscle.

Centre of Gravity:

The centre of gravity for Face-M1 reflects the weighted centre in the Face-M1 representation for a recorded muscle. It represents the area within the Face-M1 that

has the maximum number of ICMS positive sites with the lowest threshold for evoking an EMG response for the muscle.

Rehabilitation:

Rehabilitation refers to the restoration of structure and/or function of any damaged or degenerated part of the body.

Motor Control:

Motor control is defined as the interaction of neuromuscular, musculoskeletal, cognitive, perceptual, and sensory components to produce functional movement.

Quality of Life:

Quality of Life refers a state of complete physical, mental and social well-being.

1. Introduction and Literature Review

1.1 Introduction

"Neuroplasticity refers to the ability of the central nervous system (CNS) to change and adapt in response to environmental cues, experience, behaviour, injury, or disease. Neuroplasticity can result from changes in synaptic contacts, synaptic strength, neuronal excitability, neurogenesis, or cell death" (Brosh and Barkai 2004). The origin of the term neuroplasticity in neuroscience is unclear. The term neuroplasticity was popularized by Santiago Ramón y Cajal (DeFelipe 2006). Initially the concept did not gain much attention because it contradicted the then popular belief that the brain is fixed and unchanging (DeFelipe 2006). The science gained popularity following the demonstration of long-lasting synaptic potentiation in the hippocampus (Bliss and Lomo 1973). Today there are over 20000 publications listed under Pubmed's MeSH term "Neuronal Plasticity". Research on neuroplasticity has provided new insights about the brain's response to external stimuli that can be used to treat patients with brain damage or mental illness.

Although cortical neuroplasticity has been extensively researched in relation to the cortical representation of the limbs (discussed later), very few studies have been conducted in the orofacial region. Previous work has examined the effect of pulpal deafferentation on neurons in the trigeminal brainstem nuclei in cats (Hu, Dostrovsky et al. 1986; Hu, Woda et al. 1999) and rats (Kwan, Hu et al. 1993) and the effect of manipulations (e.g. removal, trimming) of the rodent vibrissae on neurons in these nuclei (Zucker and Welker 1969; Chiaia, Bennett-Clarke et al. 1992) and ventrobasal thalamus (Waite 1973b; Waite 1973a; Waite and Cragg 1982; Shosaku 1985; Review: Shosaku, Kayama et al. 1989). In the case of the cerebral cortex, neuroplastic alterations in the receptive fields of the face primary somatosensory cortex (Face-S1) have been described following vibrissal manipulations (Waite and Cragg 1982; Rema, Armstrong-James et al. 1998; Frostig

2006; Kerr, de Kock et al. 2007) and such manipulations have also been reported to induce neuroplastic changes in motor representations within the face primary motor cortex (Face-M1) (Franchi 2000a; Franchi 2000b; Megevand, Troncoso et al. 2009). Incisor extraction in the naked mole rat induces neuroplastic changes in Face-S1 receptive fields / somatosensory representations (Henry, Marasco et al. 2005) and a recent experiment in our laboratory (Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010) reveals that extraction of a mandibular incisor is associated with neuroplastic changes in the rat Face-M1 as well as Face-S1 motor representations. However, the possible neuroplastic changes in Face-M1 induced by molar extraction have not been explored.

The aim of the experiments outlined in this thesis was to determine if neuroplastic changes occur in the rat Face-M1 following extraction of maxillary molars. This experiment is the first to test for possible neuroplastic changes in the Face-M1 neuroplasticity following the extraction of maxillary molars. The knowledge obtained through this research will provide a framework for future studies focussed on possible Face-M1 neuroplasticity associated with oral rehabilitative approaches (e.g dental implants) and thus represents an important step in applying this knowledge for the benefit of patients with reduced oral sensorimotor proficiency.

1.2 Orofacial Somatosensory and Motor Pathways

The chief sensory nerve of the orofacial region is the trigeminal (V) nerve (Shankland 2000; Periut, Salanga et al. 2003; Bereiter, Hargreaves et al. 2008; Lund, Kolta et al. 2009). The V nerve also has a motor component that supplies the muscles of mastication and other supra-hyoid muscles (Shankland 2000; Shankland 2001; Periut, Salanga et al. 2003; Lund, Kolta et al. 2009). As the name indicates, there are three sensory branches of the V nerve, namely the Ophthalmic, Maxillary and Mandibular. These three sensory branches pass through the trigeminal ganglion (Sessle 1987; Periut, Salanga et al. 2003; Bereiter, Hargreaves et al. 2008; Lund, Kolta et al. 2009) which is similar to a dorsal root ganglion of a spinal nerve. It contains the primary cell bodies of the afferent trigeminal sensory nerve fibres. From here the fibres run to the V brainstem sensory nuclear complex. The sensory fibres include rapidly conducting large-diameter fibres and slowly conducting small-diameter fibres. Most of the large-diameter fibres end peripherally in low-threshold mechanoreceptors that respond to tactile or pressure stimuli and most of the slow small-diameter fibres respond to nociceptive stimuli. Apart from this, the mandibular nerve also carries large-diameter fibres that supply golgi tendon organs and muscle spindles of the muscles of the first embryonic arch (Sessle 2006). The motor component of the V nerve arises from the motor nucleus of V, by-passes the V ganglion and merges with the mandibular branch of V (Shankland 2001; Periut, Salanga et al. 2003; Bereiter, Hargreaves et al. 2008; Lund, Kolta et al. 2009).

The V Brainstem Nuclear Complex

The V brainstem nuclear complex includes the mesencephalic nucleus, the chief sensory nucleus, chief motor nucleus and spinal nucleus of V. The mesencephalic nucleus contains primary afferent neurons of the jaw muscle spindles and some

periodontal mechanoreceptors. From here, the proprioceptive impulses are transmitted to the V motor nucleus, or to adjacent nuclei (e.g. supratrigeminal nucleus and V subnucleus oralis) where they excite interneurons that are involved in craniofacial reflex functions (Cruccu, Iannetti et al. 2005; Kaas, Qi et al. 2006; Sessle 2006; Bereiter, Hargreaves et al. 2008; Matesz, Szekely et al. 2009). The chief sensory nucleus of V receives mainly low-threshold mechanosensitive input and the spinal nucleus of V receives these inputs plus most of the nociceptive and thermosensitive inputs. The spinal nucleus of V is subdivided into three subnuclei, namely oralis, interpolaris, and caudalis as shown in Fig 1 (Shankland 2000; Periut, Salanga et al. 2003; Sessle 2006; Bereiter, Hargreaves et al. 2008; Lund, Kolta et al. 2009). The subnucleus caudalis is continuous with the dorsal horn of the spinal cord and so is a laminated structure with 6 layers; layer 2 is also known as the substantia gelatinosa (Shankland 2000; Periut, Salanga et al. 2003; Sessle 2006; Bereiter, Hargreaves et al. 2008; Lund, Kolta et al. 2009).

Mechanosensitive neurons are present in all three subnuclei but nociceptive neurons are most concentrated in the subnucleus caudalis. Most of the low-threshold V mechanosensitive primary afferent nerves terminate in the rostral part of the V brainstem complex and in laminae III–VI of subnucleus caudalis; also, a few V nociceptive cutaneous and intra-oral afferents, including dental pulp afferents, terminate in the rostral components. However, most of the small-diameter V nociceptive afferents terminate in subnucleus caudalis, in its laminae I, and II (Sessle 2006; Bereiter, Hargreaves et al. 2008; Dostrovsky, Craig et al. 2008; Heinricher, Ingram et al. 2008; Willis Jr, Allan et al. 2008).

In addition to its predominant input from V nerve afferents, the V brainstem complex (especially its subnucleus caudalis) may also receive afferent inputs from the upper cervical nerves (Sessle 2006). The subnucleus caudalis also receives input from the Facial, Glossopharyngeal, Vagus and Hypoglossal nerves (Sessle 2006).

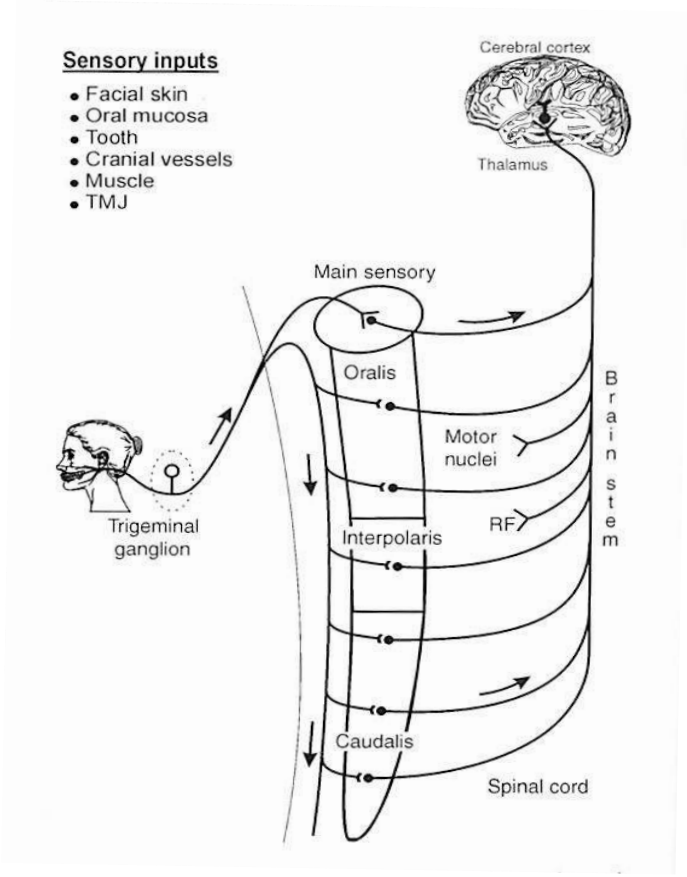

Fig 1: Chief sensory and spinal nuclei of the Trigeminal Nuclear complex (Sessle 2006)

The nuclei and subnuclei in the V brainstem complex each show somatotopic organization. In each, the neurons receiving mandibular afferents are located more dorsally and those that receive ophthalmic afferent inputs are located ventrally; afferents from the maxillary region terminate in between, and the oral and peri-oral structures are represented in the medial region (Sessle 2006; Bereiter, Hargreaves et al. 2008; Dostrovsky, Craig et al. 2008; Heinricher, Ingram et al. 2008; Willis Jr, Allan et al. 2008). In the subnucleus caudalis, this pattern shifts, and the peri-oral regions are represented in the rostral part of the subnucleus and the lateral regions of the face are represented in the caudal end; this somatotopic pattern in subnucleus caudalis is referred to as an 'onion-skin' arrangement (Sessle 2006; Bereiter, Hargreaves et al. 2008; Dostrovsky, Craig et al. 2008; Heinricher, Ingram et al. 2008; Willis Jr, Allan et al. 2008).

The Sensory Pathway

The sensory pathway begins from the receptors and nerve endings of the sensory nerve fibres of the V nerve and nerve impulses are conducted along the nerve fibres into the V brainstem sensory nuclear complex (Sessle 2006; Bereiter, Hargreaves et al. 2008; Kaas, Allan et al. 2008b). Relay neurons from the V brainstem complex project directly or indirectly to the thalamus (Sessle 2006; Bereiter, Hargreaves et al. 2008; Kaas, Allan et al. 2008b). Many of these second-order neurons have axons that cross over and ascend to the ventrobasal (ventroposterior in primates) nucleus of the thalamus. However, some second-order neurons may communicate with the reticular formation, cranial nerve motor nuclei or terminate intrinsically, and may act as interneurons. The ventrobasal thalamus is somatotopically arranged with most of the neurons projecting directly to the orofacial region (Face-S1) of the primary somatosensory cortex (S1) (Sessle 2006; Dostrovsky, Craig et al. 2008; Kaas, Allan et al. 2008b). The sensory signals that reach the ventrobasal nucleus of the thalamus are relayed through third-order neurons to the various regions of the cerebral cortex. The ventrobasal nucleus relays most of the sensory V brainstem input to the somatosensory cortex. The neurons in this nucleus have a small receptive field and are considered to be associated with sensory discrimination. However, the neurons in the medial thalamus have a wide receptive field and relay the sensory V brainstem input to cingulate cortex and are considered to be associated with the motivational aspect of the sensory stimuli. (Sessle 2006; Dostrovsky, Craig et al. 2008; Kaas, Allan et al. 2008b). In primates, cutaneous information from the thalamic ventroposterior nucleus is mainly transmitted to the Brodmann areas 3b and 1 of the S1, while information from muscle spindles is primarily relayed through the ventroposterior superior nucleus to the Brodmann areas 3a and 2 of the S1 (Kaas 2004).

The Motor Pathway

The motor pathway of interest begins in the orofacial region (Face-M1) of the primary motor cortex (M1). The Face-M1 receives input from afferents supplying superficial, deep orofacial tissues and the Face-S1 of both sides. This convergence of input contributes to the bilateral sensorimotor coordination in orofacial and masticatory movements (Sessle 2006). Many neurons in Face-M1 are output neurons that project as corticobulbar fibres to the brainstem. Based on the area of activation, these neurons synapse with motor neurons in the respective contralateral cranial nerve nuclei in the floor of the fourth ventricle of primates (Jenny and Saper 1987). However, in sub-primates, few such neurons synapse directly with motor neurons in the motor nuclei of the respective cranial nerves (Ohta, Ishizuka et al. 1989). Corticobulbar fibres from the Face-M1 and some other cortical areas descend through the internal capsule to form the cerebral peduncles (Jenny and Saper 1987). Some corticobulbar nerves in the cerebral peduncles reach the reticular formation and are considered to mediate voluntary control over the central pattern generators (CPGs) for chewing movements (Nozaki, Iriki et al. 1986) and swallowing (Jean, Amri et al. 1983). Intracortical Microstimulation (ICMS) studies in primates and sub-primates have shown that each muscle is represented multiple times within the M1, indicating that each output zone of the Face-M1 may control one of the many functions of the muscle (Sessle, Yao et al. 2005; Tandon, Kambi et al. 2008).

1.3 Somatosensory and Motor Cortex in Humans and Other Mammals

1.3.1 Methods Used to Study Cortical Organization

Many techniques have been used to study the organization of the somatosensory and motor cortices. Single neuron recordings, Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) are common methods

employed to map and locate the mechanoreceptive fields of the S1. ICMS, fMRI, PET, Electroencephalography (EEG), Magnetoencephalography (MEG) and Transcranial Magnetic Stimulation (TMS) are common techniques used to map the M1 (Hatsopoulos and Donoghue 2009).

Each technique has a different temporal and spatial resolution and a different level of invasiveness. The temporal resolution refers to the time frame (i.e. milliseconds, seconds, hours, months etc.) at which the technique can identify a change and the spatial resolution is the ability of the technique to locate (i.e. µm, mm) the precise location of any observed neuronal activity. For example, ICMS has a good spatial resolution and can detect neuronal activity within 500µm from the point of stimulation (Asanuma, Stoney et al. 1968; Stoney, Thompson et al. 1968) whereas fMRI has poor spatial resolution and can only detect gross changes in activity patterns of the cortex.

Single neuron recording techniques use microelectrodes to monitor the electrophysiological activity of a single or multiple nerve cells. E.g. spontaneous activity, movement related discharge or responses evoked by peripheral stimulation. It has been used in animals to study S1 receptive fields (Stojic, Lane et al. 2000; Toda and Taoka 2001) and M1 efferent zones (Gu, Staines et al. 1999; Wang, Chan et al. 2010).

fMRI is a non-invasive technique that can be used to study the somatosensory, motor and other cortical regions during function. The major advantage of this technique is that neuronal function can be observed dynamically in more than one cortical region. fMRI is one of the most versatile techniques with good spatiotemporal resolution and minimal invasiveness. This technique has been used in many studies to investigate changes in the cortical organization in rats, primates and humans (Review:Darian-Smith, Allan et al. 2008; Nudo, Barbay et al. 2009; Weber, Fliessbach et al. 2009).

PET is a nuclear medicine-imaging technique which produces a three-dimensional image or map of functional processes in the body. Images of metabolic activity are reconstructed by computer analysis aided by a Computed Tomography (CT) scan. It is a minimally-invasive technique and is used to study the functional changes of degenerative diseases in humans (Tanaka, Ohyagi et al. 2005; Hou, Hong et al. 2010).

ICMS has excellent spatial and temporal resolution but is relatively more invasive. Hence, it is the method of choice to map the motor cortex in animals (Arthur W. Toga 2002; Cheney, Arthur et al. 2002). The major advantages of using this technique include the improved spatial resolution due to the small size of the microelectrode and stimulation parameters used, and the ability to record the Motor Evoked Potentials (MEPs) of a specific group of muscles evoked by ICMS of a few neurons (Buys, Lemon et al. 1986; Fetz, Cheney et al. 1989; Sanes and Donoghue 2000; Arthur W. Toga 2002; Cheney, Arthur et al. 2002). ICMS was used in this project because the effect of stimulation on the cortical activity could be studied with considerable spatial and temporal precision. Microstimulation is particularly powerful because ICMS allows investigators to measure the behavioral effects of an increase in the output signal of a group of physiologically characterized neurons. A detailed description of the protocol is provided under Materials and Methods.

TMS is the popular method used to record MEPs in humans. Even though it has relatively poor spatiotemporal resolution, it is a noninvasive technique that can produce cortical stimulation (Diehl, Salek-haddadi et al. 2003; Shibasaki 2008). Many studies have also used TMS to induce or study neuroplastic changes in the cortex (Butefisch, Khurana et al. 2004; Butler and Wolf 2007; Boros, Poreisz et al. 2008; Baad-Hansen, Blicher et al. 2009).

EEG and MEG measure the flow of electric signals in the cortex. They have good temporal resolution but relatively poor spatial resolution. They have been used in conjunction with fMRI for studying cortical organization and function in humans (Cohen, Halgren et al. 2009; Lopes da Silva, GonÁalves et al. 2009).

1.3.2 Somatosensory and Motor Cortex in Humans

"The sensorimotor cortex is that part of the cerebral cortex which is directly concerned with movement of the body and perception of stimuli (especially related to touch, pressure, temperature and pain)" (Gilbert, Dobyns et al. 2005; Nudo, Frost et al. 2007; Qi, Preuss et al. 2008; Johansson, Flanagan et al. 2009; Moore, Noudoost et al. 2009).The various regions of the sensorimotor cortex are depicted in Fig 2.

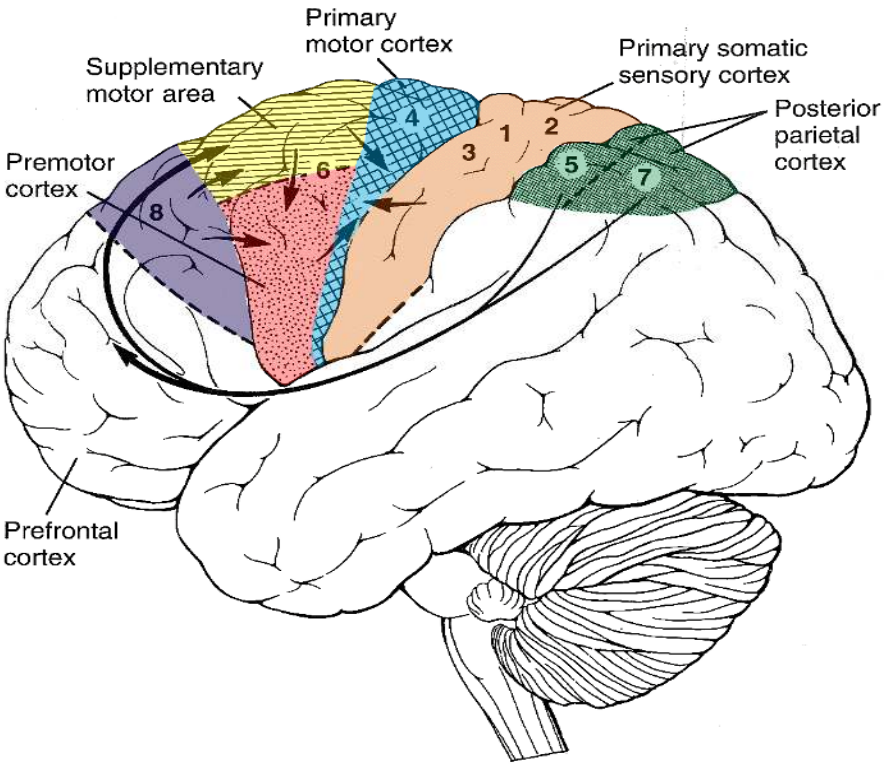

Fig 2: Lateral surface of the brain showing sensory and motor areas.(Chouinard and Paus 2006).

The M1 is located in the pre-central gyrus (Brodmann area 4). Muscles or movements are represented somatotopically in the MI as shown in Fig 3. The area of representation for each particular muscle may reflect the fineness of movement in motor control (Donoghue and Sanes 1994; Donoghue, Neil et al. 2001; Wise, Neil et al. 2001; Kaas, Stepniewska et al. 2002; Nudo, Frost et al. 2007). In humans, the mouth, tongue and the hands have very large representations. Apart from the M1, other cortical regions involved in motor function are collectively termed the secondary motor areas; these regions include the posterior parietal cortex (Brodmann area 5 and 7), the premotor cortex (Brodmann area 8), and the supplementary motor area (SMA) (Brodmann area 6)(Donoghue and Sanes 1994; Donoghue, Neil et al. 2001; Wise, Neil et al. 2001; Kaas, Stepniewska et al. 2002; Nudo, Frost et al. 2007). The posterior parietal cortex is involved in transforming visual information into motor commands. The posterior parietal area communicates with the premotor cortex and the SMA. The premotor cortex is involved in the sensory guidance of movement, and controls muscles of the trunk, muscles of facial expression etc. (Donoghue and Sanes 1994; Donoghue, Neil et al. 2001; Wise, Neil et al. 2001; Dum and Strick 2002; Kaas, Stepniewska et al. 2002; Review: Morecraft, Stilwell-Morecraft et al. 2004; Gong, DeCuypere et al. 2005; Nudo, Frost et al. 2007). The SMA is divided into a caudal part that projects to the M1 and a rostral part that receives communication from the premotor area. The SMA is involved in the planning of complex movements with bilateral coordination (Donoghue and Sanes 1994).

The somatosensory cortex comprises the S1, the secondary somatosensory cortex (S2) and the parietal ventral (PV) area (Kaas 2004; Reep, Sarko et al. 2007; Erzurumlu, Allan et al. 2008; Qi, Preuss et al. 2008; Hsiao, Fitzgerald et al. 2009; Villanueva, Monconduit et al. 2009). The S1 is also somatotopically organized as shown in Fig 4. In humans, the S1 includes Brodmann's areas 1, 2 and 3. Area 3 is

divided into 2 parallel strips, 3a and 3b, with mirrored somatotopic representations. Areas 3b and 1 receive primarily cutaneous information from the thalamic ventroposterior nucleus, while the thalamic ventroposterior superior nucleus provides areas 3a and 2 with information from muscle receptors, joints, teeth etc. (Kaas 2004; Kaas and Larry 2004; Reep, Sarko et al. 2007; Erzurumlu, Allan et al. 2008; Qi, Preuss et al. 2008; Hsiao, Fitzgerald et al. 2009; Villanueva, Monconduit et al. 2009). Each of the three areas show somatotopic representation of the entire body wherein, the foot, leg, trunk, forelimbs, and face are represented in a medial to lateral arrangement (Kaas and Larry 2004; Reep, Sarko et al. 2007; Erzurumlu, Allan et al. 2008; Qi, Preuss et al. 2008; Hsiao, Fitzgerald et al. 2009; Villanueva, Monconduit et al. 2009). The S1 also projects to the posterior parietal cortex (Brodmann areas 5,7) and to the M1 .

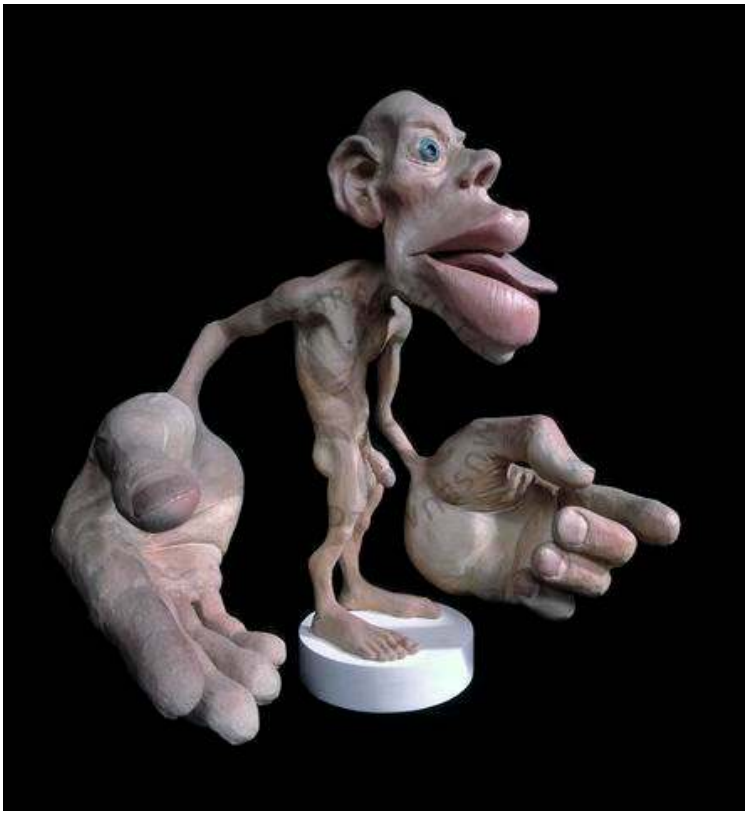

Fig 3: Motor Homunculus. The ‘Little Man’ models in the Natural History Museum ©.

The S2 is located posterior to S1, and processes information from S1 and relays it to the PV area. Both S2 and the PV area are somatotopically arranged and communicate with areas 3a, 3b, 1 and S2, PV of the contralateral hemisphere. (Kaas and Larry 2004; Reep, Sarko et al. 2007; Erzurumlu, Allan et al. 2008; Qi, Preuss et al. 2008; Hsiao, Fitzgerald et al. 2009; Villanueva, Monconduit et al. 2009). The somatosensory and motor representations of the human body in S1 and M1 are arranged according to the sensitivity and the fine motor control of each part and is illustrated as the homunculus. The homunculus has a grossly enlarged face and hands compared to the torso and proximal limbs (Figs 3,4).

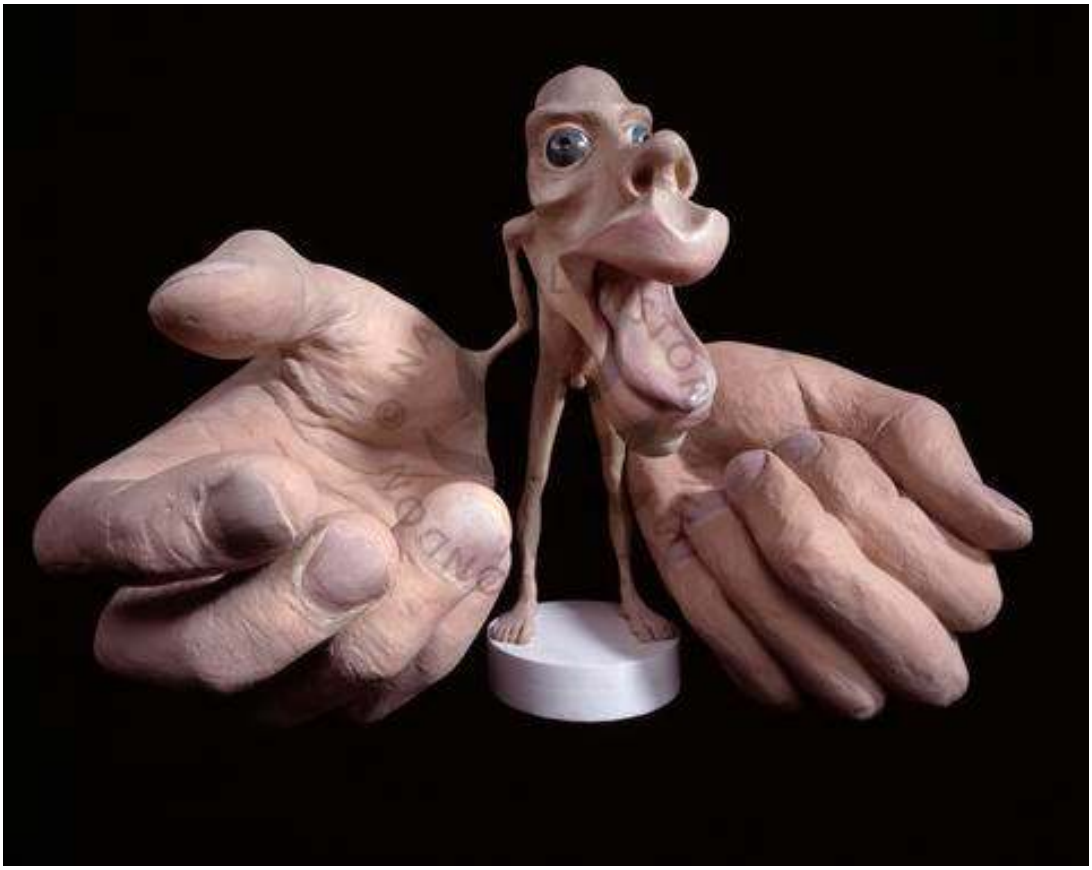

Fig 4: Sensory Homunculus. The 'Little Man' models in the Natural History Museum ©.

1.3.3 Somatosensory and Motor Cortex in Non-human Primates and Sub-primates

The rat is one of the most commonly used sub-primate animal models in neuroscience (Manger, Cort et al. 2008). A brief comparison and evolutionary significance of the cytoarchitectonic features of other non-human primates and sub-primates have been included in this section. Since, the present study has been performed on rat models, the cytoarchitectonic features of the rat sensorimotor cortex have been described here in greater detail.

Organization of the M1 in Non-human Primates and Sub-primates

The M1 in monkeys closely resembles the human brain in cytoarchitecture. It is located in the pre-central gyrus and is somatotopically organized. It lacks a prominent granular layer and is referred to as agranular cortex (Huntley and Jones 1991; Burish, Stepniewska et al. 2008).

Sub-primates like cats and rats do not have a central sulcus (Donoghue and Wise 1982; Ghosh 1997). However, the motor cortex of cat has three sub-divisions that resemble the premotor cortex of non-human primates (Ghosh 1997).

ICMS studies in rats have helped clarify the organization (and neuroplasticity) of Limb-M1 (Karl, Sacrey et al. 2008; Maggiolini, Viaro et al. 2008). ICMS studies have shown the detailed somatotopic organization of Limb-M1 in rats with multiple representation for each muscle. Similarly, studies using single neuron recordings have revealed proprioceptive input from the peripheral tissues to the Limb-M1 (Gu, Staines et al. 1999).

ICMS mapping of the rat motor cortex in our laboratory (Sessle, Adachi et al. 2007; Adachi, Murray et al. 2008; Avivi-Arber, Lee et al. 2010) revealed a topographic organization of the orofacial musculature, consistent with earlier

findings (Gioanni and Lamarche 1985; Neafsey, Bold et al. 1986; Ptitsyna, Vol'nova et al. 1989; Sanes and Donoghue 2000).

Within the Face-M1, the tongue and jaw muscles have a bilateral representation, but the contralateral responses are usually 3-4 ms shorter in latency than the ipsilateral responses. Also, simple motor activity as well as semiautomatic rhythmic motor activity could be elicited from different areas of the Face-M1, with multiple representations for each movement (muscle) (Lemon, Griffiths et al. 2004; Haiss and Schwarz 2005; Nudo, Frost et al. 2007; Schieber, Andrew et al. 2007; Sanes and John 2008; Avivi-Arber, Lee et al. 2010). Several single neuron labeling studies have revealed the motor cortex projections to other parts of the CNS in rats (Veinante, Lavallee et al. 2000; Veinante and Deschenes 2003; Chakrabarti and Alloway 2006). Similarly, lesioning studies on the Face-M1 have shown inter-hemispheric interactions that regulate motor control (Maggiolini, Veronesi et al. 2007).

Organization of the S1 in Non-human Primates and Sub-primates

The S1 in monkeys is similar to humans with four distinct cytoarchitectonic areas located posterior to the central sulcus (Huntley and Jones 1991; Burish, Stepniewska et al. 2008). However, cats lack a central sulcus but the S1 can be histologically distinguished from the M1 by the presence of a thin lamina IV layer and overall reduction in cortex thickness. In rats, the S1 can be histologically identified by the presence of a granular layer. However, distinct cytoarchitectonic divisions are absent within the S1 of rats. Instead, the S1 is divided based on the presence of a dense granular layer into a dense ‘granular cortex’ and a less dense ‘dysgranular cortex’ (Donoghue and Wise 1982; Woolsey and Larry 2009). Overlapping of S1 and the respective M1 areas have been reported for the hindlimb and parts of the forelimb in sub-primates (Gioanni and Lamarche 1985; Neafsey,

Bold et al. 1986; Remple, Henry et al. 2003). Several single neuron recordings and lesioning techniques have shown that Limb-S1 plays an important role in limb movement by processing information regarding position, force, direction and velocity of movement in non-human primates and sub-primates (Shanks, Pearson et al. 1985; Erzurumlu, Allan et al. 2008; Hsiao, Fitzgerald et al. 2009).

The functional morphology of S1 in the rat brain shows a massive orofacial representation. The S1 in rats has a larger area of representation for the teeth, vibrissae and paws than for other parts of the body (Chapin and Lin 1984; Sanderson, Welker et al. 1984; Catania and Remple 2002; Remple, Henry et al. 2003; Henry, Remple et al. 2006). The Face-S1 has individual cortical areas representing the incisors and tongue, probably because they are key components in sensorimotor function of rats (Fig 5) (Catania and Remple 2002).

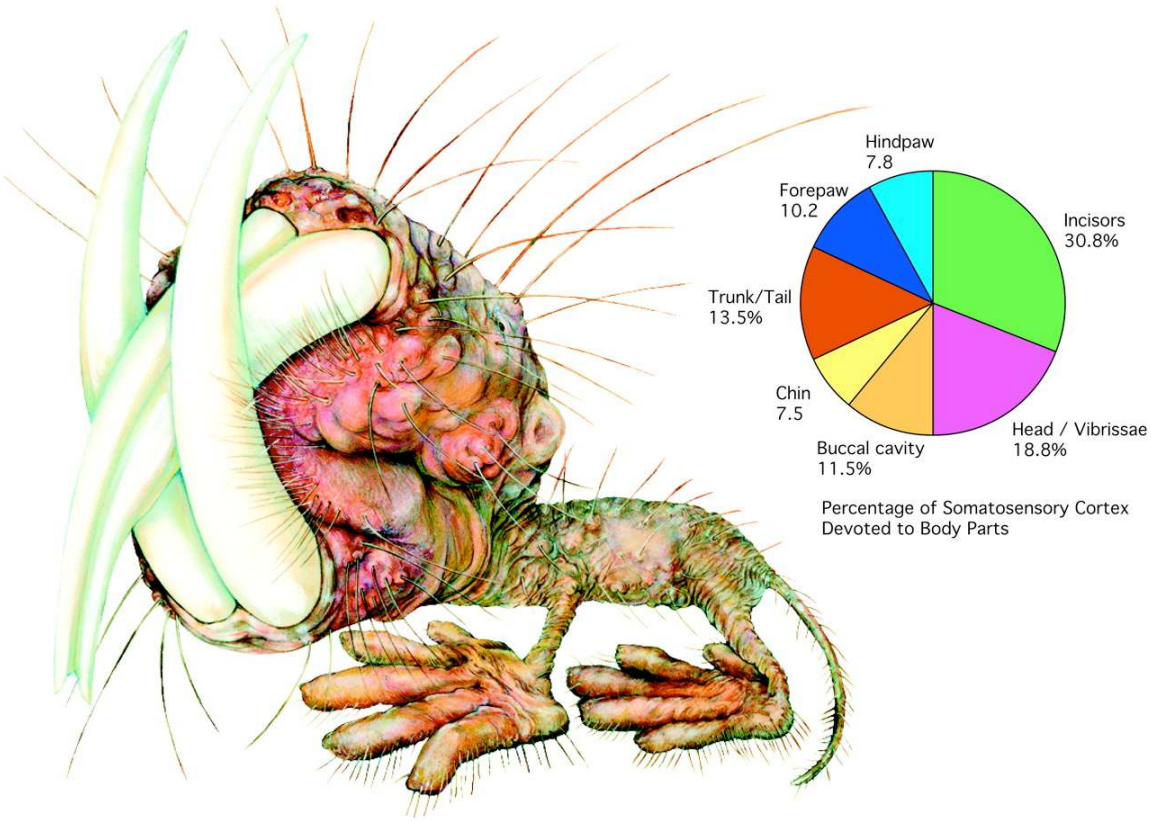

Fig 5: Cortical representation of a rat (Catania and Remple 2002).

Overlapping representation of the buccal pad, lower incisors and the lower jaw of the Face-S1 with distal digits of the forelimb in the Limb-S1 has also been observed (Wise and Jones 1977; Catania and Remple 2002; Remple, Henry et al. 2003; Henry, Remple et al. 2006a).

The Face-S1 also contains pyramidal cells which may give rise to motor fibres (Wise and Jones 1977; Zhang and Sasamoto 1990). ICMS-evoked motor responses have been observed in the Face-S1 in cats (Hiraba, Yamaguchi et al. 1997; Hiraba and Sato 2004), rabbits (Lund and Dellow 1971; Lund, Sasamoto et al. 1984), rats (Sasamoto, Zhang et al. 1990; Zhang and Sasamoto 1990; Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010) and monkeys (Huang, Hiraba et al. 1989). The role of Face-S1 in the motor control of the orofacial muscles has also been reported in monkeys (Lin, Murray et al. 1994a; Lin and Sessle 1994c; Keller, Weintraub et al. 1996; Nudo, Friel et al. 2000; Kaas, Qi et al. 2006; Iyengar, Qi et al. 2007). Similarly, impairment of orofacial motor function following cold block of the Face-S1 (Lin, Murray et al. 1993; Martin, Murray et al. 1997; Yao, Yamamura et al. 2002) has also been reported.

1.4 Neuroplasticity

Neuroplasticity can be expressed either physiologically or morphologically (Bavelier, Neville et al. 2002; Butefisch 2006; Kingham, Terenghi et al. 2009; Smith and Larry 2009). Physiological neuroplasticity involves the alteration in function of existing neurons or neuronal pathways and reactivation of previously dormant pathways. The micromolecular interactions across many synaptic junctions characterise the nature and the extent of this neuroplasticity (Brecht and Schmitz 2008). Morphological or structural neuroplasticity refers to the formation of new connections between different areas in the CNS. A neuroplastic change observed in the cerebral cortex is termed cortical neuroplasticity (Bavelier, Neville et al. 2002; Butefisch 2006; Kingham, Terenghi et al. 2009; Smith and Larry 2009).

Previously, neuroplasticity was thought to be limited to changes in the neuronal networks and/or their connections (synapses). Recently, glial cells have been shown to participate in neuroplastic changes associated with the central sensitization of the V brain stem nuclei (Chiang, Wang et al. 2007; Xie, Zhang et al. 2007; Okada-Ogawa, Suzuki et al. 2009).

At the molecular level, many neurotransmitters and neuromodulators that regulate neuroplastic changes have been identified. For example, pluripotent regulators of neuron-astrocyte interactions such as ephrinA-EphA are reported to mediate rapid structural and functional neuroplasticity in the CNS (Nestor, Mok et al. 2007). Also, chemicals such as endocannabinoids (Kyriakatos and El Manira 2007; Vigh and von Gersdorff 2007; Lovinger 2008), nitric oxide (Kyriakatos and El Manira 2007), androgens (Morris, Jordan et al. 2008) and steroids (Meitzen, Moore et al. 2007) play a significant role in neuroplasticity.

1.4.1 Functional Neuroplasticity

As noted above, physiological neuroplasticity involves a change in the function of existing neurons or neuronal pathways. This may include reactivation of previously dormant neurons or pathways and or shift in control over a specific part of the body. Functional neuroplasticity involves changes in the micromolecular interaction between existing synapses. Shouval and Castellani (2002) reported that the most common synaptic receptors involved in neuroplasticity include the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor (also known as AMPA receptor, AMPAR, or quisqualate receptor) and the N-methyl D-Aspartate receptor (NMDAR) channel (Malenka 1991; Clarke, Ballyk et al. 1997; Huntley, Vickers et al. 1997; Benke, Luthi et al. 1998; Lauri, Delany et al. 2001; Shouval, Castellani et al. 2002; Schwenkreis, Maier et al. 2003; Palmer, Lim et al. 2005). The AMPAR contributes to the majority of the depolarizing current in an excitatory

synapse. The NMDAR on the other hand, is involved in the initiation of synaptic plasticity (Stevens, Tonegawa et al. 1994; Huntley, Vickers et al. 1997; Schwenkreis, Maier et al. 2003). Sometimes, the neuroplasticity may occur independent of the NMDAR; in such instances, other presynaptic receptors such as Kainate or metabotropic receptors are involved (Clarke, Ballyk et al. 1997; Lauri, Delany et al. 2001).

The magnitude of the post-synaptic response to stimulation is known as the synaptic strength (Stevens, Tonegawa et al. 1994; Costa-Mattioli, Sonenberg et al. 2008; Lovinger 2008; Lovinger and John 2008; Martin and Larry 2009; Raghavachari, Lisman et al. 2009). Synaptic strength can modulate the duration of the neuroplasticity from milliseconds (short-term) to hours to weeks (long-term) and can be increased or decreased by altering the level of post-synaptic depolarization (Stevens, Tonegawa et al. 1994; Costa-Mattioli, Sonenberg et al. 2008; Lovinger 2008; Lovinger and John 2008; Martin and Larry 2009; Raghavachari, Lisman et al. 2009).

According to Stevens, Tonegawa et al. (1994), the methods of modulating synaptic strength include:

1. Change in the quantity of glutamate release into the synaptic cleft: the greater the quantity of release, the greater the strength of the neuroplasticity.
2. Change (Insertion / Removal) in the number of AMPARs. Increase in receptor number increases the synaptic potential.
3. Phosporylation / Dephosporylation-induced change in AMPARs conductance. The AMPAR are modified to pass more current (keep the channels opened) to allow for greater depolarization and effectively lead to stronger neuroplasticity.

Other forms of functional neuroplasticity include diaschisis and unmasking and cross-modal plasticity. Diaschisis is the reversible depression of functions in a damaged area (Gonzalez-Aguado, Marti-Fabregas et al. 2000). It is considered to

play an important role in the plasticity, recovery and rehabilitation of stroke patients (Lee and van Donkelaar 1995; Chen, Cohen et al. 2002). On the other hand, unmasking is the reactivation of latent or redundant circuits. Unmasking of latent synapses can be due to several mechanisms that include increased excitatory neurotransmitter release, increased density of postsynaptic receptors, changes in membrane conductance that enhance the effects of weak or distant inputs, displacement of presynaptic elements to a more favorable site, decreased inhibitory inputs or removal of inhibition of excitatory inputs (unmasking excitation)(Kaas 1991). Cross-modal neuroplasticity is another form of functional neuroplasticity wherein the functional area responsive to one sensory input becomes responsive to another sensory input. Cross-modal neuroplasticity has been most extensively investigated following loss of vision (Chen, Cohen et al. 2002).

1.4.2 Structural Neuroplasticity

Structural neuroplasticity can occur due to synaptogenesis or axon sprouting (Duffau 2006; Chapleau, Pozzo-Miller et al. 2008; Hawkins and John 2008; Bourne, Harris et al. 2009; Ferrari, Goda et al. 2009; Theodosis and Larry 2009). Synaptogenesis refers to the formation of new synapses to enable the formation of newer circuits. Synaptogenesis is closely related to neuroplasticity in newly forming axons (Muller, Nikonenko et al. 2002; Lamprecht and LeDoux 2004; Stoeckli and Zou 2009). Synaptogenesis has been studied in the V system, for example in the V brainstem complex following deafferentation of the infraorbital nerve and related structures (Henderson, Woolsey et al. 1992; Klein, Blaker et al. 1992; Renehan, Crissman et al. 1994; Golden, Demaro et al. 1997; Shetty, Shoykhet et al. 2003).

Axonal sprouting is a form of structural neuroplasticity where there is regeneration of axons of injured but alive nerve cells. The newly formed sprouts emerge to

connect with other neighboring neurons (Kaas 1991). Axonal sprouting has also been observed in the V brainstem complex following deafferentation of the infraorbital nerve (Chiaia, Allen et al. 1988; Henderson, Woolsey et al. 1992; Klein, Blaker et al. 1992; Chiaia, Rhoades et al. 1995; De Riu, Russo et al. 2008) .

1.4.3 Short-Term and Long-Term Neuroplasticity

Irrespective of the structural or functional changes, neuroplasticity can also be classified, based on the duration of its expression, as short-term neuroplasticity and long-term neuroplasticity.

Short-term Neuroplasticity

Short-term neuroplasticity usually ranges from a few milliseconds to around 5 seconds (Zucker 1989; Nicoll and Schmitz 2005; Neher 2007). Short-term neuroplasticity may either be expressed as paired-pulse neuroplasticity or post-tetanic(PTP) potentiation and longer-lasting short-term neuroplasticity.

Paired-Pulse Facilitation and Depression:

These are produced by the interaction of two adjacent impulses. “When two stimuli are delivered within a short interval (less than 20 ms), the response to the second stimulus can be either enhanced or depressed relative to the response to the first stimulus” (Citri and Malenka 2008). However, their effects (facilitation or depression) depend on the recent history of activation of the synapse (Citri and Malenka 2008).

Facilitation and Depression Following Trains of Stimuli:

Repetitive or tetanic stimulation of synapses with prolonged (approximately 200 ms to 5 seconds) trains of stimulation applied at high frequencies (10–200 Hz) can

produce longer-lasting forms of short-term neuroplasticity (Citri and Malenka 2008). Such repetitive activations can lead to facilitation or depression of certain synapses that can last for several seconds.

Long-term Neuroplasticity

Long-term neuroplasticity denotes neuroplastic changes that last for hours to years. Experimental support confirming the presence of such long-lasting, activity-dependent changes in synaptic strength was lacking until the early 1970s when Bliss and Lomo (1973) reported that "repetitive activation of excitatory synapses in the hippocampus caused a potentiation of synaptic strength that could last for hours or even days". Longer-lasting forms of neuroplasticity are commonly associated with structural and functional changes like axonal sprouting, unmasking, synaptogenesis and diaschisis. Long-term neuroplasticity may either be long-term potentiation (LTP) or long-term Depression (LTD). Most synapses that exhibit LTP also express one or more forms of LTD. The mechanisms of LTP and LTD vary depending way the synapse functions in a network (Citri and Malenka 2008).

LTP

This long-lasting enhancement of synaptic transmission discovered by Bliss and Lomo (1973) is considered to be the potential mechanism for learning and memory formation. LTP has been reported to occur through increased glutamate release, activation of silent synapses etc. (Isaac, Nicoll et al. 1995; Isaac 2003). The most common mechanism involves an increase in the single channel conductance (Benke, Luthi et al. 1998; Teyler, Neil et al. 2001; Allan et al.2008; Crair, Shah et al. 2009; Doherty, Fitzjohn et al. 2009; Sweatt and Larry 2009) or an increase in the number (Benke, Luthi et al. 1998; Teyler, Neil et al. 2001; Allan et al.2008; Crair, Shah et al. 2009; Doherty, Fitzjohn et al. 2009; Sweatt and Larry 2009) of post-synaptic AMPA receptors.

LTD:

LTD is a long-lasting reduction in synaptic transmission. LTD along with LTP is believed to be involved in the formation and regulation of memory. LTD is a Ca^{2+}-dependent process that involves hippocalcin (Palmer, Lim et al. 2005). Hippocalcin is a member of the neuronal calcium sensor (NCS) family that acts as the calcium sensor in the cascade that couples NMDAR activation with the internalization of the AMPAR.

Homeostatic Neuroplasticity and Metaplasticity

Recently, additional forms of synaptic plasticity have been identified namely, homeostatic neuroplasticity and metaplasticity (Citri and Malenka 2008). The most common form of homeostatic neuroplasticity is 'synaptic scaling', where the strengths of all the synapses in a cell are adjusted in response to prolonged changes in activity. For example, prolonged decreases in the activity may cause a scaling up of all the synaptic strengths whereas prolonged increases produce a scaling down of synaptic strengths. Although homeostatic neuroplasticity is slower than LTP or LTD, it is important for the development of neural circuits.

Metaplasticity is a 'higher-order' form of synaptic plasticity that changes the sensitivity of a cell to subsequent synaptic plasticity. In other words, metaplasticity is the 'plasticity of plasticity'. For example, repeated stimulation of the CA1 of the hippocampus produces prolonged increases in sensitivity of the CA1 to short-term plasticity (Malenka 1991; Abraham and Bear 1996; Abraham, Mason-Parker et al. 2001).

1.4.4 Neuroplasticity of Limb Somatosensory and Motor Cortex

The literature on cortical representation of the limbs is more extensive and complete in comparison with the orofacial region. Cortical mapping studies have identified that the neuroplastic capacity of Limb-M1 and Limb-S1 may reflect dynamic, adaptive or maladaptive cortical mechanisms related to motor learning and memory (Recanzone, Merzenich et al. 1992; Blake, Byl et al. 2002) Both Limb-S1 and Limb-M1 demonstrate also significant neuroplasticity subsequent to changes in their afferent or efferent pathway. For example, the somatotopic organization of Limb-M1 and Limb-S1 can be changed by altering the sensory inputs as a result of injury to the peripheral nerves or changes in behavioural sensory experience, and the organizational changes can be transient or long-lasting depending on the type of alteration to the sensory inputs (Garraghty and Kaas 1991) (Nudo and Milliken 1996; Nudo, Plautz et al. 2001).

1.4.4.1 Neuroplasticity of Limb Somatosensory Cortex

Humans

Numerous studies have been conducted in humans to study Limb-S1 neuroplasticity. e.g. fMRI analysis of chronic regional pain syndrome (Maihofner, Baron et al. 2007), cortical deafferentation (Waberski, Dieckhofer et al. 2007), upper-arm amputation (Elbert, Flor et al (1994). An increase in the somatosensory evoked potential (SEP) has been reported to occur in the Limb-S1 following limb deafferentation (Tinazzi, Zanette et al. 1997; Murphy, Taylor et al. 2003; Rosso, Aglioti et al. 2003). This implies that there is an increase in the sensitivity of the affected area. This change can be utilized in designing myoelectric devices. TMS can also increase the excitability of the Limb-S1 (Ogawa, Ukai et al. 2004; Ragert, Becker et al. 2004; Dieckhofer, Anne et al. 2006; ; Roy, Norton et al. 2007). TMS is gaining therapeutic significance in improving patients' adaptability. However,

direct current stimulation reduces the excitability of Limb-S1 (Dieckhofer, Anne et al. 2006; Matsunaga, Nitsche et al. 2004). This could be of use in patients with epilepsy and neuralgia. Many reviews have described the role of neuroplasticity in phantom limb pain, hemiplegia and dystonia in humans (Nudo, Plautz et al. 2001; Butler and Wolf 2003; Cauraugh and Summers 2005; Quartarone, Siebner et al. 2006; Forrester, Wheaton et al. 2008; Masiero and Carraro 2008; Di Pino, Guglielmelli et al. 2009; Hinkley, Webster et al. 2009; Oujamaa, Relave et al. 2009).

Non-human Primates

Expansion of the Limb-S1 representation has been reported following peripheral nerve injury (Garraghty and Kaas 1991; Blake, Strata et al. 2005; Churchill and Garraghty 2006; Garraghty, Arnold et al. 2006), peripheral deafferentation (amputation of middle and distal phalanges) (Xerri, Coq et al. 1996; Jones, Woods et al. 2002) or partial spinal deafferentation (Jain, Qi et al. 2008) in monkeys.

Learning can also be associated with neuroplasticity of the Limb-S1. For example, Blake, Strata et al (2005) demonstrated increased Limb-S1 excitability following coincident inputs delivered to two digits in monkeys. Similarly, Xerri, Merzinich et al (1999) have observed refinements in the cutaneous representation in 3b of Limb-S1 following retrieval exercise training. Also, Limb-S1 may undergo complex reorganization and expansion following limb-training (Recanzone, Merzenich et al. 1992a; Recanzone, Merzenich et al. 1992b; Recanzone, Merzenich et al. 1992c; Xerri, Merzenich et al. 1998; Xerri, Merzenich et al. 1999) and limb amputation (Merzenich, Nelson et al. 1984; Allard, Clark et al. 1991).

Sub-primates

Many neuroplasticity studies have been conducted on the Limb-S1 of sub-primates (Spenger, Josephson et al. 2000; Coq and Xerri 2001; Moxon, Hale et al. 2008). Reorganization of the S1 has been reported following forelimb deafferentation in rats (Pearson, Li et al. 1999; Guenot, Bullier et al. 2002; Bowlus, Lane et al. 2003; Pearson, Li et al. 2003; Endo, Spenger et al. 2007; Wu, Lauschke et al. 2009). Limb amputation can produce an expansion of the Limb-S1 in rats (Dawson and Killackey 1987; Bowlus, Lane et al. 2003; Pluto, Lane et al. 2003; Pluto, Chiaia et al. 2005; Lane, Pluto et al. 2008). However, reorganization of the Limb-S1 can occur following peripheral deafferentation (Wall and Cusick 1984; Kudryashov and Kudryashova 2001; Jung and Shin 2002; Pearson, Li et al. 2003; Pawela, Biswal et al. 2009). Interestingly, the patterns of neuroplastic changes that occur in the S1 cannot be accurately predicted. It seems that expansion in cortical representation may occur when there is partial peripheral deafferentation wherein the S1 continues to receive residual inputs from adjacent peripheral areas whereas shrinkage of the cortical representation may occur following complete deafferentation of a peripheral structure wherein the functional zone in the S1 cannot continue to obtain residual inputs from adjacent peripheral structures (Wall and Cusick 1984; Wall, Xu et al. 2002).

1.4.4.2 Neuroplasticity of Limb Motor Cortex

Humans

Non-invasive human studies have reported on neuroplasticity of Limb-M1 in patients undergoing mirror therapy (Fukumura, Sugawara et al. 2007), and in patients with multiple sclerosis (Mainero, Pantano et al. 2006; Wang and Hier 2007; Castellano and White 2008; Prakash, Snook et al. 2009) or recovering from hemiparesis (Takeda, Gomi et al. 2007). Many studies have also examined the role of neuroplasticity in M1 in the recovery of hemiplegic patients (Nudo, Plautz et al.

2001; Cauraugh and Summers 2005; Forrester, Wheaton et al. 2008; Masiero and Carraro 2008; Oujamaa, Relave et al. 2009). TMS has been used to induce neuroplasticity to enhance motor training (Butler and Wolf 2003; Butler and Wolf 2007; Ameli, Grefkes et al. 2009; Makin, Holmes et al. 2009; Takeuchi, Tada et al. 2009). TMS has also been used in the treatment of focal hand dystonia (Butefisch, Khurana et al. 2004; Abarca, Van Steenberghe et al. 2006; Beck, Richardson et al. 2008; Machado, Bittencourt et al. 2008; Schabrun, Stinear et al. 2009). Changes in peripheral sensory input can also produce neuroplastic changes in the M1. Excitability of the Limb-M1 has been reported to increase following peripheral deafferentation (Calancie, Alexeeva et al. 1999; Roy, Norton et al. 2007; Kofler, Valls-Sole et al. 2008; Liang, Murakami et al. 2008; Nardone, Golaszewski et al. 2008; Saturno, Bonato et al. 2008). Similarly, an increase in excitability of M1 may occur following limb amputation (Karl, Birbaumer et al. 2001; Mercier, Reilly et al. 2006; Reilly, Mercier et al. 2006; Gagne, Reilly et al. 2009).

Non-human primates

Many studies have reported on neuroplastic changes in motor representations in the Limb-M1 of non-human primates (Nudo and Milliken 1996a; Nudo, Milliken et al. 1996b; Barbay, Plautz et al. 2006; Eisner-Janowicz, Barbay et al. 2008). For example, an increase in excitability of the Limb-M1 occurs following peripheral deafferentation. Cross-modal representation of intact muscles has been reported following limb amputation (Schieber and Deuel 1997; Wu and Kaas 1999; Qi, Stepniewska et al. 2000; Karl, Birbaumer et al. 2001; Kaas and Qi 2004; Mercier, Reilly et al. 2006; Reilly, Mercier et al. 2006; Gagne, Reilly et al. 2009). Extensive reorganization with expansion of the Limb-M1 has been reported to occur following learned limb movements in monkeys (Brinkman and Porter 1983; Pavlides, Miyashita et al. 1993; Nudo, Milliken et al. 1996b; Liu and Rouiller 1999; Barbay, Plautz et al. 2006).

Sub-primates

Sub-primates have also been used to study neuroplasticity in the Limb-M1. For example, experimental lesions of the Limb-M1 have produced expansion of the contralateral Limb-M1 (Vol'nova and Lenkov 1982; Ptitsyna, Vol'nova et al. 1988; Ptitsyna, Vol'nova et al. 1989). Accelerated recovery and expansion of the infarcted Limb-M1 following TMS has been reported in rats (Bolay, Gursoy-Ozdemir et al. 2000; Farkas, Racekova et al. 2003; Mei, Liu et al. 2006; Zhang, Mei et al. 2007). Expansion was also observed following movement suppression (Maggiolini, Viaro et al. 2008) and repeated ICMS stimulation (Donoghue and Sanes 1988; Nudo, Jenkins et al. 1990; Sanes, Wang et al. 1992) and following trained movements. However, shrinkage of the Limb-M1 produced by cortical lesions has been reported (Piecharka, Kleim et al. 2005; Adkins, Hsu et al. 2008). Functionally, expansion in cortical representation may indicate increased motor control whereas shrinkage may indicate decreased motor control. The magnitude of changes in the periphery that induce cortical neuroplasticity and the cortical representation of the structures neighboring the peripheral change are important factors that determine the nature (expansion or shrinkage) and extent of cortical plasticity (Wall, Xu et al. 2002 [Review]; Kleim, Jones et al. 2003; Kleim, Hogg et al. 2004; Piecharka, Kleim et al. 2005). Expansion as-well-as shrinkage in the cortical representation can either be an adaptive or maladaptive change based on the benefit to the subject.

1.4.5 Neuroplasticity of Face Somatosensory and Motor Cortex

The number of cortical neuroplasticity studies related to orofacial function is relatively fewer than those available for limb function. Nonetheless, these studies have evaluated reorganization of the Face-M1 and Face-S1 following peripheral stimulation, peripheral deafferentation, cortical lesions etc.

1.4.5.1 Neuroplasticity of Face Somatosensory Cortex

Humans

Neuroplasticity of the Face-S1 has been observed in certain conditions and may reflect adaptive or maladaptive changes. Neuroplastic expansion of the Face-S1 has been reported, for example following tongue and lip stimulation (Allison, McCarthy et al. 1996; Hoshiyama, Ryusuke et al. 1996; Maegaki, Najm et al. 2000; Sato, Nariai et al. 2005; Wu, van Gelderen et al. 2005; Sakamoto, Nakata et al. 2008), forelimb amputation (Elbert, Flor et al. 1994; Harris 1999; Lotze, Grodd et al. 1999; Lotze, Flor et al. 2001), and in patients with congenitally missing forelimbs (Kamping, Lutkenhoner et al. 2004). Neuroplastic changes in the activity of the Face-S1 has also been observed in fMRI recording of patients with implant-supported prosthesis (Yan, Ye et al. 2008; Chen, Lin et al. 2009). Neuroplastic expansion of Face-S1 into Limb-S1 has been reported in V neuralgia patients (Tinazzi, Valeriani et al. 2004; Hodaie, Chen et al. 2009). As previously discussed, the extent and location of altered peripheral input may contribute to the adaptive / maladaptive neuroplastic changes.

Non-human primates

Many studies have described the neuroplasticity of the Face-S1 in monkeys following deafferentation. Expansion of Face-S1 has been reported following peripheral injuries, limb amputation (Calford and Tweedale 1991; Florence, Taub et al. 1998; Florence, Hackett et al. 2000; Fang, Jain et al. 2002; Jain, Qi et al. 2008; Tandon, Kambi et al. 2009) (Fang, Jain et al. 2002; Jain, Qi et al. 2008) Fang, Jain, et al. (2002), Jain, Qi, et al. (2008), and following limb deafferentation (Merzenich, Kaas et al. 1983; Inoue, Kato et al. 1989; Manger, Woods et al. 1996; Jones and Pons 1998; Jain, Qi et al. 2008). Expansion of Face-S1 following long-term denervation of an upper limb in monkeys can be coupled with similar neuroplasticity changes in the brainstem and thalamus (Jones and Pons 1998).

Sub-primates

Several experimental studies have documented Face-S1 neuroplasticity resulting from peripheral damage to orofacial sensory inputs in adult and neonatal sub-primates (Buonomano and Merzenich 1998; Sanes and Donoghue 2000; Kaas, Qi et al. 2008). For example, extraction of single lower incisor in mole-rats may cause neuroplastic changes in Face-S1 such that the deafferented tooth area in the Face-S1 becomes represented by surrounding structures including the contralateral upper incisor, ipsilateral lower incisor, tongue area and the buccal pad (Henry, Marasco et al. 2005). Neuroplasticity of Face-S1 has also been studied with rhythmic stimulation of vibrissae in mice (Megevand, Troncoso et al. 2009), cats (Batuev, Alexandrov et al. 1989) and extraction of lower incisors in rats (Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010). Similarly, extensive spatial reorganization and incomplete maturation of the S1 barrel cortex and related thalamo-cortical connections has been reported following deafferentation of the infra-orbital nerve in rats (Klein, Misra et al. 1991; Henderson, Woolsey et al. 1992; Klein, White et al. 1998; Higashi, Crair et al. 1999). Learning or experience-dependent neuroplasticity in S1 barrel cortex has been reported following cutting and sparing vibrissa in rats (Delacour, Houcine et al. 1987; Diamond, Armstrong-James et al. 1993; Rema, Armstrong-James et al. 1998; Sachdev, Egli et al. 2000; Rema, Armstrong-James et al. 2003) and mice (Yang, Seif et al. 2002).

1.4.5.2 Neuroplasticity of Face Motor Cortex

Humans

Changes in the excitability of the Face-M1 following trained tongue tasks (Svensson, Romaniello et al. 2003; Svensson, Romaniello et al. 2006; Boudreau, Romaniello et al. 2007), peripheral deafferentation (Yildiz, Yildiz et al. 2004; Halkjaer, Melsen et al. 2006; Zhang, Boudreau et al. 2009) and following

experimental pain (Romaniello, Cruccu et al. 2000; Boudreau, Romaniello et al. 2007; Boudreau, Romaniello et al. 2007) have been reported in humans. Similarly, TMS studies have shown bilateral changes in Face-M1 following unilateral facial paralysis (Rodel, Laskawi et al. 1999; Rodel, Tergau et al. 2004; Yildiz, Bademkiran et al. 2007).

These novel studies in humans together with our correlated findings in monkeys and rats, have provided new insights into the regenerative capacity or neuroplasticity of the sensorimotor cortex and its adaptive processes. This may explain how clinical oral rehabilitation may restore orofacial sensorimotor functions and enhance learning and acquisition of new sensorimotor skills. Therefore changes in sensory input from teeth, periodontium, bone and dental implants may account for differences in oral sensorimotor functions among dentate and edentate patients and patients rehabilitated with implant-supported prostheses.

Non-human Primates

Recent novel studies in monkeys show that neuroplasticity of Face-M1 occurs when the primate learns a new motor orofacial task or when the oral environment changes the sensory feedback to the CNS. In tongue-protrusion task studies (Martin, Kemppainen et al. 1999; Yao, Yamamura et al. 2002a; Sessle, Adachi et al. 2007), monkeys were trained to perform a tongue task in different directions (protrusion, lateral movement)(Murray and Sessle 1992). Single neuronal activity in the Face-M1 and S1 had several discharge patterns in relation to the trained motor behaviour and the cortical representation of tongue protrusion in S1 and M1 markedly changed when the monkey learned the new tongue-protrusion behaviour. There was a change in ICMS-defined cortical representation of the different facial, tongue and jaw movements. Furthermore, after training, 80% of the neuronal population in M1 fired in relation to tongue protrusion compared to 20% prior to

the tongue-task training. In addition, there was concurrent increase in the proportion of neurons in S1 that were active in tongue protrusion (25% before, 54% after). However no such increases could be observed in the cortical masticatory area (CMA / swallow cortex).

Sub-primates

Recent results from ongoing Face-M1 ICMS mapping studies in our laboratory involving lingual nerve transection and alterations in dental occlusion suggest that alterations in sensory input from tongue and teeth may result in adaptive or maladaptive neuroplastic changes in the rat Face-M1 (Lee, Sessle 2004; Adachi, Murray et al. 2008). For example, the decreased excitability of Face-M1 observed following prolonged noxious stimulation could conceivably be an adaptive neuroplastic change (Adachi, Murray et al. 2008). However, changes like neuroplastic expansion of Face-M1 following extraction of a mandibular incisor (Avivi-Arber, Lee et al. 2010) (Avivi-Arber 2009)and shrinkage of Face-M1 following trimming the incisors (Lee, Sessle 2004) have not been completely understood and so may either be an adaptive or maladaptive change. This information is important in that it can provide the foundation to evaluate the neuroplastic changes following dental rehabilitation procedures and other changes in occlusion. The present study provides more vital information on the complex neuroplastic changes in the brain in response to orofacial changes. Also the above-mentioned studies examined the neuroplastic changes in the Face-M1 only at one week after the dental manipulation. Whether neuroplastic changes occur at longer time intervals is unknown. In addition the possible neuroplastic effects of other dental manipulations such as replacement of teeth and placement of implants are yet to be studied, as noted below. Nonetheless, the studies to date suggest sensorimotor mechanisms exist in Face-M1 not only for the control of orofacial

motor functions (e.g. jaw opening, mastication, swallowing) but also for adaptive / maladaptive neuroplastic changes and learning adjustments to an altered orofacial environment.

1.4.6 Neuroplasticity and Osseoperception

Neuroplastic changes in Face-M1 and Face-S1 may be clinically relevant in osseoperception and its relation to rehabilitation with dental implants. The term osseoperception was proposed (Branemark, Hansson et al. 1977) to recognize oral kinesthetic perceptual abilities in the absence of a functional periodontal mechanoreceptive input. Klineberg and Murray (1999) defined osseoperception as "depending on central influences from corollary discharge from corticomotor commands to jaw muscles, and contributions from peripheral mechanoreceptors in orofacial and temporomandibular tissues. The processing of central influences is considered with the recognition of the neuroplasticity of neuromotor mechanisms that occurs to accommodate the loss of dental and periodontal inputs." Hence, osseoperception is reflective of neuroplastic changes in the Face-S1 and the Face-M1.

Many studies have quantified objective and subjective changes related to osseoperception. For example, a significant decrease in tactile perception (Crum and Loiselle 1972; Rissin, House et al. 1978; McCartney 1981; Drago and Rugh 1984; Billek-Sawhney, Perry et al. 2006; Rowin, Meriggioli et al. 2007) and masticatory function (Boretti, Bickel et al. 1995; Sheiham and Steele 2001; Sheiham, Steele et al. 2001; Steele, Sanders et al. 2004; Ueno, Yanagisawa et al. 2008; Ueno, Yanagisawa et al. 2009) has been reported following tooth loss, and an increase in tactile perception has been reported following the restoration of lost teeth with implants (Benzing, Weber et al. 1994; Bakke, Holm et al. 2002; Sansone, Filho et al. 2006; Berretin-Felix, Nary Filho et al. 2008; Berretin-Felix,

Machado et al. 2009). However, neuroplastic changes in Face-M1 and Face-S1 that contribute to the observed changes in osseoperception have not been extensively studied. For example, the reasons for the improvement in tactile perception following implant-supported restoration of missing teeth is poorly understood (Klineberg and Murray 1999; Klineberg 2005; Klineberg, Calford et al. 2005; Abarca, Van Steenberghe et al. 2006; Batista, Bonachela et al. 2008).

Increased blood oxygen-level dependent signals in the Face-S1 of patients with implant-supported prosthesis has been observed in fMRI studies (Jacobs and Van Steenberghe 2006; Yan, Ye et al. 2008; Chen, Lin et al. 2009). These findings provide further evidence that changes in the activity of the Face-S1 may occur following restoration of lost teeth with implant-supported prosthesis. An ICMS analysis with high spatiotemporal resolution is required to calibrate the magnitude of neuroplastic changes in the Face-M1 and the Face-S1 associated with changes in osseoperception observed following loss of teeth and prosthetic rehabilitation of teeth with implant-supported prosthesis.

1.5 Research Rationale

1.5.1 Statement of the Problem

It is well known that partial or complete edentulism can affect an individual's chewing efficiency (Boretti, Bickel et al. 1995; Sheiham and Steele 2001; Ueno, Yanagisawa et al. 2008; Ueno, Yanagisawa et al. 2009) and the quality of life (Trulsson, Engstrand et al. 2002; Gilbert, Meng et al. 2004; Steele, Sanders et al. 2004; Mack, Schwahn et al. 2005; Wong and McMillan 2005; Muller, Naharro et al. 2007; Brennan, Spencer et al. 2008; Pallegedara and Ekanayake 2008). The chewing ability and the quality of life can be improved following rehabilitation of lost teeth (Laurell and Lundgren 1985; Lundgren, Laurell et al. 1987; Trulsson,

Engstrand et al. 2002; Feine and Lund 2006; Strassburger, Kerschbaum et al. 2006; Stanford 2007).

Many studies have examined the effects of manipulation of rodent vibrissae (e.g. removal, trimming) on the V brainstem nuclie (Zucker and Welker 1969; Chiaia, Bennett-Clarke et al. 1992), ventrobasal thalamus (Waite 1973a; Waite and Cragg 1982; Land, Buffer et al. 1995; Keller and Carlson 1999), Face-S1 (Megevand, Troncoso et al. 2009), and the Face-M1(Franchi 2000a). Previous studies have also examined the effects of pulpal deafferentation on neurons in the V brainstem nuclei in cats (Hu, Dostrovsky et al. 1986; Hu, Woda et al. 1999) and rats (Kwan, Hu et al. 1993). Neuroplastic changes in the Face-M1 and Face-S1 following extraction and trimming of mandibular incisors in sub-primates (rats) have also been observed (Lee, Sessle 2004; Sessle, Adachi et al. 2007; Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010). However, the possible neuroplastic changes within the Face-M1 following the extraction of maxillary molars have not been previously studied. The effect of maxillary molar extraction on cortical organization could vary from the neuroplastic changes in motor representation observed following mandibular incisor extraction because the maxillary molars are innervated by the maxillary nerve while the mandibular incisors are innervated by the mandibular nerve (Byers and Kish 1976). Also, the molar teeth are involved in chewing, grinding food and their loss may have a significant impact on the neuromuscular control of the muscles of mastication. It is feasible that the loss of input from molar dental mechanoreceptors could change the sensory input from the oral environment and jaw which together with possible changes in functional motor behaviour might result in cortical reorganization and other neuroplastic changes in Face-S1 and Face-M1. These changes may be crucial for the ability of patients to learn and adapt to the altered oral environment and for the restoration of improved oral function and quality of life. The factors that may control the changes in orofacial function following extraction include the structural / functional reorganization of

bone and temporomandibular joint mechanoreceptors, and neuroplasticity (Klineberg, Calford et al. 2005; Abarca, Van Steenberghe et al. 2006). Recent reviews (Sessle, Yao et al. 2005; Sessle, Adachi et al. 2007) elaborating upon the neuroplastic changes observed in the Face-M1 explain the role of neuroplasticity in learning new functional tasks and adapting to an altered oral environment.

It is clear from the review of the literature that the possible neuroplastic changes following extraction of maxillary molar teeth have not been detailed. Thus, this project proposed experiments of the Face-M1 of rats to provide novel data and insights into the framework of motor reorganization following the extraction of maxillary molars. This will be accomplished by determining if the ICMS-defined features of Face-M1 of rats following maxillary molar extraction are different from those of Naive and Sham control rats. The knowledge obtained through this research will help clarify if Face-M1 neuroplasticity plays a role in how animals and humans adapt, or not, to the loss of teeth.

1.5.2 Hypothesis

Null Hypothesis: Ho = There are no statistically significant neuroplastic changes in Face-M1 following maxillary molar extractions.

Alternate Hypothesis: Ha = There are statistically significant neuroplastic changes in Face-M1 following maxillary molar extractions.

1.5.3 Aim

To determine if the extraction of unilateral maxillary molars produces contralateral Face-M1 neuroplastic changes reflected in the number of positive ICMS tracks, number of positive ICMS sites, number of positive ICMS sites with overlapping representation, threshold and onset latency of ICMS-evoked responses in the LAD, RAD and GG muscles.

2. Materials and Methods

2.1 Overview of Study Design

This controlled cohort investigation compared three animal groups that were exposed to standardized treatment (environment, ICMS experiment protocol) except for the intervention of dental manipulation.

Groups: The Rats were randomly allocated into three groups namely, Naive, Sham Extraction and Extraction.

Sample size: A sample of 6 rats per group was chosen based on the magnitude of results observed with similar sample sizes in previous studies of rat Face-M1 in our laboratory (Lee, Sessle 2004; Adachi, Lee et al. 2007; Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010).

Period of Observation: ICMS was carried out 1 week post-intervention in accordance with these previous studies showing statistically significant neuroplastic changes in the Face-M1.

Statistical Analysis - One way ANOVA.

Table 1. Experimental timeline and sample distribution. Time line of experimental interventions and the number of animals in each group after exclusion.

Groups	Sample (n)	Arrival	1 week	2 weeks
Naive	6	Measure Weight	Measure Weight	Measure Weight + ICMS
Sham Extraction	7	Measure Weight	Measure Weight + Sham extraction	Measure Weight + ICMS
Extraction	6	Measure Weight	Measure Weight + Extraction	Measure Weight + ICMS

2.2 Animals and Maintenance Protocol

All experimental procedures were carried out on rats and were approved by the University of Toronto Animal Care Committee, in accordance with the Canadian Council on Animal Care Guidelines and the regulations of the Ontario Animals for Research Act (R.S.O. 1990). Careful attention was paid to minimize discomfort and pain.

The rats were maintained in plastic cages measuring 27 x 45 x 20 cm containing a plastic shelter tube under controlled temperature (21 ± 1 °C) and humidity (50 ± 5 %), with 12 hrs light/dark cycles (light cycle began at 07:00 am) . Since neuroplasticity might be influenced by gender effects (Jonasson 2005; Cahill 2006), the experiments were performed only on male adult Sprague-Dawley rats (150-175g on arrival, 300-400g on day of cortical mapping). To ensure that all rats had a continuous and similar growth rate, body weight and food consumption were monitored regularly from the first day of rats; at the vivarium until the ICMS experiment. Rats that failed to demonstrate a continuous growth following dental manipulation were excluded from the study. Other exclusion criteria were; failure of histological confirmation of positive sites within M1 area; excessively deep state of anaesthesia; rat death during experiment; electrical system failures during experiment and brain damage during craniotomy. Although the experiments were performed on 8 animals in each group, 5 animals were excluded due to the above-mentioned reasons. Hence, 6 animals in the Naive, 7 animals in the Sham Extraction and 6 animals in the Extraction groups were included in the final analysis (Table 1)

2.3 Dental Manipulations

The dental manipulation procedures were carried out in the rats of the Extraction and the Sham Extraction groups one week after their arrival at the vivarium. The procedures were carried out under aseptic conditions as described by Elsubeihi and Heersche (2004).

2.3.1 Surgical Preparation

The rat for each experiment was chosen in a random order among the three groups. An envelope form of randomization was used; every week three randomized envelopes were opened and the experimental groups were assigned to three rats that arrived that week [to avoid effect of the investigator's experience of experimental results]. The chosen animal was weighed again using a digital scale.

2.3.1.1 General Anaesthesia

The animal was transferred to an inhalation chamber and exposed to 4% Isofulrane in 1L/min oxygen. The onset of anaesthesia was determined by loss of the pinch-withdrawal reflex of the hindlimb. The animal was immediately transferred to the surgical table and 3% Isoflurane was administered with a nose piece to induce anaesthesia. Buprenorphine Hydrochloride 0.05 mg/kg and ketoprofen 0.05 mg/kg was injected subcutaneously for pre-surgical analgesia. The heart rate and oxygen levels were monitored using a pulse oximeter. Dental manipulation procedures were started only after the heart rate and oxygen levels were stable.

2.3.1.2 Local Anaesthesia

A solution of 0.1ml 2% lidocaine hydrochloride with 1:100000 dilution epinephrine was injected into the labial and lingual sides of the right and left maxillary molars to achieve good vasoconstriction. 0.1ml 0.5% bupivacaine with 1:200000 dilution epinephrine was injected to prolong the effect of the local anaesthesia.

2.3.2 Naive Group Protocol

Naive animals did not undergo any surgical procedure. They were weighed and transferred to new cages.

2.3.3 Extraction Group Protocol

The attached gingiva around the molars were reflected using a small PKT (index) carver. The right maxillary molar teeth were engaged using a modified curved artery forcep. All three teeth were extracted using vertical force. The extraction site was allowed to heal without suturing. The rats were weighed before the surgical procedure and transferred into new cages after the procedure.

2.3.4 Sham Extraction group Protocol

As in the extraction group, the gingiva was reflected using a PKT carver. The reflected area was allowed to heal without suturing. The rats were weighed before the surgical procedure and transferred into new cages after the procedure.

2.3.5 Followup

All animals were monitored on a daily basis for 1 week after the intervention. An analgesic solution of 0.1 ml Buprenorphine Hydrochloride 0.05 mg/kg and ketoprofen 0.05 mg/kg was injected subcutaneously every 8 -12 hours for 1 to 3 days after the intervention. A week later, if the rat failed to show continuous weight gain, the animal was excluded from the study.

2.4 Intracortical Microstimulation (ICMS)

ICMS has been used in our laboratory to map the cortical representation of orofacial muscles in monkeys as well as rats (Huang, Sirisko et al. 1988; Huang, Hiraba et al. 1989; Adachi, Lee et al. 2007; Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010). In the present experiments, the ICMS was delivered by a microelectrode to the Face-M1 and the electromyographic (EMG) activity of the orofacial, neck muscles and vibrissae was monitored for evoked responses (Fig 6).

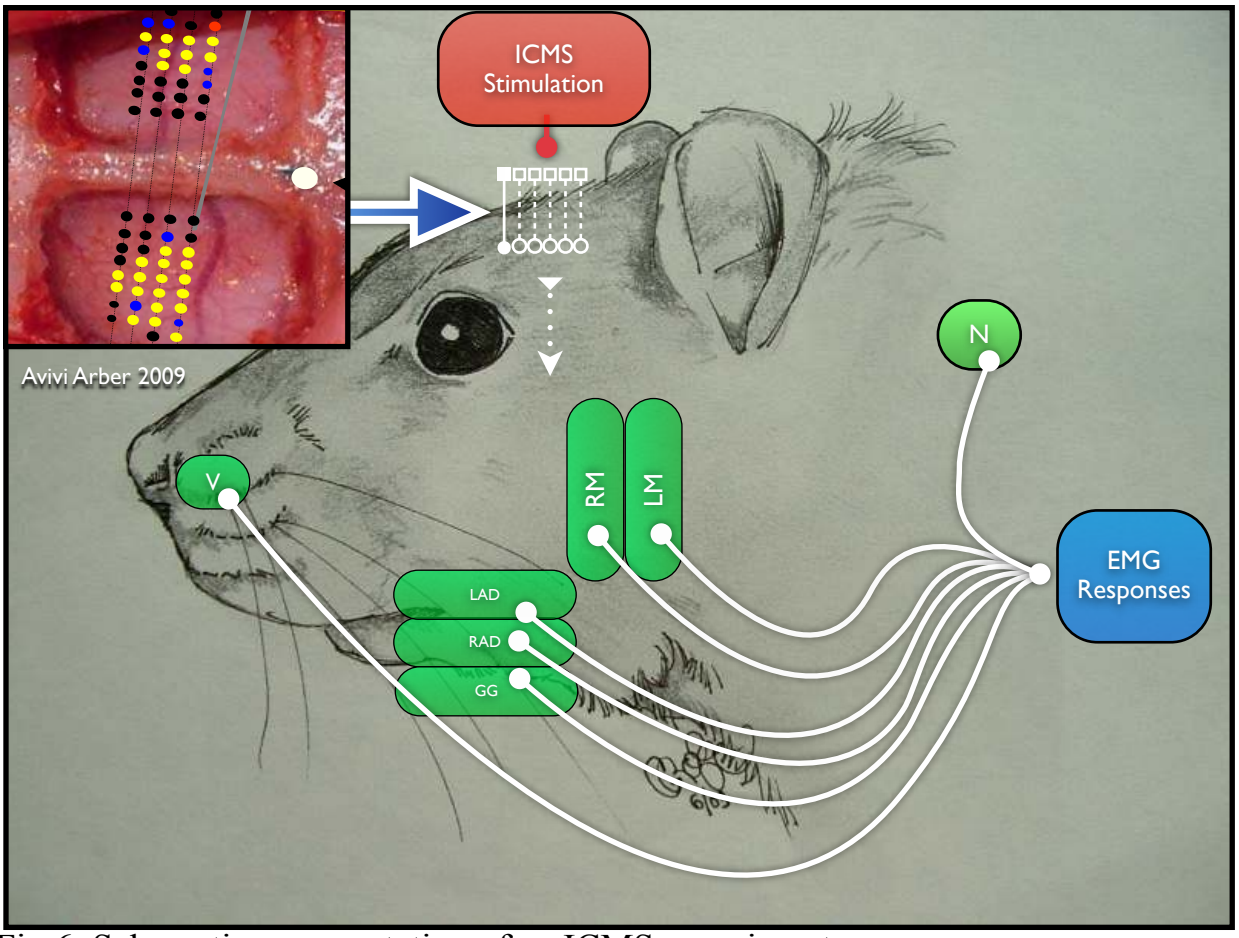

Fig 6: Schematic representation of an ICMS experiment.

2.4.1 Surgical Preparation

2.4.1.1 General Anaesthesia - Initial Dose and Animal Preparation

The rat was secured in a plastic funnel, the hind-paw was retracted and the calculated initial dose of anaesthetics [Ketamine HCL 75 mg/kg + Xylazine 25 mg/ Kg] was slowly injected intramuscularly (IM) into the thigh muscle. Subsequently, the rat was placed back into the plastic cage over paper napkins to avoid choking. Once the rat showed a negative pinch-withdrawal reflex, it was shaved in the following areas:

1. The ventral surface of the abdomen from the midline to the right limb about 3 cm wide anteroposteriorly.

2. The ventral surface of the neck from the imaginary line connecting the posterior border of the jaw to as far anterior as possible. Care was taken not to shave the submandibular vibrissae or cut the skin under the lower jaw.
3. The dorsal surface of the head from the nape of the neck to the imaginary line connecting the two eyeballs anteriorly. Mediolaterally, the hair was shaved until the ear on both sides.

The shaved area was wiped clean and the rat was positioned on the surgical table with a temperature-controlled bed. The tongue was retracted to avoid choking, the limbs were held in place. The pulse oximeter was connected to the left hindlimb to constantly monitor the heart rate and oxygen levels.

2.4.1.2 Local Anaesthesia and IV Cannulation

The skin was disinfected using ethanol, and then 0.1 ml lidocaine (2%) and 0.1 ml bupivacaine (0.5%) were injected subcutaneously in the femoral area. A 2.0 cm long incision running parallel to the femoral vein was made and the femoral vein, femoral artery and sciatic nerve were exposed. The flaps were retracted using sterile hooks. The femoral vein was separated with a fine forceps from the femoral artery and sciatic nerve. The separated vein was isolated with 4 silk sutures. One suture was used to tie the femoral vein as far distally as possible. The isolated vein was carefully punctured using a scissor and a cannula was inserted; care was taken not to puncture the vessel with the cannula. The cannula was secured in place with another suture. The syringe attached to the cannula was retracted to check for patency of the catheter and accurate placement within the vein. The retracted blood was immediately injected back to avoid clotting within the catheter. The remaining 2 suture threads were also tied to secure the catheter with the vein. The flaps were tightly sutured to avoid moisture and temperature loss.

The animal was transferred to the stereotaxic table that had a temperature-controlled bed. A rectal thermometer was inserted and secured with tape. The anaesthetic catheter was also secured with a tape to the tail of the rat. The anaesthetic vial loaded with ketamine was connected to a drug infusion pump. The rate of anaesthetic delivery was adjusted to 75 mg/kg.

2.4.1.3 Placement of EMG Electrodes

The skin of the neck was disinfected with ethanol, and 2% lidocaine 0.1 ml and 0.5% bupivacaine 0.1 ml were injected subcutaneously. A midline incision was started distal to the the submandibular vibrissae and extended caudally by 2 cm. The subcutaneous tissue was carefully reflected to expose the jaw muscles. The flaps were reflected laterally until the right and left masseters were visible. Anteriorly, the flaps were reflected until the origin of the anterior bellies of the diagastric were clearly visible on either side. Posteriorly, the flaps were reflected until the intermediate tendon the of digastric was visible.

Paired 40-gauge, single-stranded, Teflon-insulated stainless-steel EMG electrodes hooked within 26-gauge needles were inserted into the left anterior digastric (LAD), right anterior digastric (RAD), genioglossue (GG), the left masseter (LM) and right masseter (RM) muscles. Electrode placement within the muscles was verified by muscle contractions and/or associated facial movements evoked by 200 μA electrical stimulation applied to the EMG electrode. Accurate placement was determined by the presence of jaw-opening for the LAD and RAD, tongue protrusion for the GG and jaw-closing for the RM and LM. Electrode placement was repeated until the placement was verified with the appropriate response to stimulation. The flaps were carefully sutured to avoid muscle dehydration. The electrodes were connected to the bipolar nodes of the channels programmed for each muscle in the ICMS unit. Two EKG electrodes were hooked to the skin over the cardiac region and connected to their nodes.

2.4.2 Stereotaxic Mounting, Local Anaesthesia and Craniotomy

The animal was carefully turned to a prone position and its head was positioned in the stereotaxic frame. Two ear rods were carefully positioned into the external auditory meatus and tightened to position the head in the midline. Once the midline was determined, the maxillary incisors were positioned in the anterior mouth piece. After positioning the head, EMG electrodes were placed in the right and left facial vibrissae and in the right and left trapezius muscle of the neck. The EMG electrode placement was verified by observing vibrissal movements and twitching of the neck, respectively by 200μA electrical stimulation of EMG electrodes.

For the craniotomy over the left hemisphere, the skin was disinfected with ethanol. 0.1 ml of 2% lidocaine and 0.1 ml of 0.5% bupivacaine were injected subcutaneously. A midline incision extending from an imaginary line connecting the two eyeballs anteriorly to an imaginary line connecting the ear rods posteriorly was made. The cortex was exposed and the bregma was marked with a indelible marker. A slow-speed dental drill was used to mark an anteroposterior (AP) groove parallel and 1 mm lateral to the mid-sagittal suture, from 1 mm to 6 mm anterior to the bregma. A mediolateral (ML) groove was marked perpendicular to the posterior end of the first groove, and it extended up to 5.5 mm leftwards from the bregma. A third groove was created perpendicular to anterior end of the first groove to run leftward as far lateral as possible. The last groove joined the lateral ends of the second and third grooves. The grooves were carefully deepened without damaging the cortical tissue and the cut cranium was carefully removed with a rongeur instrument and the sharp edges of the craniotomy were smoothed. The exposed brain was covered with warm mineral oil maintained at 37^{o}C.

2.4.3 Microelectrode Placement and Coordinate Mapping

Glass-insulated tungsten microelectrodes (1 - 3 MΩ impedance at 1 kHz, 10 µA in saline, 50-100 µm exposed tip with a diameter of approximately 10µm, Alpha Omega Engineering®) were used in this experiment. A micromanipulator device attached to the stereotaxic frame carrying the microelectrode was positioned over the exposed cortex. The Face-M1 and the adjacent Face-S1 were mapped with a vertical and horizontal AP, ML spatial resolution of 0.3 mm. The micromanipulator was adjusted horizontally according to the resolution-defined coordinates. A microscope was used to adjust the vertical position of the micromanipulator until the microelectrode penetrated the dura. The stimulating microelectrode and the ground electrode were connected to the respective ports in the stimulus isolator (Harvard Instruments®). The stimulus isolator was connected to the computer and was used to trigger ICMS stimuli. Each coordinate of penetration was termed a track and each ICMS point within a track was called an ICMS site.

Anteroposteriorly, the tracks were mapped from 3.0 mm anterior to bregma and were advanced in 0.3 mm steps until there were no more positive tracks. Subsequently, the planes 2.7 mm anterior to the bregma and 2.4 mm anterior to bregma were mapped. Mediolaterally, each plane was mapped from 3.0 mm lateral to the bregma until the lateral-most point possible and returned medially until there were no more positive tracks.

In all tracks, the microelectrode was advanced to a minimum depth of 4.5 mm except in the lateral-most areas where it was stopped at 3.9 mm to avoid damage to the tip of the microelectrode by contact with the bone. If a track had positive responses, a lesion was created at the final stimulation depth in the track by applying DC current of 10µA for 5 seconds from the stimulus isolator.

2.4.4 Microstimulation and Recording Procedures

The Spike 2® Program (Cambridge Electronic Design Limited, Cambridge, England) was launched and the base-line spontaneous EMG activities were recorded for 1 minute. The intravenous anesthetic infusion rate was adjusted until only 3-4 spontaneous responses per minute were recorded from the jaw and tongue muscles and there was no pinch-withdrawal reflex of the hindlimb. Additionally, the heart rate was also monitored through the EKG channel and displayed in Spike 2®.

Cathodal currents were used as they more readily elicit ICMS-evoked EMG responses than anodal currents (Stoney, Thompson et al. 1968). The intensity of the ICMS current was controlled manually for each stimulus train. Sequencer and script codes written in Spike 2® program and CED 1401 pulse system (Cambridge Electronic Design Limited, Cambridge England) were used to generate constant-current stimulation trains that were comprised of 12 pulses of 0.2 ms at 333 Hz, with 2.8 ms intervals. Similar stimulation parameters have been used previously to stimulate the cortex (Donoghue and Wise 1982; Neafsey, Bold et al. 1986). The initial stimulation set consisted of five ICMS trains delivered at 1 Hz with a supra-threshold intensity of 60μA (Fig 6).

A positive site was defined as a site from which an EMG response could be evoked within 40ms of stimulation in at least 3 of 5 stimulation trains and with an amplitude greater than two standard deviations of the background EMG level in one of the recorded muscles. A track with at least one positive site was defined as a positive track. If an ICMS site failed to produce an evoked response in the first 2 stimulation trains, then the stimulation at that site was interrupted and the microelectrode was advanced to the next depth. If ICMS at that site evoked a response within the first 2 trains, then all 5 trains were applied without interruption. However, if the stimulus train of a positive site was accidentally

interrupted after 2 trains, then the site was re-stimulated with 3 trains only. All positive sites were re-stimulated with lower intensity currents until the evoked EMG response disappeared. The lowest intensity of ICMS current that elicited an evoked EMG response was recorded (at a resolution of 1μA) as the threshold of that particular ICMS site.

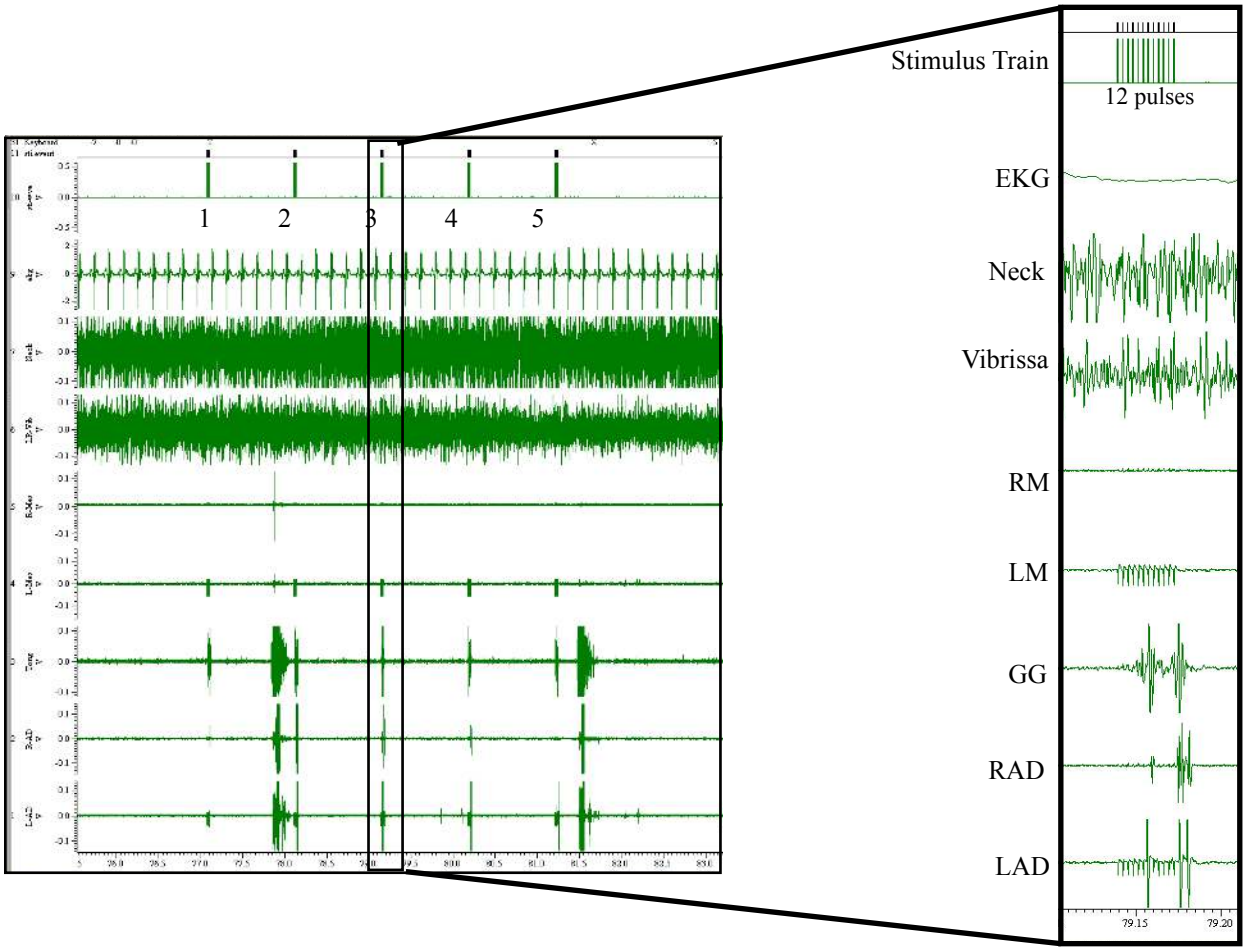

Fig 7: ICMS-evoked EMG responses. EMG waveforms observed in the Spike® Program showing positive responses in all 5 stimulation trains. An expanded view of a single ICMS train shows positive responses in the LAD, RAD and GG channels.

2.4.5 Perfusion, Excision and Fixation of the Brain

After the mapping was completed, the infusion rate of the ketamine + xylazine solution was increased to decrease the heart and respiratory rate. The animal was turned to its supine position and the EMG electrodes were rechecked for accurate placement, i.e their stimulus evoked a muscle response at an intensity ≤ 200μA. Subsequently, the electrodes were disconnected and the thermometer was removed. The rat with the catheter was transferred to the perfusion chamber. A large transverse incision was made in the abdomen. A sagittal incision along the sternum was made to expose the heart and lungs. The aorta was identified and isolated. The perfusion needle was inserted into the left ventricle to reach the aorta. The perfusion needle was secured in place with a clamp or suture. The right atrium was cut open and saline was injected through the perfusion needle to clear the blood in the vessels. Saline was pumped until the animal died and all the blood in the circulation was flushed out. The saline perfusion container was refilled with 10 % buffered formalin and the animal was fixed. After completing the perfusion, the brain was exposed, carefully removed and stored in 10% buffered formalin for at least 24 hours (Katelaris, Kencian et al. 1994).

2.5 Histology

The histological analysis of the cortical mapping area, based on the location of the electrolytic lesions, determined whether the positive sites were located within the cortical or sub-cortical regions or within the granular (S1) or agranular (M1) cortex. All histological procedures were carried out by our laboratory histologist.

2.5.1 Slide Preparation

A soft tissue microtome was used to slice the stored brain specimens into 75µm sections. The slices were loaded onto glass slides and stained with Cresyl violet (Nissl stain).

2.5.2 Digitization and Anatomical landmarks

The slides were photographed with a digital camera and the images were calibrated using the Adobe Photoshop®. USA. The accuracy of the histological distinction of cortical areas and their borders can be influenced by the orientation of the sectioning plane, thickness of the section and the functional overlap between various cytoarchitectonic zones. To minimize these influences, cytoarchitectural differences between the S1, M1 and the sub-cortex described by Donoghue and Wise (1982) and Paxinos and Watson (1995) were used to determine the location of the positive sites. The positive tracks were reconstructed on brain sections based on the location of the lesions made at the bottom of each positive track. Based on the reconstructed data, the micromanipulator measurements and the recorded depth of the positive sites the location of the sites were corrected.

2.6 Data Analysis

Customized Spike® scripts and LabView® software scripts created in our laboratory were used for data analysis. First the keyboard inputs (microelectrode depth and ICMS intensities) were extracted and repetitions were removed. Later, the EMG responses evoked from positive sites were identified and counted by the program and matched with the rectified keyboard inputs. Previous experiments from our laboratory have reported that in comparable AP and ML planes, the EMG activities of the LM and RM muscles were only evoked in < 1% of the mapped ICMS sites (Lee, Sessle 2004; Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010) and

therefore the LM and RM activities were not analyzed in this study. The baseline EMG activities of the vibrissal and neck muscles showed numerous artifacts and noise that made it difficult for the computer program to distinguish the ICMS-evoked responses from the baseline levels and so were not included in the analysis. Thus, only those responses in the LAD, RAD and GG (alone or in combination) that were evoked by positive Face-M1 ICMS sites were analyzed. Data analysis was also performed to identify the area of representation of each of the LAD, RAD and GG muscles in the Face-M1 and any overlap in the representations (e.g. RAD and GG). Hence, the positive sites were also classified based on the number and type of muscles evoked individually and in combination. The various combinations included:

1. LAD only - LAD activity was evoked but no other muscles were activated.
2. RAD only - RAD activity was evoked but no other muscles were activated.
3. GG only - GG activity was evoked but no other muscles were activated.
4. LAD + RAD only - Both LAD and RAD activities were evoked but no other muscles were activated.
5. AD ± other - Both LAD and RAD activities were evoked and the other muscles could have been activated.
6. LAD + GG only - Both LAD and GG activities were evoked but no other muscles were activated.
7. RAD + GG only - Both RAD and GG activities were evoked but no other muscles were activated.
8. LAD + RAD + GG - The LAD, RAD and GG activities were evoked.

2.6.1 Motor Maps

Cortical motor maps were constructed by plotting all the ICMS sites on the coronal sections of the brain. The ICMS sites were plotted with specific colour codes, namely blue for LAD, green for RAD, red for GG and black for non-responsive sites.

2.6.2 Centre of Gravity (CG)

The CG for Face-M1 represents the weighted centre in the Face-M1 representation that was calculated from the average number and location of positive sites within each group of animals (Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010). The CG was plotted for each AP plane and each muscle individually.

The formulae for X coordinate: $X = \Sigma aiXi/\Sigma ai$ and Y coordinate: $Y = \Sigma aiYi/\Sigma ai$ were used to plot the CG. ai was the mean threshold number of evoked muscles in each group of animals at each positive site; Xi was the coordinate of the X-axis (distance of the ICMS site from the mid-sagittal plane), and Yi was the coordinate of the Y-axis (depth of the ICMS site from the surface of penetration) (Wassermann, McShane et al. 1992; Ridding, Brouwer et al. 2000).

2.6.3 Analysis Procedure

The procedure for analyzing the EMG data involved four major steps. In step 1, keyboard channel extracting scripts were prepared using the Labview® A1 program. These scripts were used to create track scripts after extracting keyboard inputs from Spike® data files.

In step 2, the track scripts were run in the Labview® A2 program to detect the trigger points associated with the keyboard inputs and export the data to an Excel spreadsheet. The data in the spreadsheet was verified with the Spike® scripts and duplicate inputs were removed.

In step 3, the Labview® B1 program was used to convert the key tables into spike scripts for exporting 100ms data segments. The scripts created in Labview® B1 were run on the Spike® data files and 100ms segments were exported as text files. In step 4, the Labview® B2 program was run to detect onset latency. The onset latency was measured automatically by the program and it reflected the time from the beginning of the stimulus artifact to the positive EMG response (i.e. 2 SD above baseline) at a resolution of 1ms. The key table was imported again into the program and the program processed the 100ms segments and exported the key table with all the required data. Steps 1 to 4 were repeated for each positive track.

The positive sites and the penetration depth obtained from the data analysis of the positive tracks were corrected after histological verification. Based on the corrected measurements, the positive sites were classified into positive sites in the M1, positive sites in the S1, and positive sites in the sub-cortex. Only the positive sites in the M1 were counted and entered for statistical analysis.

2.7 Statistical Analysis

Statistical analysis was performed using SPSS V15® USA. Descriptive statistics (mean, standard deviation and standard error) were carried out for each animal. A series of ANOVA (Analysis of Variance) tests were performed to compare different variables across the study groups. If a significant ($p < 0.05$) difference was observed in ANOVA, further analysis with Bonferroni - adjusted pairwise comparisons was conducted.

2.7.1 Statistical Variables

The variables that were considered in the analysis included:

Independent Variables

1. Study groups: Extraction, Sham Extraction and Naive groups.
2. EMG muscle activity: GG, LAD, RAD.
3. Cortical Area: Face-M1

Dependent Variables

1. Body Weight
2. Positive tracks
    1.1. Number and AP distribution of positive tracks
    1.2. Number and ML distribution of positive tracks
3. Positive ICMS sites
    1.1. Number of positive sites for each muscle.
    1.2. ICMS threshold for each muscle.
    1.3. Overlapping representations of muscles.
    1.4. Mean onset latency for each muscle.
    1.5. CG of representation for each muscle.
        a.1. Distance lateral to the bregma.
        a.2. Depth.

3. Results

The findings of this study reject the null hypothesis Ho and support the alternate hypothesis Ha and are presented below in sections 3.3 and 3.4.

3.1 Data Analysis

The ICMS data was analyzed and ICMS sites were verified histologically. The positive sites were classified based on their histological location as Face-M1, Face-S1 and sub-cortical sites. The positive sites in the Face-M1 were used in the final analysis. One experiment from the Extraction group and one experiment from the Naive group in which the histological specimens were damaged were excluded from data analysis. Data analysis was completed on 6 Naive, 7 Sham Extraction and 6 Extraction experiments. There were very few ICMS sites that evoked activity in the RM and LM (2.17 ± 3.13 SD) within the mapped area across all three groups and so these sites were excluded from the data analysis. The spontaneous movement of the vibrissae and neck at the maintained level of anaesthesia confounded the results. Hence, the evoked responses in the vibrissae and neck were not included in the analysis.

3.2 Rat Weight

There was no significant difference in weight gain across the Sham Extraction and Extraction groups (oneway ANOVA p= 1.00). Naive rats did not undergo any surgical procedure and showed significantly more weight gain as compared with the other two groups (Fig 8, Table 1), but there was no statistical significance in the post-hoc Bonferroni adjusted comparisons.

3.3 Number of Positive Tracks in the Face-M1

According to the histological calibration, the Face-M1 extended from 2.4 mm to 4.5 mm anterior to the Bregma. The mean number of positive tracks in the Face-M1 was higher in the Extraction group than in the Naive and Sham Extraction

groups, but this difference was not significant in the case when all AP and ML planes were considered (Table 2). However, when the positive tracks were compared across the Naive, Sham Extraction and Extraction groups in each AP plane within the Face-M1, the Extraction group had significantly more positive tracks at AP 3.9 mm and 4.2 mm planes (Fig 9, Table 3). The distribution of positive tracks in the Face-M1 was also analyzed in the ML planes. The horizontal spatial resolution was 0.3 mm and the the Face-M1 extended from 2.7 mm up to 4.8 mm lateral to the Bregma. The Extraction group showed significantly more positive tracks in the ML planes 3.3 mm and 3.6 mm than the other two groups (Fig 10, Table 4).

3.4 Positive Sites in the Face-M1

3.4.1 Number of Positive Sites

The overall number of positive sites was higher for the Extraction group, however there was no significant difference (Table 5) in the overall number of positive sites within Face-M1 across the study groups. Similarly, the number of RAD sites in the contralateral (left) Face-M1 was greater than LAD sites, but there were no significant differences in the number of positive sites (Table 6) for each of the LAD, RAD or GG muscles in the Face-M1 across the study groups.

Positive sites were compared across the Naive, Sham Extraction and Extraction groups in each AP plane within the Face-M1. The Extraction group had significantly more positive sites in the AP 3.9 mm and 4.2 mm planes (Fig 10, Table 7). The distribution of positive sites in the Face-M1 was also analyzed in the ML planes. The Extraction group showed significantly more positive sites in the ML planes 3.3 mm and 3.6 mm (Fig 12, Table 8) than the other two groups.

3.4.2 Overlapping Representations

Positive sites in the Face-M1 from which ICMS-evoked EMG activity in more than one muscle were compared for the various combination of muscles activated. ANOVA with multiple comparisons revealed that there was no difference in overlapping representations of the LAD, RAD and GG muscles in the Face-M1 across the study groups (Table 9).

3.4.3 Onset latency

The mean onset latency for each muscle in each group was calculated and compared. Although the Extraction group had the shorter LAD and RAD onset latencies, oneway ANOVA revealed no significant difference in the onset latency of the LAD and RAD muscles in the Face-M1 across the study groups (Table 10). There was also a decrease in onset latency of the GG muscle in the Face-M1 of the Extraction group but this was not statistically significant.

3.4.4 Threshold

The mean threshold intensity of the positive sites in the Face-M1 was calculated and compared across the groups. There were no significant differences (Table 11) across the study groups in the LAD, RAD or GG threshold intensities in the Face-M1.

3.4.5 Centre of Gravity (CG)

The weighted centre in depth (y-axis) (Table 12) and the weighted centre in the distance lateral to the Bregma (x-axis)(Table 13) of the LAD, RAD and / or GG representations in the Face-M1 were calculated and compared across the study groups. There was no significant difference in the centre of gravity of the LAD, RAD and GG muscles across the study groups.

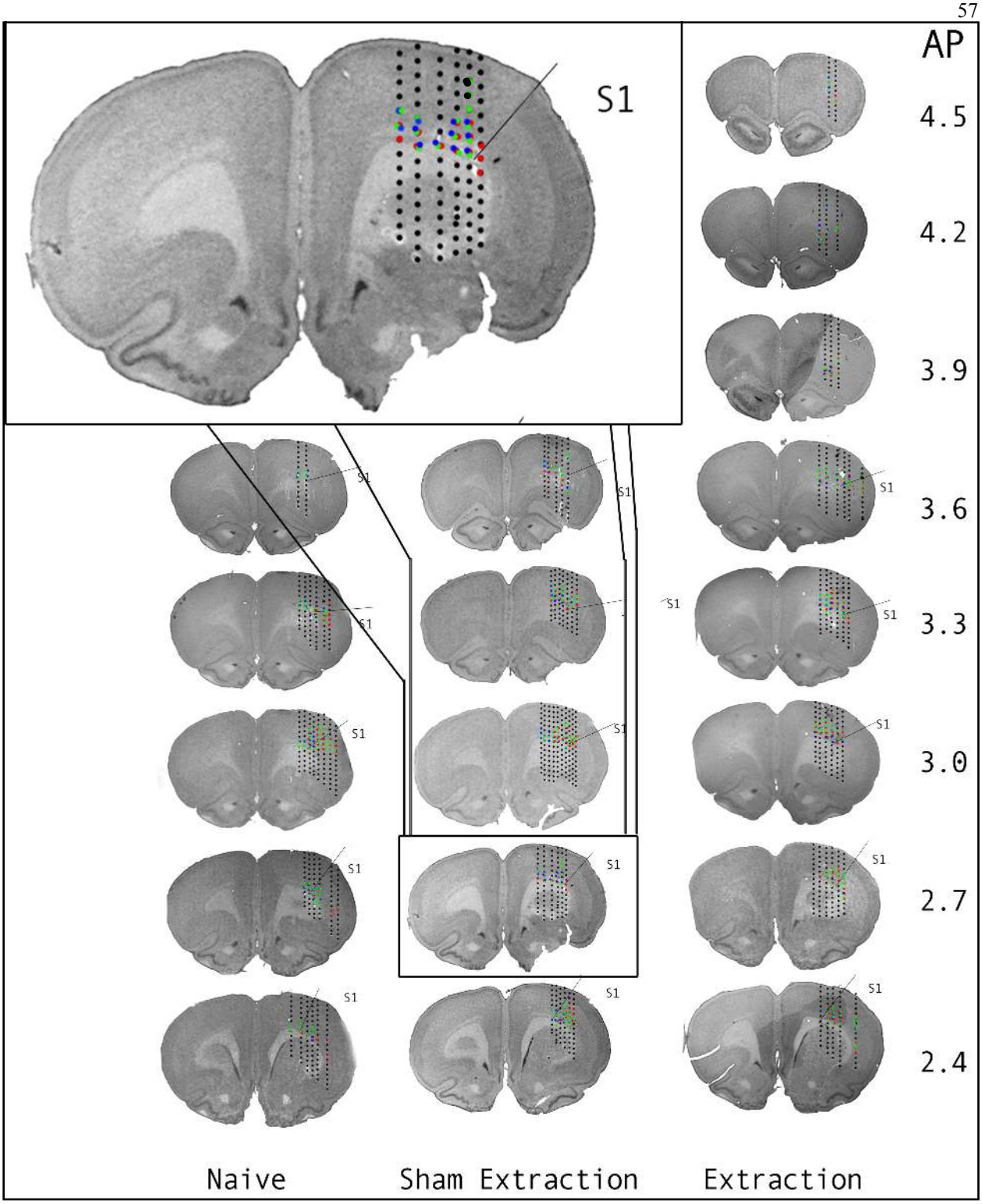

Fig 8: Motor maps in the Face-M1 and Face-S1 representing the LAD (blue), RAD (green) and GG(red) in a Naive, a Sham Extraction and an Extraction rats. Each site from which ICMS-evoked a positive response in a particular muscle was plotted on brain cross-sections in a specific colour at the corresponding AP, ML coordinate. ICMS at sites marked black evoked no response. Only tracks that had at least one ICMS-evoked response were plotted in this figure.

Table 2: Rat Weight Gain in grams. The Naive group had significantly more weight gain than the Sham Extraction and the Extraction groups (Anova p= 0.04). However, there was no statistical significance in post-hoc Bonferroni adjusted comparisons. Values shown in mean ± 1SD (grams).

	Naive	Sham extraction	Extraction	ANOVA	Bonferroni
Rat Weight	164.83 ± 23.76	135.71 ± 10.89	137.67 ± 25.27	df = 2,16 F = 3.90 **p = 0.04**	p= 0.06

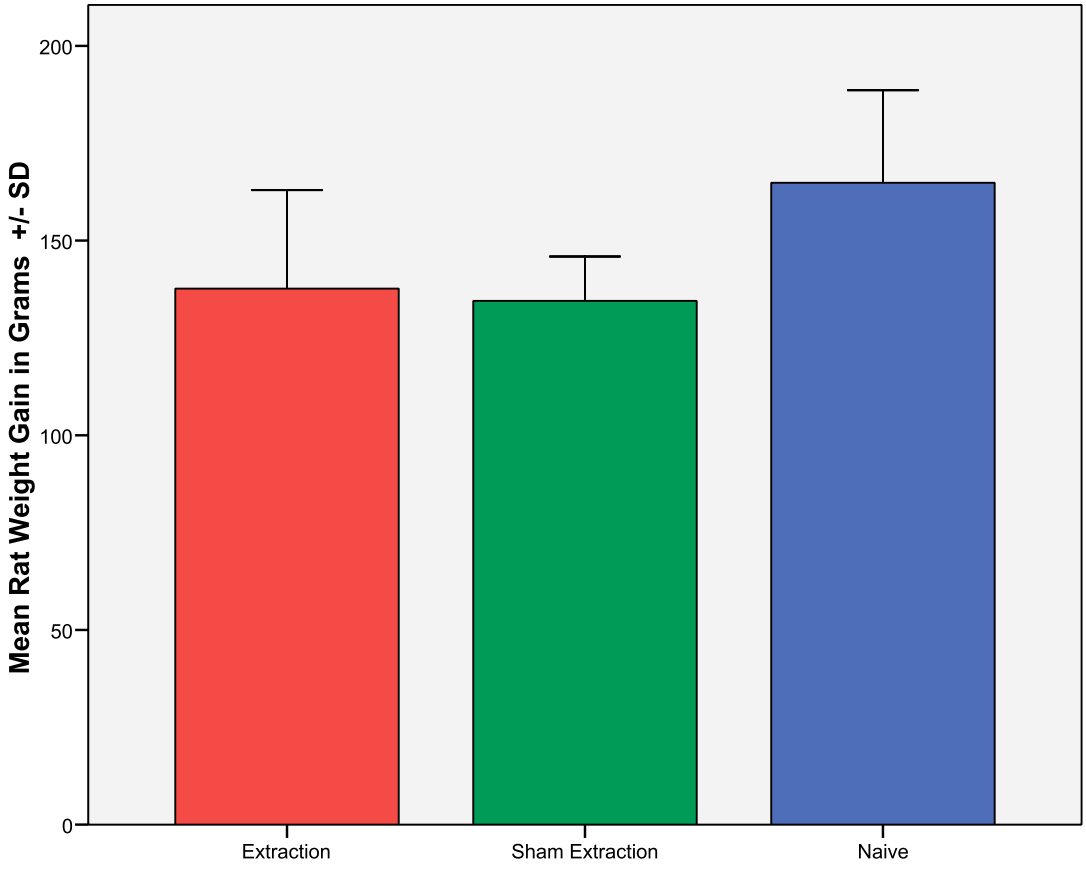

Fig 9: Rat weight gain in grams. Mean weight gain in the Naive (blue), Extraction (red) and Sham Extraction (green) groups plotted in this figure show that the Naive group had significantly more mean weight gain by the end of the study period than the Sham Extraction and the Extraction groups (oneway ANOVA p< 0.05). However, there was no statistical significance in post-hoc Bonferroni adjusted comparisons.

Table 3. Positive tracks in the Face-M1. There was no significant difference (oneway ANOVA p> 0.05) across the study groups in the mean overall number of positive tracks in the Face-M1. Values shown in mean ± 1SD.

	Naive	Sham Extraction	Extraction	ANOVA
Positive Tracks in the Face-M1	13.83 ± 3.97	15.83 ± 5.35	20.17 ± 4.96	df = 2, 16 F = 2.74 p = 0.10

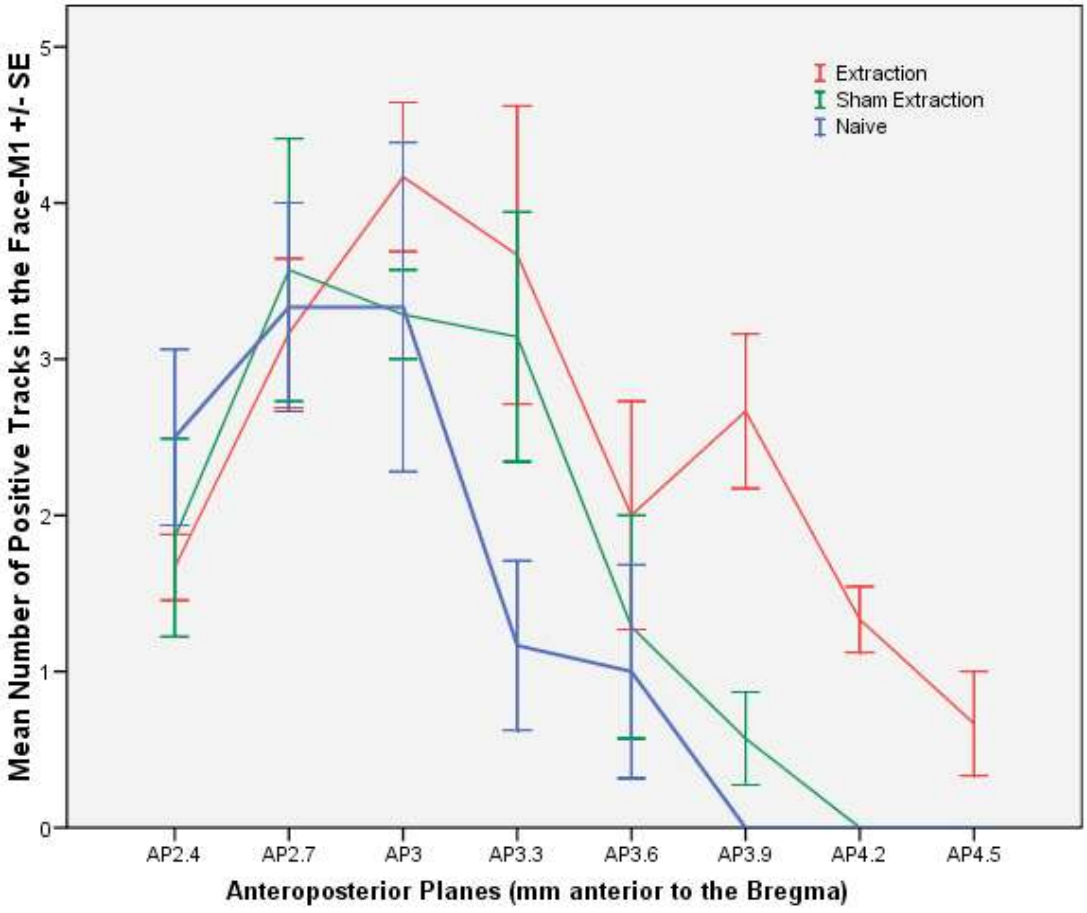

Fig 10: AP distribution of positive tracks in the Face-M1. Line graphs of the mean AP distribution of positive ICMS tracks in the Extraction, Sham Extraction and Naive groups showed significantly more positive tracks at AP 3.9 and 4.2 (oneway ANOVA, Bonferroni p< 0.01) planes in the Extraction group.

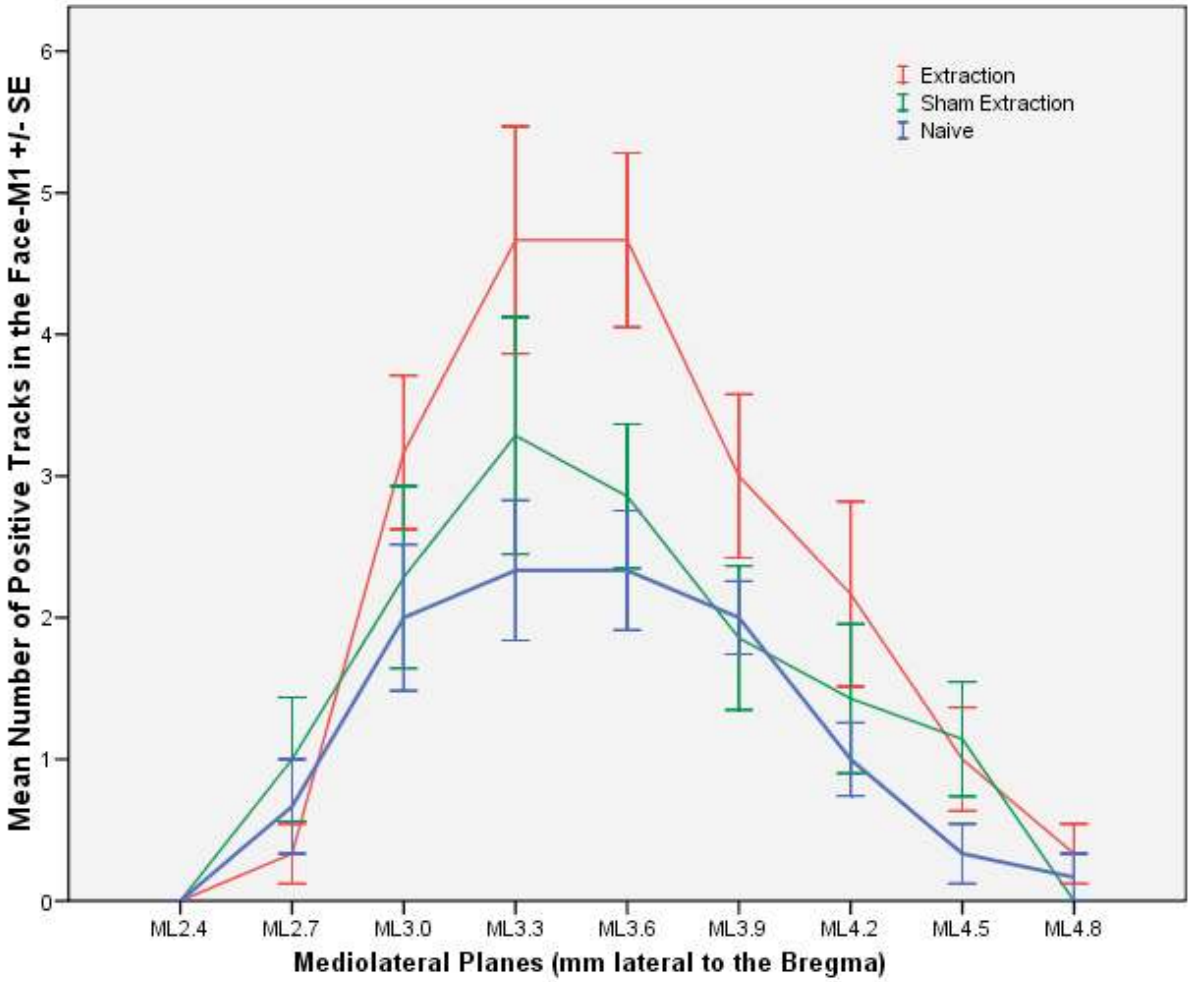

Fig 11: ML distribution of positive tracks in the Face-M1. Line graphs of the mean ML distribution of positive ICMS tracks in the Extraction, Sham Extraction and Naive groups showed significantly more positive tracks at ML 3.3 and ML 3.6 (oneway ANOVA, Bonferroni $p < 0.01$) planes in the Extraction group.

Table 4: AP distribution of positive tracks in the Face-M1. Oneway ANOVA showed that the Extraction group had significantly more positive tracks than the Naive and Sham Extraction groups in planes AP 3.9 ($p< 0.01$) and AP 4.2 ($p< 0.01$) planes. Values shown in mean ± 1SD.

Anteroposterior Plane	Naive	Sham extraction	Extraction	Anova	Bonferroni
AP 2.4	2.33 ± 1.86	0.57 ± 1.13	1.83 ± 1.17	df = 2,16 F = 2.72 p = 0.096	-
AP 2.7	4.33 ± 1.63	3.71 ± 1.38	2.83 ± 0.98	df = 2,16 F = 1.85 p = 0.190	-
AP 3.0	4.17 ± 2.5	5.17 ± 0.69	4.83 ± 1.60	df = 2,16 F = 0.52 p = 0.604	-
AP 3.3	2 ± 2.12	3.71 ± 2.13	4.33 ± 1.21	df = 2,15 F = 2.23 p = 0.142	-
AP 3.6	1.33 ± 2.42	1.71 ± 2.05	2 ± 0.89	df = 2,16 F = 0.18 p = 0.83	-
AP 3.9	0	0.57 ± 0.78	2.67 ± 1.21	df = 2,16 F = 17.31 **p < 0.01**	**p< 0.01**
AP 4.2	0	0	1.33 ± 0.52	df = 2,16 F = 43.79 **p < 0.01**	**p< 0.01**
AP 4.5	0	0	0.33 ± 0.52	df = 2,16 F = 2.74 p = 0.09	-

Table 5: ML distribution of positive tracks in the Face-M1. Oneway ANOVA of the ML planes showed significantly more positive tracks in the ML 3.3 and ML3.6 planes. Post-hoc Bonferroni-adjusted pairwise comparison also showed significantly more positive tracks in the Extraction group than the other two groups in ML 3.3 and 3.6 planes. Values shown in mean ± 1SD.

Mediolateral Plane	Naive	Sham extraction	Extraction	Anova	Bonferroni
ML 2.4	0.17 ± 0.41	0.14 ± 0.38	0	df = 2,16 F = 0.47 p= 0.63	-
ML 2.7	0.5 ± 0.55	1.43 ± 0.98	0.67 ± 0.52	df = 2,16 F = 3.03 p= 0.07	-
ML 3.0	2.5 ± 1.38	3.43 ± 1.27	3.67 ± 1.37	df = 2,16 F = 1.30 p=0.3	-
ML 3.3	3 ± 1.27	3.14 ± 1.07	5.5 ± 1.05	df = 2,16 F = 9.50 **p= 0.002**	**p= 0.004**
ML 3.6	2.33 ± 1.37	2.43 ± 0.98	4.67 ± 2.16	df = 2,16 F = 4.46 **p= 0.029**	**p= 0.05**
ML 3.9	1.17 ± 0.41	1.57 ± 1.27	2.5 ± 1.52	df = 2,16 F = 2.05 p = 0.16	-
ML 4.2	0.67 ± 0.52	1 ± 0.82	1.83 ± 1.60	df = 2,16 F = 1.92 p = 0.17	-
ML 4.5	0.17 ± 0.41	0.43 ± 0.79	0.67 ± 0.82	df = 2,16 F = 0.76 p = 0.48	-
ML 4.8	0	0	0.17 ± 0.41	df = 2,16 F = 1.10 p = 0.35	-

Table 6. Positive sites in Face-M1. There was no significant difference (oneway ANOVA p> 0.05) across the study groups in the overall mean number of positive sites in Face-M1. Values shown in mean ± 1SD.

	Naive	Sham Extraction	Extraction	ANOVA
Positive Sites in Face-M1	19.67 ± 6.44	18.57 ± 9.55	37.00 ± 22.01	df = 2,16 F = 3.33 p = 0.062

Table 7. Positive sites in Face-M1 for Each Individual Muscle. There were no significant differences (oneway ANOVA p> 0.05) across the study groups in the mean numbers of LAD, RAD or GG positive sites in Face-M1. Although the mean number of RAD positive sites was higher than the LAD and GG in all three study groups, oneway ANOVA revealed no significant difference. Values shown in mean ± 1SD.

	Naive	Sham Extraction	Extraction	ANOVA
LAD Face-M1	8.67 ± 8.52	11.29 ± 8.20	13.50 ± 12.21	df = 2,16 F = 0.37 p = 0.695
RAD Face-M1	14.33 ± 7.99	20.00 ± 14.33	32.50 ± 27.61	df = 2,16 F = 1.55 p = 0.242
GG Face-M1	4.67 ± 4.37	10.14 ± 11.45	13.33 ± 19.47	df = 2,16 F = 0.67 p = 0.528

Table 8: AP distribution of positive sites in the Face-M1. The Extraction group had significantly more positive tracks than the Naive and Sham Extraction groups in AP 3.9 and AP 4.2 planes ($p< 0.01$ oneway ANOVA, $p< 0.01$ Bonferroni). Values shown in mean ± 1SD.

Anteroposterior Plane	Naive	Sham extraction	Extraction	Anova	Bonferroni
AP 2.4	6.33 ± 6.44	5.14 ± 5.11	3.67 ± 2.94	df = 2,16 F = 0.42 p = 0.66	-
AP 2.7	8.33 ± 5.05	7.86 ± 5.52	7.33 ± 3.62	df = 2,16 F = 0.06 p = 0.94	-
AP 3.0	9.67 ± 9.5	7.57 ± 4.08	11.33 ± 10.82	df = 2,16 F = 0.33 p = 0.73	-
AP 3.3	3.17 ± 3.97	7.43 ± 7.53	10 ± 7.67	df = 2,16 F = 1.61 p = 0.23	-
AP 3.6	2.17 ± 3.71	3.00 ± 4.51	5.83 ± 5.49	df = 2,16 F = 1.05 p = 0.37	-
AP 3.9	0	0.71 ± 0.95	7 ± 4.69	df = 2,16 F = 12.57 **p < 0.01**	**p< 0.01**
AP 4.2	0	0	3.17 ± 3.25	df = 2,16 F = 6.23 **p < 0.01**	**p< 0.01**
AP 4.5	0	0	1.33 ± 1.75	df = 2,16 F = 3.21 p = 0.07	-

Table 9: ML distribution of positive sites in the Face-M1. Oneway ANOVA of the ML planes showed significantly more positive tracks (P< 0.05) in the planes ML 3.3 and ML3.6. Post-hoc Bonferroni - adjusted pairwise comparison also showed significantly more positive tracks in the Extraction group than the other two groups in ML 3.3 (p=0.004) and ML 3.6 planes (p=0.05). Values shown in mean ± 1SD.

Mediolateral Plane	Naive	Sham extraction	Extraction	Anova	Bonferroni
ML 2.7	2.00 ± 2.76	1.43 ± 1.62	1.00 ± 1.55	df = 2,16 F = 0.36 p = 0.70	-
ML 3.0	4.33 ± 3.88	5.29 ± 3.68	6.33 ± 4.50	df = 2,16 F = 0.37 p = 0.70	-
ML 3.3	5.33 ± 3.14	6.57 ± 4.20	10.17 ± 5.50	df = 2,16 F = 6.99 **p = 0.01**	**p= 0.004**
ML 3.6	6.67 ± 4.08	8.0 ± 5.06	12.67 ± 6.61	df = 2,16 F = 3.38 **p = 0.05**	**p= 0.05**
ML 3.9	6.17 ± 2.93	5.00 ± 3.74	10.17 ± 7.36	df = 2,16 F = 1.86 p = 0.19	-
ML 4.2	2.17 ± 1.47	2.00 ± 2.08	5.33 ± 3.83	df = 2,16 F = 3.17 p = 0.07	-
ML 4.5	0.67 ± 1.21	2.00 ± 2.08	2.67 ± 2.58	df = 2,16 F = 1.50 p = 0.25	-
ML 4.8	0.67 ± 1.63	0	0.83 ± 1.60	df = 2,16 F = 0.79 p = 0.47	-

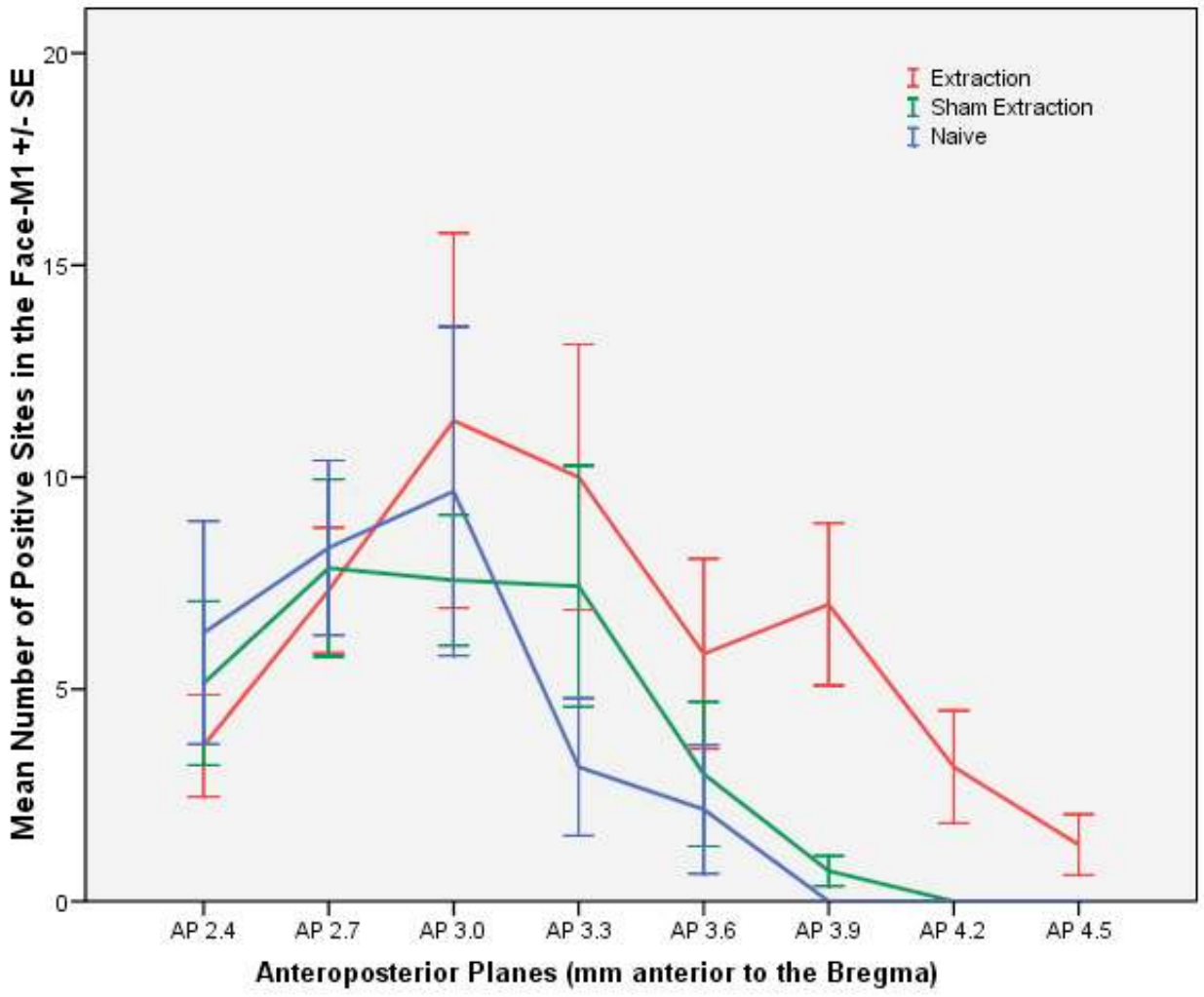

Fig 12: AP Distribution of positive sites in the Face-M1. Line graphs of the mean AP distribution of positive sites in the Extraction, Sham Extraction and Naive groups showed significantly more positive sites at AP 3.9 and 4.2 (oneway ANOVA $p< 0.01$ Bonferroni $p< 0.05$) planes in the Extraction group.

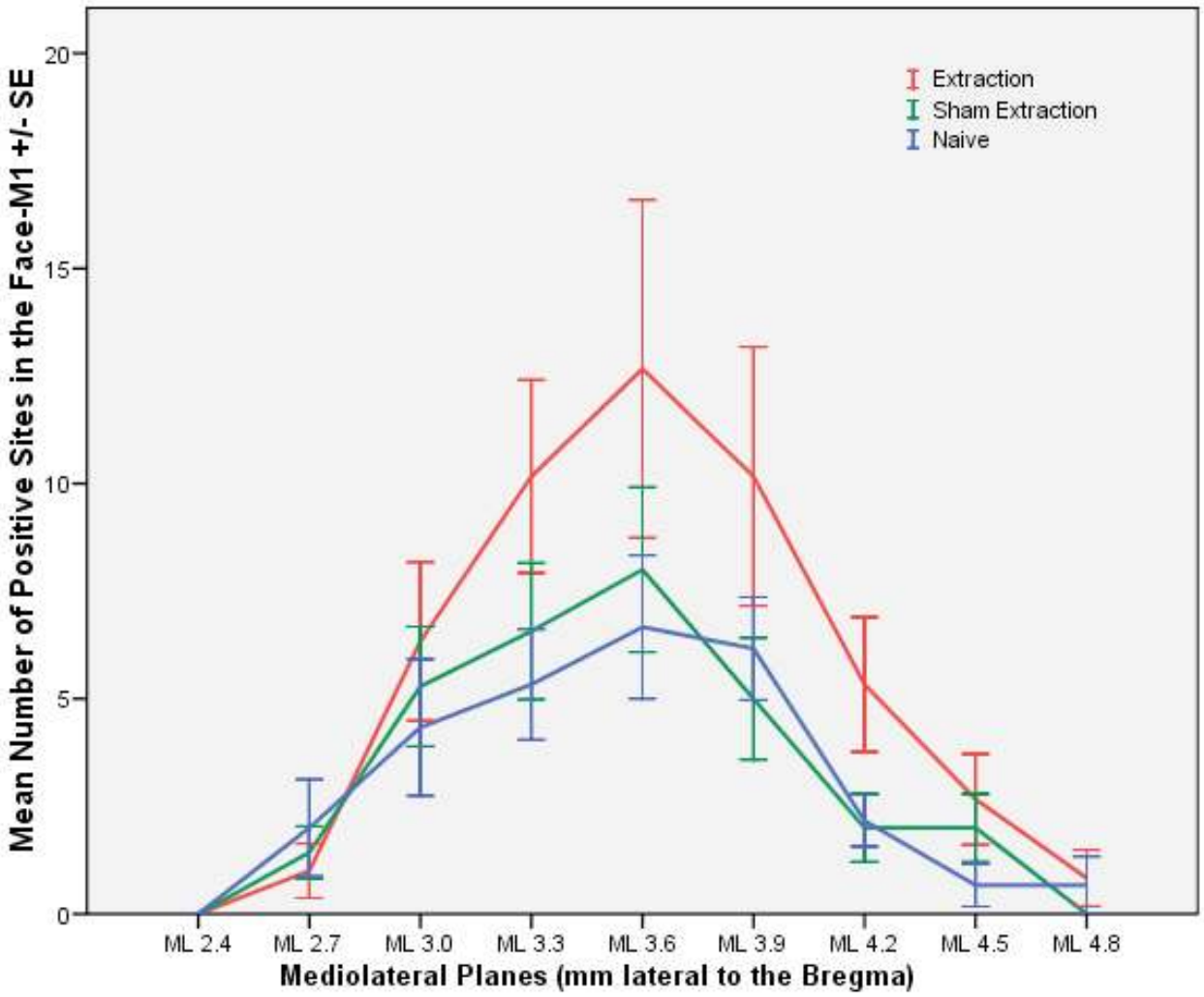

Fig 13: ML distribution of positive sites in the Face-M1. Line graphs of the mean ML distribution of positive sites in the Extraction, Sham Extraction and Naive groups showed significantly more positive sites at ML 3.3 and ML 3.6 (oneway ANOVA Bonferroni $p< 0.05$) planes in the Extraction group.

Table 10. Overlapping representation in the positive sites of Face-M1. Oneway ANOVA showed no significant difference ($p > 0.05$) across the Naive, Extraction and Sham Extraction groups in the mean number of positive sites for the various combinations of overlapping representations of the LAD, RAD and GG muscles. Values shown in mean ± 1SD.

	Naive	Sham Extraction	Extraction	ANOVA
LAD Only	1.50 ± 1.64	0.86 ± 1.22	1.00 ± 1.27	df = 2,16 F = 0.38 p= 0.69
RAD Only	8.00 ± 4.19	6.57 ± 2.37	13.17 ± 10.99	df = 2,16 F = 1.67 p= 0.22
GG Only	1.33 ± 1.96	1.57 ± 2.44	6.0 ± 7.53	df = 2,16 F = 2.00 p= 0.17
LAD and RAD Only	5.00 ± 6.63	4.14 ± 5.53	8.00 ± 8.53	df = 2,16 F = 0.63 p= 0.26
LAD and RAD All	9.5 ± 4.88	7.42 ± 1.61	14.16 ± 11.65	df = 2,16 F = 1.49 p= 0. 55
LAD and GG	0.17 ± 0.40	0.29 ± 0.48	0	df = 2,16 F = 0.94 p= 0.41
RAD and GG	1.33 ± 1.97	1.29 ± 1.60	4.17 ± 6.40	df = 2,16 F = 1.12 p= 0.35
LAD AND RAD AND GG	2.33 ± 1.506	3.86 ± 4.81	4.67 ± 3.56	df = 2,16 F = 0.63 p= 0.54

Table 11. Onset latency of Face-M1 Evoked Responses (ms) There were no significant differences (oneway ANOVA p> 0.05) across the study groups in the mean onset latencies in the LAD, RAD or GG responses evoked from positive sites in the Face-M1. Values shown in mean ± 1SD (ms).

	Naive	Sham Extraction	Extraction	ANOVA
LAD Latency	18.38 ± 2.88	18.16 ±3.47	16.92 ± 2.68	df = 2,16 F = 0.41 p= 0.67
RAD Latency	15.17 ± 2.33	14.08 ± 1.94	13.3 ± 1.13	df = 2,16 F = 1.50 p= 0.252
GG Latency	19.43 ± 3.75	19.11 ± 3.90	15.05 ± 2.17	df = 2,16 F = 3.16 p= 0.07

Table 12. Threshold of positive sites in the Face-M1. There were no significant differences (oneway ANOVA p> 0.05) across the study groups in the mean threshold of LAD, RAD or GG positive sites in the Face-M1. Values shown in mean ± 1SD (μA).

	Naive	Sham Extraction	Extraction	ANOVA
LAD Threshold	57.08 ± 2.97	53.66 ± 4.51	54.33 ± 4.85	df = 2,16 F = 1.94 p= 0.34
RAD Threshold	54.06 ± 3.15	54.14 ± 3.67	53.95 ± 3.352	df = 2,16 F = 0.15 p= 1.00
GG Threshold	55.15 ± 5.01	57.0 ± 2.89	56.38 ± 5.12	df = 2,16 F = 0.13 p= 0.27

Table 13. Centre of gravity - depth (mm). Oneway ANOVA showed no significant difference ($p > 0.05$) in the centre of gravity of the mean representation of the muscles LAD, RAD and GG across the Naive, Extraction and Sham Extraction groups. Values shown in mean ± 1SD.

	Naive	Sham Extraction	Extraction	ANOVA
LAD	2.30 ± 0.51	2.46 ± 0.22	2.47 ± 0.36	df = 2,16 F = 0.57 p= 0.74
RAD	2.21 ± 0.74	2.45 ± 0.28	2.42 ± 0.31	df = 2,16 F = 0.33 p= 0.69
GG	1.75 ± 0.68	2.33 ± 0.22	2.48 ± 0.41	df = 2,16 F = 1.49 p= 0.07

Table 14. Centre of gravity - distance lateral to the bregma (mm). There was no significant difference ($p > 0.05$ oneway ANOVA) in the distance of the centre of gravity lateral to the Bregma for the mean representation of the muscles LAD, RAD and GG across the Naive, Extraction and Sham Extraction groups. Values shown in mean ± 1SD.

	Naive	Sham Extraction	Extraction	ANOVA
LAD ± SD	3.31 ± 0.13	3.25 ± 0.13	3.13 ± 0.17	df = 2,16 F = 0.40 p= 0.81
RAD ± SD	3.34 ± 0.11	3.48 ± 0.25	3.40 ± 0.18	df = 2,16 F = 0.71 p= 0.52
GG ± SD	3.41 ± 0.19	3.38 ± 0.16	3.60 ± 0.21	df = 2,16 F = 1.51 p= 0.18

4. Discussion

This study has shown a small but significant anterior increase in the representation of the LAD, RAD and GG in the contralateral Face-M1 one week following unilateral extraction of maxillary molars in rats. A previous study from our laboratory showed a significant increase in the Face-M1 representation following rat incisor extraction (Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010). These findings suggest that the cortical representation of the jaw and tongue muscles in the Face-M1 may expand in response to extraction (dental deafferentation).

The present study is a continuation of an ongoing series of experiments conducted in our laboratory that estimated the effects of not only incisor extraction (Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010), but also of other dental manipulations such as incisor trimming (Lee, Sessle 2004) on the cortical neuroplasticity of the Face-M1 and Face-S1. The ICMS technique used in this experiment has been widely used to study cortical representation of the M1 in rats (e.g. Donoghue and Wise 1982; Sanderson, Welker et al. 1984; Gioanni and Lamarche 1985; Neafsey, Bold et al. 1986; Lee, Sessle 2004; Adachi, Lee et al. 2007; Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010). In this experiment, the rat cortex was mapped anteroposteriorly, from 2 mm to 4.8 mm anterior to the bregma and mediolaterally from 2.4 mm to 4.8 mm lateral to the bregma. These mapping coordinates encompass most of the Face-M1 representation of the jaw and tongue muscles and are consistent with areas mapped in previous studies in our laboratory (Lee, Sessle 2004; Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010). The horizontal mapping resolution was increased from 500μm to 300 μm to improve the accuracy of detecting the threshold of the evoked responses in the LAD, RAD and GG muscles and also to detect subtle changes representation of the jaw and tongue muscles in the Face-M1 (Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010).

This study measured evoked responses in the LAD, RAD and GG muscles. The evoked responses from the vibrissae and neck were excluded from the analysis due to noise and spontaneous movements that occurred within the maintained anaesthetic level. The masseter muscle was excluded from the analysis due to the few LM and RM responses (2.17 + 3.13) which is consistent with a previous study from our laboratory (Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010).

4.0.1 Rat Weight

The study showed a significant difference in weight gain across the animals in the Naive group and the animals in the Sham Extraction and Extraction groups. The Naive animals did not undergo any operative procedure that might have interfered with their normal growth rate and weight gain. Stress-induced weight loss has been reported previously (Curzon, Joseph et al. 1972; Shimizu, Oomura et al. 1989; Lennie 1999; Varma, Chai et al. 1999; van Kuyck, Casteels et al. 2007). Post-surgical weight loss and stress-induced anorexia has been reported to delay growth and hamper weight gain for up to 17 days following the exposure to stress (Shimizu, Oomura et al. 1989; Lennie 1999; Varma, Chai et al. 1999). There was however, no significant difference in the average weight gain between the Extraction and Sham Extraction groups. This indicates that the decrease in weight gain observed in the Extraction and Sham extraction groups in comparison with the Naive group was likely due to the surgical stress and not due to the effects of unilateral maxillary molar extraction.

4.1. ICMS Findings

4.1.1 Positive Tracks

The Face-M1 extended from 2.4 to 4.5 mm anterior to the bregma and 2.7 to 4.8 mm laterally, which is consistent with the findings of our previous experiments

(Lee, Sessle 2004; Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010). Although there were more positive tracks in the Face-M1 of the Extraction group than in the Sham Extraction and Naive groups, this finding was not statistically significant, possibly because of the large variation observed within the extraction group. However, significant differences were observed in the distribution of the tracks in the Extraction group. There were significantly more positive tracks 3.9 mm to 4.2 mm anterior to the bregma in the Extraction group than in the Sham Extraction and the Naive groups. Mediolaterally the Extraction group also had significantly more positive tracks at the ML planes 3.3 mm and 3.6 mm lateral to the bregma. There was no significant difference in the number of positive tracks in the planes >3.6 mm lateral to the bregma. This suggests that there may have been no actual lateral expansion of the Face-M1 representation in the Extraction group. However, lateral expansion has been previously observed following incisor extraction (Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010). A possible explanation could be related to the influence of the Face-S1 on the Face-M1. The cortical representation of the mandibular incisors is larger than maxillary molar teeth (Shigenaga, Matano et al. 1974; Catania and Remple 2002; Henry, Marasco et al. 2005; Henry, Remple et al. 2006a; Henry and Catania 2006b). The mandibular incisors are represented in the lateral area of the Face-S1 and are closely related to the representation of the tongue (Remple, Henry et al. 2003). Also, certain oromotor functions such as incisor biting and gnawing behaviour could conceivably be more affected by incisor extraction and many studies have reported neurophysiological changes in various parts of the CNS associated with changes in gnawing behaviour (Roberts and Carey 1965; Cooper and Van Hoesen 1972; Cooper and Trowill 1974; Waldbillig 1975; Martins, Nobrega et al. 2008).

4.1.2 Positive Sites

The overall number of positive sites in the Face-M1 of the Extraction group was higher than the Sham Extraction and Naive groups. However, this finding was not statistically significant. There was also no significant difference in the Face-M1 representation of the LAD, RAD and GG across the Naive, Sham Extraction and Extraction groups. Nonetheless, analysis of the individual muscles within the positive sites revealed that the RAD had a larger representation than the LAD and GG in all the study groups but this was not statistically significant. The large representation of the RAD may be explained by the mapping being carried out in the contralateral cortex (left). Previous studies have documented a contralateral predominance of the AD representation in the Face-M1 (Lee, Sessle 2004; Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010).

A significant increase in the mean numbers of positive tracks and sites was observed in the AP planes 3.9 and 4.2 which might be explained by the reactivation of latent synapses (Jacobs and Donoghue 1991; Keller 1993) or by disinhibition of horizontal inhibitory influences (Huntley 1997; Farkas, Perge et al. 2000). However, there were no significant changes associated with the overall mean numbers of positive tracks and sites, possibly due to high variability in the number of positive sites observed between animals in each of the study groups.

4.1.3 Overlapping Representations

The cortical representation in the Face-M1 appears to be organized according to the movement rather than the individual muscles (Kakei, Hoffman et al. 1999; Graziano, Taylor et al. 2002a; Graziano, Taylor et al. 2002b; Aflalo and Graziano 2006). When multiple muscles control a movement, then overlapping representation of these muscles may improve coordination. Such overlapping representations have been observed in the Face-M1 (Sessle and Wiesendanger 1982; Gioanni and Lamarche 1985; Neafsey, Bold et al. 1986; Huang, Sirisko et al.

1988; Murray and Sessle 1992; Burish, Stepniewska et al. 2008; Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010). A significant increase in overlapping muscle representation has been observed following trained coordinated movements (Kwan, Murphy et al. 1987; Sanes, Donoghue et al. 1995; Nudo, Wise et al. 1996c), incisor trimming (Lee, Sessle 2004) and incisor extraction (Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010). However, in this experiment, there was no difference in the overlapping representation across the groups.

4.1.4 Threshold and Onset Latency

Changes in threshold or onset latency of cortically evoked responses could indicate changes in synaptic efficacy of cortical and sub-cortical sites (Stoney, Thompson et al. 1968; Ranck 1975; Asanuma 1976; Ridding and Rothwell 1997; Butovas and Schwarz 2003; Tehovnik, Tolias et al. 2006). There were however, no significant difference in the thresholds and onset latencies of the LAD, RAD and GG muscles in the Naive, Sham Extraction and Extraction groups. There was a decrease in onset latency of the GG in the Extraction group but this was not statistically significant. A previous experiment from our laboratory also showed no change in onset latency following extraction of incisor teeth (Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010).

4.2 Study Inferences

The confounding factors that could have altered the observed neuroplastic changes in this study e.g. exposure to oral operatory procedures, pain induced by soft tissue trauma, general anaesthesia and local anaesthesia were controlled by the use of a Sham Extraction group. The Sham Extraction group experienced all the operatory procedures performed on the Extraction group except for the removal of the teeth and showed no significant changes in the Face-M1.

4.2.1 Effects of Oral Operatory Procedures

The oral operatory procedures were performed on the Sham Extraction and the Extraction groups. Animals that were exposed to the oral operations showed decreased weight gain when compared to the Naive group. This could have been due to surgical stress (Curzon, Joseph et al. 1972; Shimizu, Oomura et al. 1989; Lennie 1999; Varma, Chai et al. 1999; van Kuyck, Casteels et al. 2007) or postoperative pain (LaBanc 1991; Topper, Foltys et al. 2003; Robinson, Boissonade et al. 2004). However, the confounding effect of these factors in the neuroplastic changes observed in the Face-M1 of the Extraction group was controlled by the use of a Sham Extraction group. The effects of local anaesthetic-induced sensory deprivation on the Face-M1 (Nicolelis, Lin et al. 1993; Faggin, Nguyen et al. 1997; Yildiz, Yildiz et al. 2004; Halkjaer, Melsen et al. 2006) is another potential confounder that was also controlled by the use of the Sham Extraction group which did not show any significant changes in the Face-M1.

4.2.1.1 Effects of Pain Induced by Soft Tissue Trauma

Noxious stimuli have been shown to produce neuroplastic changes in the Face-M1 (Boudreau, Romaniello et al. 2007; Adachi, Murray et al. 2008). Additional measures such as the use of a long-acting local anaesthetic (Bupivacaine®) and post-operative analgesia (Ibuprofen®) were followed to minimize the effect of pain on the neuroplasticity of the Face-M1. However, the confounder was also controlled by the use of the Sham Extraction group which did not show any significant changes in the Face-M1.

4.3 Neuroplastic Changes

In this experiment, an anterior increase in the representation of the Face-M1 in the left cerebral cortex was observed following the extraction of the right maxillary

molars. The nature of the underlying neuroplastic changes within the brain could not be accurately determined in this study. Several mechanisms and loci are possible, as noted below.

4.3.1 Mechanisms of Underlying Neuroplasticity of Face-M1

This experiment showed a small but significant increase in the Face-M1 representation of the muscles LAD, RAD and GG in the AP planes 3.9 and 4.2 of the Extraction group. This could have been due to activation of latent synapses (Jacobs and Donoghue 1991; Keller 1993; Huntley 1997a) or due to disinhibition of lateral horizontal connections (Huntley 1997a; Farkas, Perge et al. 2000; Farkas, Racekova et al. 2003).

Pulpal and periodontal denervation following dental extraction can lead to neuroplastic changes in the V brainstem nuclei (Hu, Dostrovsky et al. 1986; Hu and Sessle 1989; Kwan, Hu et al. 1993; Hu, Woda et al. 1999), Face-S1 (Henry, Marasco et al. 2005), and the Face-M1 (Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010). Hence, the changes in Face-M1 observed in the Extraction group of this study could also be due loss of sensory input to the Face-M1 and Face-S1 that could be coupled with related neuroplastic changes in the V brainstem complex and/or ventrobasal thalamus.

Loss of teeth can also affect the entire stomatognathic system. Changes in condylar width and growth following extraction of molar teeth have been reported in rats (Endo, Mizutani et al. 1998). Molar extraction and loss of occlusal contacts produced changes in the periodontal ligament of the opposing teeth due to hypofunction (Kinoshita, Tonooka et al. 1982; Ohshima, Komatsu et al. 1991). Alterations in occlusion could also produce changes in the chewing pattern generator (CPG) in the brain stem (Lund and Dellow 1971; Nakamura 1985; Barlow and Estep 2006; Lund and Kolta 2006). Also, learning disability following

extraction of molar teeth has been reported in rats (Andoh, Sakuma et al. 2009). It is possible that the adaptation of the stomatognathic system to changes in occlusion may have a learning component. Numerous studies have reported on the neuroplastic changes in the Face-M1 following trained movements in the limb (Nudo, Milliken et al. 1996b; Kleim, Swain et al. 1998; Remple, Bruneau et al. 2001; Barbay, Plautz et al. 2006) and tongue (Svensson, Romaniello et al. 2003; Svensson, Romaniello et al. 2006; Boudreau, Romaniello et al. 2007). Skill acquisition and trained motor coordination has been shown to produce an increase in the overlapping muscle representation (Kwan, Murphy et al. 1987; Sanes, Donoghue et al. 1995; Nudo, Wise et al. 1996c), but in this study there was no significant difference between Naive, Sham Extraction and Extraction groups in the overlapping muscle representation of the LAD, RAD and GG muscles in the Face-M1.

4.3.2 Neuroplasticity in Other Parts of the CNS Following Orofacial Interventions.

The neuroplastic changes observed in this study could involve not only the Face-M1 itself but also other areas of the sensorimotor network. For example, the modulation of the Face-M1 output at the sub-cortical level has been observed during rhythmic jaw movements (e.g. Zhang and Sasamoto 1990; Hatanaka, Tokuno et al. 2005; Satoh, Ishizuka et al. 2006; Satoh, Ishizuka et al. 2006). Hence, based on the results of the present study, changes in the sub-cortex cannot be ruled out. Alterations in the corticomotor control of the tongue have been reported following local anaesthesia (Halkjaer, Melsen et al. 2006). Similarly, neuroplastic changes in the ascending V system following noxious stimuli (Florenzano and De Luca 1999; Chiang, Wang et al. 2007; Xie, Zhang et al. 2007; Okada-Ogawa, Suzuki et al. 2009) and following pulp extirpation (Hu, Dostrovsky et al. 1986; Hu

and Sessle 1989; Kwan, Hu et al. 1993; Hu, Woda et al. 1999) have also been reported. Hence, neuroplastic changes in other parts of the sensorimotor network may contribute to or account for the Face-M1 changes observed in the present study.

4.4 Clinical Implications

It is well known that partial or complete edentulism can affect an individual's chewing efficacy (Boretti, Bickel et al. 1995; Sheiham and Steele 2001; Ueno, Yanagisawa et al. 2008; Ueno, Yanagisawa et al. 2009) and the quality of life (Trulsson, Engstrand et al. 2002; Gilbert, Meng et al. 2004; Steele, Sanders et al. 2004; Mack, Schwahn et al. 2005; Wong and McMillan 2005; Muller, Naharro et al. 2007; Brennan, Spencer et al. 2008; Pallegedara and Ekanayake 2008). Treatment strategies employing the effects of cortical neuroplasticity have become popular in the field of medicine for phantom limb pain (Saitoh, Shibata et al. 1999; Taub, Uswatte et al. 1999; Karl, Birbaumer et al. 2001; Schwenkreis, Witscher et al. 2001; Schwenkreis, Maier et al. 2003; Topper, Foltys et al. 2003; Irlbacher, Kuhnert et al. 2006; Lazorthes, Sol et al. 2007), and stroke rehabilitation etc. (Lee and van Donkelaar 1995; Taub, Uswatte et al. 1999; Hallett 2001; Butler and Wolf 2003; Butefisch, Khurana et al. 2004; Cauraugh and Summers 2005; Brown, Lutsep et al. 2006; Butler and Wolf 2007; Adkins, Hsu et al. 2008; Ludlow, Hoit et al. 2008; Masiero and Carraro 2008; Robbins, Butler et al. 2008; Oujamaa, Relave et al. 2009). This study shows that unilateral extraction of maxillary molar teeth produces a small but significant increase in the representation of the LAD, RAD and GG in the contralateral Face-M1 in the AP 3.9 and 4.2 planes. This could indicate changes in the Face-M1 control of the jaw and tongue muscles. These changes could be useful to understand the neurophysiology of the orofacial region and to develop newer therapeutic methods for orofacial diseases like atypical facial pain, unilateral facial paralysis etc.

4.5 Study limitations

Although ICMS has been a popular method used to study changes in cortical neuroplasticity, it does have some limitations. The present experiment was conducted under light anaesthesia with (ketamine and xylazine), which is difficult to maintain at a constant tittered level. Any changes in anaesthetic levels might produce large variations in the excitability of the motor cortex (Donoghue and Wise 1982; Sessle and Wiesendanger 1982; Graziano, Taylor et al. 2002a; Tandon, Kambi et al. 2008). However, the potential confounding effect of anaesthesia does not apply to the present results comparing the Extraction, Sham Extraction and Naive groups as it was common to all study groups. ICMS studies have also been conducted in awake animals (Murray, Lin et al. 1991; Lin, Murray et al. 1993; Martin, Kemppainen et al. 1999; Yao, Yamamura et al. 2002a; Yao, Yamamura et al. 2002b). Hence, the potential confounding effect of the level of anaesthesia can be addressed in future studies using awake rats. The ICMS results could also be verified by using other techniques such as staining / labeling the cortex with tracers, single neuron recordings, fMRI etc. Inaccuracies in the histological designation of the Face-M1 and its borders (e.g. with Face-S1) could occur due to errors in the orientation of the section plane, thickness of the section and the functional overlap that may occur between various cytoarchitectural zones. However, this was common to the three study groups and so could not have affected any differences observed between the groups.

This study only evaluated the effect of extraction of a unilateral maxillary quadrant. Hence, it cannot provide a complete picture of the neuroplastic changes that occur in the Face-M1 following all possible orofacial interventions. Evaluation of additional parameters such as orthodontic tooth movement, replacement of lost teeth etc. is necessary to consolidate inferences regarding neuroplastic changes in the Face-M1 following orofacial interventions. Also, the study measured the

neuroplastic changes one week following molar extractions and changes at longer time periods cannot be predicted with the current findings. This study did not analyze the neuroplastic changes in the Face-S1 that could be associated with the neuroplastic changes observed in the Face-M1.

The horizontal resolution used in this study (300 μm) was higher than the resolution (500 μm) used in previous experiments in our laboratory (Lee, Sessle 2004; Avivi-Arber 2009; Avivi-Arber, Lee et al. 2010) but, subtle neuroplastic changes in muscle representation can occur within 100 μm (Asanuma, Arnold et al. 1976) and so such changes might not have been identified in the present study . However, the ICMS stimulus current used in this experiment has been reported to spread up to 500 μm (Asanuma, Stoney et al. 1968; Stoney, Thompson et al. 1968) and so the entire distance between two adjacent tracks (300μm) should have been stimulated under the current protocol. Nonetheless, the decreased distance between adjacent ICMS tracks (300m) could result in repeated stimulation of some adjacent sites leading to false over-representation of some muscles in the ICMS-defined maps (Sessle and Wiesendanger 1982; Tehovnik, Tolias et al. 2006).

Another limitation of the study is that repeated stimulation of the Face-M1 itself can produce neuroplastic changes that can affect the results (Asanuma 1991). In previous experiments, the area of mapping depended on the area of the Face-M1 representation; this variability in the mapping area could have been a huge potential confounder and affected the results. In this study, the mapping area was defined and maintained consistent (2 mm to 4.8 m anterior to the bregma and 2.4 mm to 4.8 mm lateral to the bregma) in all three groups and so the number of penetrations were also similar in across the study groups. However, the number of lesions did vary according to the number of positive tracks and this could be another potential confounder in this study. The size of the lesion produced by DC current was approximately 200μm. Hence, subsequent lesions of adjacent tracks

might have severed the sub-cortical connections and affected the results. Post-extraction pain due to extraction and soft tissue trauma could have also been another confounder, however the effect of this variable was minimized by the use of surgical anaesthesia, post-surgical analgesia and used of a sham group as noted above.

4.6 Future scope of research

The novel findings in this study will provide valuable information on the adaptive / maladaptive changes that occur in the Face-M1 following unilateral extraction of maxillary molar teeth. However, similar studies in awake rats need to be performed to avoid the potential confounding effects of general anaesthesia. This could also provide additional information on whether any changes in orofacial sensorimotor behaviour are occurring that could be driving the neuroplastic changes or whether the neuroplastic changes are contributing to any alterations in the behaviour. Future studies involving the extraction of more than one quadrant of teeth could be carried out to study the effect of greater tooth loss on Face-M1 neuroplasticity. Although changes in the Face-M1 observed in this study have good spatial and temporal resolutions, the results are limited to the Face-M1. Furthermore, the horizontal mapping resolution was increased in this experiment from 500μm (that is typically used in ICMS mapping studies such as those previously carried our in our laboratory) to 300 μm, in order to potentially improve the accuracy of detecting the threshold and subtle changes in the representation of the jaw and tongue muscles in the Face-M1. However, it is difficult to quantitatively evaluate the benefit of this approach because of differences in experimental approaches used in the present and previous studies (e.g. type and depth of general anesthesia) plus the limited data available from the previous experiments (e.g. the reporting of the mean number of positive sites (Avivi-Arber et al. 2010) or mean threshold of the MEP in

the Face-M1 (Franchi et al. 2000) does not allow for a detailed comparison between specific Face-M1 sites from the different studies). Hence, additional future analysis that compare the detailed motor maps at specific AP, ML coordinates across data of previous studies can be performed to determine the ideal mapping resolution for ICMS experiments in rats. Future studies using fMRI in humans can explore simultaneous changes taking place in other parts of the CNS after extraction such as brainstem complex and the Face-S1 which was only partially mapped in this study. Also, this study examined the neuroplastic changes in Face-M1 a week after extraction. Future studies testing for the neuroplastic changes at longer post-operative time intervals will be helpful to study the pattern and extent of functional adaptation following the extraction of maxillary molars.

Based on results of the present study, future studies comparing the effects of replacement of the lost teeth with implants in the Face-M1 and Face-S1 could be conducted. Similarly, the effects of loss of teeth in other parts of the oral cavity and their correlation with the representation of the teeth in the Face-M1 and Face-S1 could also be studied. Furthermore, extensive degenerative and regenerative changes in the V brain stem complex have been reported following the loss of deciduous teeth (e.g. Hu et al. 1992), so future studies could be conducted to determine if the loss of deciduous teeth produces similar neuroplastic changes in the Face-M1.

The results of the present study could also be supplemented with similar studies in primates and later in humans with TMS or fMRI techniques. TMS-modulated changes after extraction and restoration by implants could also be studied and further implemented for therapeutic use in the future. Also, time-dependent changes in cortical (long-term) neuroplasticity following extraction and implant placement could be examined.

5. Conclusion:

Unilateral extraction of maxillary molars in rats is associated one week later with a small but significant anterior increase in the representation of the LAD, RAD and GG in the contralateral Face-M1.

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