Turun yliopisto
University of Turku

NEURAL MECHANISMS OF OROFACIAL PAIN – EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION

Pauliina Lindholm

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
Sarja - ser. D osa - tom. 1274 | Medica - Odontologica | Turku 2017

University of Turku

Faculty of Medicine
Department of Clinical Medicine
Department of Clinical Neurophysiology
University of Turku Doctoral Programme of Clinical Investigation
Division of clinical neurosciences, Turku University Hospital

Supervised by

Professor Satu K. Jääskeläinen
Department of Clinical Neurophysiology
Turku University Hospital and
University of Turku, Turku, Finland

PhD Salla Lamusuo
Division of Clinical Neurosciences
Turku University Hospital and
University of Turku, Turku, Finland

Reviewed by

Adjunct Professor Erika Kirveskari
Department of Clinical Neurophysiology
Helsinki University Hospital and
University of Helsinki, Helsinki, Finland

Adjunct Professor Jyrki Mäkelä
BioMag Laboratory
Helsinki University Hospital and
University of Helsinki, Helsinki, Finland

Opponent

Adjunct Professor Nina Forss
Department of Neurology, Helsinki University Hospital and University of Helsinki
Head of CliniMEG-group
Department of neuroscience and biomedical engineering, Aalto University, Helsinki, Finland

ISBN 978-951-29-6757-5 (PRINT)
ISBN 978-951-29-6758-2 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama Oy - Turku, Finland 2017

ABSTRACT

Pauliina Lindholm

NEURAL MECHANISMS OF OROFACIAL PAIN – EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION

University of Turku, Faculty of Medicine, Department of Clinical Medicine, Department of Clinical Neurophysiology; Turku Doctoral Programme of Clinical Investigation; Division of clinical neurosciences, Turku University Hospital

Neuropathic orofacial pain is challenging to treat. Limited knowledge of the underlying pain-syndrome-specific pathophysiology is one of the reasons for poor response to current pharmacotherapy. Patients with treatment-resistant neuropathic pain are susceptible to concomitant psychiatric and sleep disorders. Psychiatric disorders, sleep problems, and certain personality traits may, in turn, predispose to chronic pain. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulation technique that has been shown to alleviate neuropathic pain, but the mechanisms of its action and optimal treatment parameters are still unclear.

We investigated rTMS effects in healthy subjects and chronic neuropathic orofacial pain patients, and compared the analgesic efficacy of stimulation given to different cortical targets. We also evaluated the brain mechanisms involved in rTMS-induced analgesia, especially the dopamine-opioid system. The genetically determined function of the endogenous dopamine system was also investigated regarding thermal and pain perception.

We discovered that rTMS targeted to the right secondary somatosensory cortex (S2) alleviated neuropathic orofacial pain (Cohen's d = 0.60). Pain intensity assessed in numerical rating scale was significantly lower after the S2 stimulation than after the stimulation of the primary somatosensory and motor cortex (S1/M1) ($p = 0.007$) or placebo ($p = 0.019$). The analgesic effect of stimulation of the S2 region was not mediated or predicted by comorbid psychiatric or sleep disorders. Orofacial pain patients had more psychiatric and sleep disorders than the general population and there were several associations between these comorbid disorders.

The variation caused by single nucleotide polymorphism 957C>T in dopamine receptor D2 (DRD2) gene had an effect on thermal perception and rTMS effects in healthy subjects. rTMS to S1 cortex increased heat pain detection thresholds only in subjects homozygous for the 957T allele ($F_{6,24} = 3.78$, $p = 0.009$), whose mean heat pain detection thresholds were initially lower than those of 957C allele carriers ($p < 0.05$). The "pain sensitive" 957TT genotype was overrepresented (50% vs. 27% in general population, $p = 0.019$) in our unselected group of neuropathic pain patients.

In the positron emission tomography (PET) study on healthy subjects, lower μ-opioid receptor availability indicting activation of the endogenous opioid system, was seen in a brain network associated with pain processing after active S1/M1 rTMS compared to sham ($p \leq 0.0001$).

Our results suggest that the brain dopamine-opioid system is important in the perception and modulation of pain, and in rTMS-induced analgesia. Genetic regulation of striatal DRD2 function may explain some of the individual differences in pain sensitivity and in risk for neuropathic pain.

Key words: transcranial magnetic stimulation, neuropathic orofacial pain, motor cortex, primary somatosensory cortex, secondary somatosensory cortex, dopamine-opioid system

TIIVISTELMÄ

Pauliina Lindholm

KASVOKIVUN NEURAALISET MEKANISMIT – TRANSKRANIAALISEN MAGNEETTISTIMULAATION VAIKUTUKSET

Turun yliopisto, Lääketieteellinen tiedekunta, kliininen laitos, kliinisen neurofysiologian oppiaine; Turun kliininen tutkijakoulu; Turun yliopistollisen keskussairaalan neurotoimialue.

Kroonisen neuropaattisen kasvokivun hoito on haasteellista. Neuropaattisen kasvokivun syitä ja sille altistavia tekijöitä ei vielä täysin tunneta, mikä vaikeuttaa tehokkaan hoidon löytämistä. Krooninen hoitoresistentti kipu voi altistaa mielialaongelmille ja univaikeuksille, jotka yhdessä tiettyjen persoonallisuuden piirteiden kanssa taas altistavat kivun pitkittymiselle. Repetitiivinen transkraniaalinen magneettistimulaatio (rTMS) on kajoamaton neuromodulaatiomenetelmä, jonka on osoitettu lievittävän neuropaattista kipua. Magneettistimulaation tarkat vaikutusmekanismit ja parhaat hoitoprotokollat ovat kuitenkin vielä epäselviä.

Tässä tutkimuksessa selvitimme rTMS:n vaikutusmekanismeja terveillä vapaaehtoisilla ja kroonisesta neuropaattisesta kasvokivusta kärsivillä potilailla, sekä vertasimme eri aivoalueiden stimulaation vaikutuksia kipupotilaiden kipuun, mielialaan, uneen ja elämänlaatuun. Lisäksi selvitimme rTMS:n aivotason vaikutusmekanismeja, erityisesti aivojen dopamiini-opiodi järjestelmän osalta. Tutkimme myös aivojen sisäsyntyisen dopamiinijärjestelmän geneettisen säätelyn merkitystä kivun kokemisessa ja käsittelyssä sekä sen vaikutusta neuropaattisen kivun riskiin.

Totesimme, että oikealle sekundaariselle tuntoaivokuorelle (S2) suunnattu rTMS lievitti neuropaattista kasvokipua. Kivun voimakkuus mitattuna numeerisella arviointiasteikolla oli S2-seudun stimulaation jälkeen merkittävästi matalampi kuin primaarisen tuntoaivokuoren ja liikeaivokuoren (S1/M1) stimulaation ($p = 0,007$) tai lumestimulaation ($p = 0,019$) jälkeen. S2-seudun stimulaation hoitovaste oli riippumaton potilaiden mieliala- tai unihäiriöistä. Kasvokipupotilailla oli selvästi enemmän psykiatrisia sairauksia ja uniongelmia kuin väestössä yleensä, ja näiden rinnakkaissairauksien välillä oli riippuvaisuutta.

Dopamiini D2-reseptorin (DRD2) perinnöllisellä vaihtelulla oli vaikutusta terveiden koehenkilöiden kylmä-, lämpö- ja kiputuntokynnyksiin. S1-aivokuorelle annettu rTMS nosti kuumakipukynnyksiä vain 957T-genotyypin kantajilla ($F_{6,24} = 3,78$, $p = 0,009$), joiden kuumakipukynnykset olivat lähtökohtaisesti matalammat kuin 957C-genotyypin kantajien ($p < 0,05$). Kivulle herkimmän TT-genotyypin kantajia oli enemmän kasvokipupotilaiden ryhmässä kuin väestössä yleensä (50% vs. 27%, $p = 0,019$).

Aivojen positroni-emissiotomografiatutkimuksessa (PET) todettiin, että lumehoitoon verrattuna S1/M1 rTMS laski μ-opioidireseptorien saatavuutta aivoalueilla jotka osallistuvat kiputuntemuksen käsittelyyn ($p \leq 0,000$). Löydös viittaa rTMS:n aktivoivan aivojen sisäsyntyistä opioidijärjestelmää.

Tulostemme perusteella aivojen dopamiini-opioidisysteemi vaikuttaa kivun kokemiseen ja säätelyyn, sekä rTMS-hoidon tehoon. Tyvitumakkeiden DRD2-tiheyttä säätelevä geneettinen muuntelu saattaa osaltaan selittää yksilöiden välisiä eroja kipuherkkyydessä ja alttiudessa saada neuropaattinen kipu hermovaurion jälkeen.

Avainsanat: transkraniaalinen magneettistimulaatio, neuropaattinen kasvokipu, liikeaivokuori, primaarinen tuntoaivokuori, sekundaarinen tuntoaivokuori, dopamiini-opioidisysteemi

CONTENTS

ABSTRACT **3**

TIIVISTELMÄ **4**

CONTENTS **5**

ABBREVIATIONS **7**

LIST OF ORIGINAL PUBLICATIONS **9**

1. INTRODUCTION **10**

2. REVIEW OF THE LITERATURE **12**

2.1. The somatosensory system 12
2.1.1. The mechanosensory pathways - The medial lemniscal pathway 12
2.1.2. The pain and temperature pathways – The anterolateral system 12
2.1.3. Pain processing in the brain 13
2.1.4. Basal ganglia in pain processing and modulation 16
2.1.5. Exteroception vs. interoception 16
2.2. Neuropathic pain – Chronic orofacial pain 17
2.2.1. Neuropathic pain – definition and diagnosis 17
2.2.2. Mechanisms of neuropathic pain 17
2.2.2.1. Mechanisms of neuropathic pain in the peripheral nervous system 17
2.2.2.2. Mechanisms of neuropathic pain in the spinal cord 17
2.2.2.3. Mechanisms of neuropathic pain in the brain 18
2.2.3. Etiology of neuropathic pain 19
2.2.4. Symptoms of neuropathic pain 19
2.2.5. Risk factors for neuropathic pain 20
2.2.5.1. Dopamine genetics and pain 20
2.2.5.2. Common risk factor for neuropathic pain 20
2.2.6. The comorbid disorders related to chronic neuropathic pain 22
2.3. Dopamine-opioid system and pain 22
2.3.1. General considerations 22
2.3.2. Dopamine and clinical pain syndromes 23
2.3.3. Dopamine-opioid interaction 24
2.3.4. Dopamine-opioid system in placebo analgesia 24
2.3.5. Positron emission tomography (PET) in human pain research 25
2.4. Measuring neuropathic pain and its signs 25
2.4.1. Clinical examination 25
2.4.2. Quantitative sensory testing (QST) 26
2.4.3. Neurophysiological testing 26
2.5. Therapeutic neuromodulation for chronic pain 27

2.5.1. Invasive neuromodulation – spinal cord stimulation (SCS), deep brain stimulation (DBS) and motor cortex stimulation (MCS) 28
2.5.2. Noninvasive neuromodulation – repetitive transcranial magnetic stimulation (rTMS) 28

3. AIMS OF THE STUDY 31

Outline of the work 31

4. SUBJECTS AND METHODS 32

4.1. Subjects 32
4.2. Study designs 34
4.3. Quantitative sensory testing (QST) 36
4.4. Determination of the subjects' discriminative capacity and response criterion 36
4.5. Blink reflex habituation 37
4.6. Contact heat evoked potential (CHEP) recording 37
4.7. DNA analysis 38
4.8. Repetitive transcranial magnetic stimulation (rTMS) 38
4.9. Positron emission tomography (PET) 41
4.10. Statistical analyses 42

5. RESULTS 43

6. DISCUSSION 49

7. CONCLUSIONS 54

ACKNOWLEDGEMENTS 55

REFERENCES 57

ORIGINAL PUBLICATIONS 73

ABBREVIATIONS

ACC	anterior cingulate cortex
AIC	anterior insular cortex
ANOVA	analysis of variance
AFP	atypical facial pain
BDI	Beck Depression Inventory
BG	basal ganglia
BMI	body mass index
BMS	burning mouth syndrome
BNSQ	Basic Nordic Sleep Questionnaire
BPI	Brief Pain Inventory
CDT	cool detection threshold
CHEP	contact heat evoked potential
COMT	catechol-O-methyltransferase
CPT	cold pain threshold
DA	dopamine
DBS	deep brain stimulation
DLPFC	dorsolateral prefrontal cortex
DRD2	dopamine receptor D2
EM	estimate of mean
ENMG	electroneuromyography
HF	high frequency
HPT	heat pain detection threshold
ICHD	international criteria for headache disorders
LEP	laser evoked potential
LTP	long-term potentiation
M1	primary motor cortex
MCS	motor cortex stimulation
MEP	motor evoked potentials
MET	methionine
MOS	Medical Outcomes Study Sleep Score
MRI	magnetic resonance imaging
NePIQoL	Neuropathic Pain Impact on Quality-of-Life
NRS	numerical rating scale
OCC	occipital cortex
PAG	periaqueductal gray
PET	positron emission tomography
PFC	prefrontal cortex
PIC	posterior insular cortex
PPC	posterior parietal cortex
QS	quantity of sleep
QST	quantitative sensory testing
RAND-36	health-related quality of life questionnaire
rmANOVA	repeated measures analysis of variance
RMT	resting motor threshold
rTMS	repetitive transcranial magnetic stimulation
RVM	rostroventral medulla
S1	primary somatosensory cortex

S2	secondary somatosensory cortex
SA	sleep adequacy
SCID-I	structured clinical interview for axis I disorders
SD	standard deviation
SCS	spinal cord stimulation
SE	standard error
SEP	somatosensory evoked potentials
SLD	sleep disturbance
SNR	snoring
SS	daytime somnolence
tDCS	transcranial direct current stimulation
Th	thalamus
TNP	trigeminal neuropathic pain
VAL	valine
WDT	warm detection threshold

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by Roman numericals I-IV:

I Lindholm P, Lamusuo S, Taiminen T, Pesonen U, Lahti A, Virtanen A, Forssell H, Hietala J, Hagelberg N, Pertovaara A, Parkkola R, Jääskeläinen S. **Right secondary somatosensory cortex-a promising novel target for the treatment of drug-resistant neuropathic orofacial pain with repetitive transcranial magnetic stimulation.** Pain 2015 Jul; 156(7):1276–83.

II Lindholm P, Lamusuo S, Taiminen T, Virtanen A, Pertovaara A, Forssell H, Hagelberg N, Jääskeläinen S. **The analgesic effect of therapeutic rTMS is not mediated or predicted by comorbid psychiatric or sleep disorders.** Medicine 2016 95:44:e5231.

III Jääskeläinen SK, Lindholm P, Valmunen T, Pesonen U, Taiminen T, Virtanen A, Lamusuo S, Forssell H, Hagelberg N, Hietala J, Pertovaara A. **Variation in the dopamine D2 receptor gene plays a key role in human pain and its modulation by transcranial magnetic stimulation.** Pain 2014 Oct;155(10):2180–7.

IV Lamusuo S, Hirvonen J, Lindholm P, Martikainen I, Hagelberg N, Parkkola R, Taiminen T, Hietala J, Helin S, Virtanen A, Pertovaara A, Jääskeläinen SK. **Neurotransmitters behind pain relief with transcranial magnetic stimulation – PET evidence for release of endogenous opioids.** Accepted for publication in the European Journal of Pain.

1. INTRODUCTION

Neuropathic pain is a major health problem, affecting about 7–8% of the general population (Torrance et al. 2006; Bouhassira et al. 2008). Current medical treatment for neuropathic pain is insufficient, with only 30–40% of the patients receiving satisfactory (> 50%) pain relief (Attal et al. 2006; Dworkin et al. 2007; Finnerup et al. 2015). The poor response to pharmacotherapy may partly depend on the limited knowledge of the pain state specific and individual pathophysiological mechanisms. Advanced neuroimaging and neurostimulation techniques are nowadays expanding our understanding about the neurotransmitters and genetic factors involved in pain perception and modulation.

Trigeminal neuropathic pain (TNP) is due to a lesion or disease of the trigeminal nerve. Atypical facial pain (AFP) and burning mouth syndrome (BMS) are chronic orofacial pain conditions of uncertain etiology. AFP has been described as poorly localized, mostly unilateral, diffuse aching or nagging facial pain that does not follow peripheral neuroanatomical distributions (Woda and Pionchon 1999; Forssell et al. 2007; ICHD 2013). BMS has been characterized as burning, typically bilateral intraoral pain that is usually minimal on awakening and increases in intensity as the day progresses (Scala et al. 2003; ICHD 2013; Balasubramaniam and Klasser 2014). The underlying pathophysiologies of AFP and BMS are unclear, but both central and peripheral neuropathic causes have been proposed. In quantitative sensory testing (QST), sensory deficits typical to peripheral neuropathy have been reported in AFP (Pfaffenrath et al. 1993; Jääskeläinen et. al. 1999, Forssell et al. 2007) and BMS (Jääskeläinen et al. 1997; Forssell et al. 2002; Lauria et al. 2005). Positron emission tomography (PET) studies have shown abnormalities in brain dopamine activity in both conditions (Jääskeläinen et al. 2001; Hagelberg et al. 2003 a,b). AFP and BMS have been associated with various psychiatric disorders, such as depression, anxiety and personality disorders (Scala et al. 2003; Al Quran 2004; Maina et al. 2005; Taiminen et al. 2011; Schiavone et al. 2012). It has been proposed that there could be a shared vulnerability to both chronic orofacial pain and psychiatric disorders, most probably mediated by low brain dopamine activity (Taiminen et al. 2011, Jääskeläinen et al. 2012). In addition to psychiatric disorders, BMS patients are susceptible to concomitant sleep disorders (Chainani-Wu et al. 2011; Adamo et al. 2013). This multidirectional relationship between pain, psychiatric disorders, and sleep disorders has not been thoroughly investigated in patients with neurophysiologically verified neuropathic orofacial pain.

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulation technique that allows cortical brain stimulation by magnetic fields applied to the scalp. High-frequency rTMS of the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) have been shown to have an analgesic effect on neuropathic pain (André-Obadia et al. 2008; Borckardt et al. 2009; Cruccu et al. 2010; Lefaucheur et al. 2014, Cruccu et al. 2016).The DLPFC stimulation is primarily used and especially effective in treating depression (Slotema et al. 2010; Lefaucheur et al. 2014). Precise

mechanisms behind these actions are unclear, but long-term potentiation (LTP)-like mechanisms and activation of endogenous dopamine-opioid system and neurotransmitters have been implicated (Strafella et al. 2001, 2003; Kim et al. 2008; Hoogendam et al. 2010; de Andrade et al. 2011; Viisanen et al. 2012; Moisset et al. 2015).

Here we investigated the analgesic effects and neurotransmitter mechanisms of rTMS given to different cortical targets. We also examined the role of the brain dopamine-opioid system genetics in pain perception and in rTMS effects. In addition, we evaluated whether the possible analgesic effects induced by rTMS depend on simultaneous improvement of patients' psychiatric or sleep disorders or if these baseline comorbidities could predict the treatment outcome.

2. REVIEW OF THE LITERATURE

2.1. The somatosensory system

The somatosensory system mediates a wide range of sensations, from touch, pressure, vibration, limb and body position to temperature and pain. Somatic sensations are mediated via afferent nerve fibers that have specialized peripheral receptors within the skin (exteroceptors, superficial sensation) or in muscles and joints (proprioceptors, deep sensation). Cutaneous mechanoreceptors mediate the sensation of fine touch, vibration and pressure. Proprioceptors in muscles, tendons and joints sense the position of body parts in space. Receptors in free nerve endings transmit information about painful stimuli, temperature, and coarse touch. Large diameter axons from muscle spindles (Ia, II) and touch receptors (Aβ) have the highest conduction velocity (35–120 m/s), whereas small diameter axons from free nerve endings mediating pain and thermal sensations (Aδ, C), have slow conduction velocity (Julius and Basbaum 2001). Thinly myelinated Aδ fibers responsible for transmitting sharp first pain have a bit faster conduction velocity (5–30 m/s) than the unmyelinated C fibers (0.5–2 m/s) mediating dull second pain and itch. All somatosensory afferents have their cell bodies in the dorsal root ganglia that are situated bilaterally within the spinal column or cranial nerve ganglia; in case of the trigeminal nerve, ganglion Gasseri. Trigeminal nerve innervates the skin of the face and most of the intraoral mucosa.

2.1.1. The mechanosensory pathways - The medial lemniscal pathway

The mechanosensory afferents enter the spinal cord through the dorsal roots and ascend to the medulla ipsilaterally in the dorsal column, also called the posterior funiculus - medial lemniscal pathway. In the medulla, they synapse and the second order neurons decussate forming the medial lemniscus contralaterally in the brainstem. The axons of the medial lemniscus synapse in the ventral posterior lateral nucleus of the thalamus. From the thalamus, the third order neurons project to the primary somatosensory cortex (S1) in the posterior bank of the central sulcus and to the secondary somatosensory cortex (S2) in the parietal operculum. The mechanosensory receptors of the face have their cell bodies in the trigeminal ganglion and the first synapse ipsilaterally in the trigeminal principal nucleus in mid-pons. From there, the second order neurons cross the midline and ascend to the thalamus in the trigeminal lemniscus and synapse in the ventral posterior medial nucleus of the thalamus. Third order neurons send their axons to the S1 and S2 cortices. (Review in Purves et al. 2012).

2.1.2. The pain and temperature pathways – The anterolateral system

The Aδ and C nociceptors convey information of all potentially injurious stimuli, whether mechanical, thermal or chemical (Julius and Basbaum 2001). The nociceptive afferents of the body enter the spinal cord via the dorsal roots, where the majority of fibers synapse on neurons in the superficial dorsal horn in laminas I and II

(substantia gelatinosa), yet some Aδ and C fibers terminate in lamina V. The axons from these neurons cross the midline and ascend in the anterolateral quadrant of the spinal cord, where they form the anterolateral system of ascending fibers. In general, nociceptive fibers ascend within the lateral spinothalamic tract that projects to the mesencephalic reticular formation and the thalamus (Apkarian and Hodge 1989). From the sensory nuclei of the thalamus and the reticular system, neurons project to the somatosensory areas of the cortex (S1 and S2) and other brain areas known to be concerned with pain perception (Lenz et al. 1998; Forss et al. 2005; Frot et al. 2009 and 2013). Thermal and nociceptive information of the face originates from neurons in the trigeminal ganglion and ganglia of the cranial nerves VII, IX, and X. After entering the pons, these fibers first descend to the spinal nucleus of the trigeminal complex in the caudal medulla and synapse to second order neurons that cross the midline and ascend to higher targets in the brainstem and thalamus (Purves et al. 2012). From thalamic nuclei, information is projected to a network of brain areas processing pain.

2.1.3. Pain processing in the brain

The experience of pain is multidimensional with sensory-discriminative, affective-motivational, and cognitive-evaluative components (Melzack and Casey 1968). Neurophysiological (EEG, MEG) and hemodynamic (PET, SPECT, fMRI) studies have shown that there is a wide network of brain areas activated during pain processing. The sensory-discriminative component of pain includes the stimulus location, intensity, and quality discrimination and is thought to be processed in the S1, S2, posterior parietal (PPC) and posterior insular cortices (PIC) (Coghill et al. 1999; Peyron et al. 1999; Bushnell et al. 1999; Treede et al. 1999; Forss et al. 2005; Peltz et al. 2011). The affective-motivational component of pain encompasses emotional and attentional reactions that are considered to be processed in the anterior insular cortex (AIC) and the anterior cingulate cortex (ACC) connected to the limbic system (Rainville et al. 1997; Tölle et al. 1999; Treede et al. 1999; Vogt and Sikes 2000; Peltz 2011). The cognitive axis covers attention, anticipation and memory of past experiences, which are processed in a large brain network including prefrontal (PFC), posterior, parietal and anterior cingulate cortices, periaqueductal gray (PAG), basal ganglia (BG) and thalamus (Th) (Jones et al. 1991; Derbyshire et al. 1994; Peyron et al. 1999; Coghill et al. 1999). A meta-analysis by Apkarian et al. (2005) indicates that the main components of the pain network, or often called pain neuromatrix (Melzack 1999), are S1, S2, IC, ACC, PFC, and Th. The complex circuitry between the brain areas involved in pain processing is presented in Figure 1.

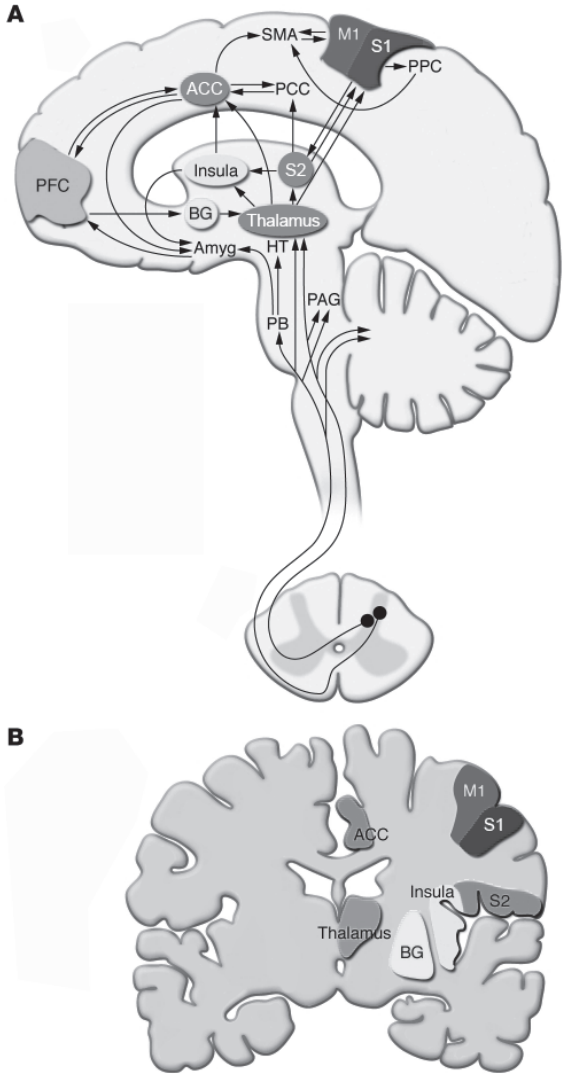


Figure 1. Pain network – the main brain areas processing pain (Modified from Schweinhardt and Bushnell 2010)

The insular cortex is suggested to play a crucial modulatory and integrative role in pain perception through its strong functional connections to this widely distributed brain network (Treede et al. 2000; Craig et al. 2000; Maihöfner et al. 2002; Baumgärtner et al. 2010; Wiech et al. 2010; Peltz et al. 2011). The parasylvian PIC and its adjoining medial operculum are the only areas in the brain where electrical stimulation causes acute pain, and focal lesions generate selective pain deficits (Garcia-Larrea 2012; Mazzola et al. 2012). Dysplasia in the PIC can trigger painful epileptic seizures that can be stopped by thermocoagulating the focus (Insard et al. 2011). A recent study showed that the activation of the AIC predicted whether a stimulus was perceived painful or not (Ploner et al. 2010). Another study of the same group showed that the activation of the AIC reflected the integration of the perceived threat value of the stimulation into the decision about pain (Wiech et al. 2010). It was also demonstrated

that anticipation of pain increased the prestimulus functional connectivity between the AIC and midcingulate cortex (Wiech et al. 2010). These findings suggested that the AIC is important in integrating information about salience into the decision-making concerning pain.

From the insular cortex, pain modulating pathways descend to periaqueductal gray (PAG), rostroventral medulla (RVM) and spinal cord, as presented in Figure 2.

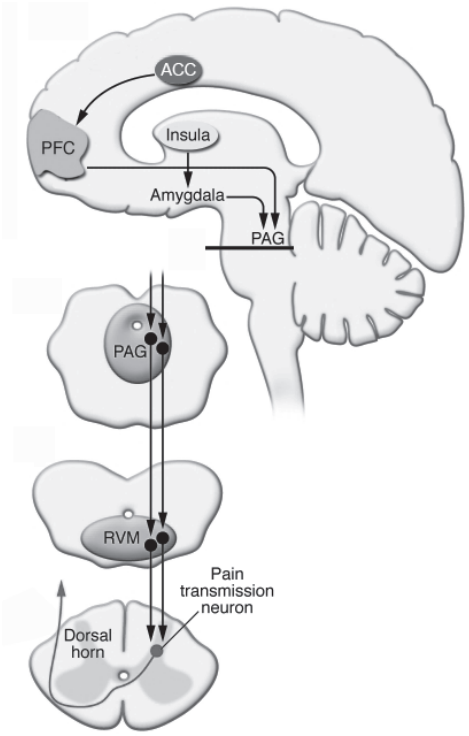


Figure 2. Descending pain pathways (Modified from Schweinhardt and Bushnell 2010)

Descending axons have direct contacts with nociceptive neurons of the spinal dorsal horn and spinal interneurons (Westlund et al. 1990). Brainstem-spinal pathways participate in the regulation of spatial (Bouhassira et al. 1995) and temporal (Pertovaara 1999) summation in the spinal nociceptive neurons, and participate both in facilitation and inhibition of ascending nociceptive input (Millan 2002; Pertovaara and Almeida 2006). Multiple neurotransmitters, such as noradrenaline and serotonin (Jones 1991; Stone et al. 1998), are released from the descending axons, and spinal horn interneurons also contain inhibitory (γ-aminobutyric acid, glycine, encephalin) and excitatory (neuropeptides) neurotransmitters (Ruda et al. 1986). The dopaminergic system appears to be important in descending control of pain, both at the supraspinal and spinal levels (Fleetwood-Walker et al. 1988; Millan 2002; Hagelberg et al. 2004; Viisanen et al. 2012).

2.1.4. Basal ganglia in pain processing and modulation

The BG include the striatum, the external and internal segments of globus pallidus, the subthalamic nucleus, and the substantia nigra. The striatum is further divided to caudate, putamen, and the core of the nucleus accumbens (Kreitzer and Malenka 2008; Borsook et al. 2010). The role of the BG in motor functions has been well established. Recent clinical, neurophysiological, and functional imaging studies suggested that the BG also contribute to many aspects of pain perception, processing, and top-down modulation (Bernard et al. 1992; Chudler and Dong 1995; Altier and Steward 1999; Wood 2008; Portvin et al. 2009; Borsook et al. 2010).

The BG receive information ascending from the nociceptive spinothalamic track and descending from various cortical brain regions (Barker 1988; Chudler and Dong 1995; Braz et al. 2005; Borsook et al. 2010). The BG pathways, feedback loops and dopamine (DA) signaling in them are extremely complex and here is only a brief overview. The nigrostriatal DA pathway projecting from the substantia nigra to dorsal striatal structures has a well-defined function in sensorimotor control and coordination. The mesocorticolimbic DA pathway projects from the ventral tegmental area of the midbrain to subcortical structures, and cortical regions, including areas important in pain processing, such as the AIC (Chudler and Dong 1995; Borsook et al. 2010). The mesocorticolimbic pathway participates in attention, motivation, and reward processes (Le Moal and Simon 1991; Spanagel and Weiss 1999). Both DA pathways also respond to arousing and salient events, regardless of the reward value of the stimuli (Horvitz 2000). In addition, striatal neurons respond to stimuli of various modalities and thus participate in gating of multimodal sensory information (Chudler and Dong 1995). Dopaminergic modulation of pain will be discussed further in chapter 2.3. The BG also contain other neurotransmitters that contribute to pain processing such as opioids and serotonin (Basbaum and Fields 1978; Cross et al. 1987; Jones et al. 1991; Millan 2002; Baumgärtner et al. 2006).

2.1.5. Exteroception *vs.* interoception

One could wonder why there is such an enormous system of multiple parallel pathways and networks for nociception only. It has been argued that the anterolateral system including the wide network of brain areas connected to it could have a broader function than just the perception and modulation of pain. In addition to mediating nociception, the anterolateral system is capable of mediating innocuous temperature changes and slow mechanical stimulation, the so-called sensual touch (Purves et al. 2012). These sensations are distinct from mere touch because of the emotional value they carry, and the feelings they evoke. These feelings form the foundation for the sense of one's physical being, the sensory aspect of ongoing homeostasis (Craig et al. 2002). This modality has been called interoception, distinctive from exteroception (simple touch) and proprioception (Craig et al. 2002). Keeping the homeostasis is essential for survival, and that could explain the wide network controlling the autonomic and emotional responses to interoceptive information. This concept could actually help us understand the emotional distress caused by pain, which can be considered to be a major threat to the crucial homeostasis and integrity of the body.

2.2. Neuropathic pain – Chronic orofacial pain

2.2.1. Neuropathic pain – definition and diagnosis

Neuropathic pain is by current definition pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (Treede et al. 2008, IASP 2010). Central neuropathic pain is caused by a lesion or disease of the central somatosensory system and peripheral neuropathic pain by a lesion or disease of the peripheral somatosensory system. Thus, the diagnosis of neuropathic pain requires a history and evidence for a lesion or disease process affecting a neuroanatomically identifiable part of the somatosensory system that is concordant with the distribution of the pain (Treede et al. 2008).

2.2.2. Mechanisms of neuropathic pain

2.2.2.1. Mechanisms of neuropathic pain in the peripheral nervous system

The development of neuropathic pain requires a lesion of afferent pathways (Baron 2006). Then, there are several mechanisms that may lead to neuropathic pain. Purely demyelinating nerve lesions usually recover well and rarely cause long-lasting pain. Conversely, axonal lesions never recover completely. After a peripheral axonal nerve lesion, the distal end of the nerve degenerates. The injured nerve endings start to fire spontaneously, and this ectopic activity is evident even in the neighboring uninjured nociceptive afferents (Wu et al. 2002; Amir et al. 2005). The ectopic activity correlates with increased expression of sodium channels, which are abnormally active in neuropathic pain (Tal et al. 1999; Lai et al. 2003; Cummins et al. 2007). The abnormal ectopic activity induces secondary hyperalgesia through barrage to the spinal cord. Nerve injury also induces a release of proinflammatory cytokines (interleukins, tumor necrosis factor α), inflammatory mediators (bradykinin, prostaglandins), and growth factors (nerve growth factor, NGF) (Nickel et al. 2011). These changes lead to peripheral sensitization, hyperalgesia, and allodynia (Somner and Kress 2004; Pezet and McMahon 2006). Nerve injury also induces expression of receptor proteins such as the transient receptor potential V1 (TRPV1) that is normally located on the peripheral nociceptive nerve endings and is activated by heat and capsaicin (Lumpkin and Caterina 2007). The TRPV1 activation produces burning pain experience and heat hyperalgesia (Baron et al. 2010; Nickel et al. 2011). In neuropathic pain, the intracellular signaling is also altered. Second messengers, protein kinases, and nitric oxide signaling pathways undergo changes that lead to peripheral sensitization (Hucho and Levine 2007). Sometimes, after partial nerve injury, axons begin to express α-adrenoceptors, which makes them sensitive to circulating catecholamines and noradrenaline released from postganglionic sympathetic terminals (Woolf and Mannion 1999). The sympathetic hyperactivity increases spontaneous pain and mechanical hyperalgesia (Choi and Rowbotham 1997; Ali et al. 2000; Baron et al. 2002).

2.2.2.2. Mechanisms of neuropathic pain in the spinal cord

Peripheral nerve injury produces changes in the dorsal horn neurons through various mechanisms. The inhibitory interneurons in lamina II may simply perish after peripheral

nerve injury, possibly through an excitotoxic mechanism (Sugimoto et al. 1990). The following disinhibition may lead to central sensitization, secondary allodynia, and hyperalgesia. After nerve injury, the inhibitory neurotransmitters of the dorsal horn (such as GABA) are downregulated (Moore et al. 2002), and excitatory amino acids and neuropeptides are upregulated. These changes lead to phosphorylation of NMDA and AMPA receptors and voltage-gated sodium channels, which additionally contributes to hyperexcitability (Ultenius et al. 2006; Hains et al. 2004).

2.2.2.3. Mechanisms of neuropathic pain in the brain

Both functional and structural changes in the brain have been demonstrated relating to neuropathic pain and chronic pain in general. The association between chronic pain and plastic changes in the brain may be bidirectional, with pain inducing plastic brain changes and maladaptive brain plasticity maintaining chronic pain.

Experimental pain-induced brain activity may be different between patients with clinical pain and healthy subjects (Derbyshire and Jones 1994; Derbyshire 1999; Derbyshire et al. 1999; Jones and Derbyshire 1997; Gracely et al. 2002; Lorenz et al. 2002). Apkarian et al. (2005) compared the areas activated by pain in healthy subjects (68 studies) to those activated in pain patients (30 studies) and discovered significant differences. In pain patients, PFC was activated in 81% compared to 55% in healthy subjects, whereas, in healthy subjects S1, S2, Th, and ACC were activated in 82% compared to 42% in pain patients. From these results Apkarian et al. (2005) concluded that chronic pain states may have stronger cognitive and emotional components than acute pain conditions.

Brain activation to heat pain in the insular cortices, the ACC and the Th has been presented to be abnormally weak in patients with herpes simplex virus infection-induced pain (Vartiainen et al. 2009a). These same pain patients had decreased gray matter density in the ACC, as well as frontal and prefrontal cortices (Vartiainen et al. 2009a). The functional and/or structural changes of higher pain processing areas may occur with functionally intact ascending pain pathways i.e. without a lesion of the spinothalamic tract (Kirveskari et al. 2015).

In complex regional pain syndrome (CRPS) patients, changes in the thalamic activity (Fukumoto et al. 1999), abnormal motor cortex reactivity (Kirveskari et al. 2010), and reorganization of the cortical representation area of the affected hand (Juottonen et al. 2002) have been demonstrated. In studies regarding phantom limb pain, it has been shown that the cortical representation area of the injured limb shrinks and the amount of pain correlates with the amount of cortical reorganization (Flor et al. 1995; Knecht et al. 1998; Montoya et al. 1998; Grusser et al. 2001; Karl et al. 2001). Functional reorganization of the S1 cortex has also been found in patients with unilateral chronic pain associated with herpes simplex virus infection (Vartiainen et al. 2009b). The maladaptive cortical reorganization may be reduced by effective therapy, like regional anesthesia (Birbaumer et al. 1997) or somatosensory training (Flor et al. 2001, Huse et al. 2001).

A better understanding of the causality and predisposing factors for brain level changes regarding chronic and neuropathic pain are still required to achieve better treatment outcomes.

2.2.3. Etiology of neuropathic pain

Central neuropathic pain is a consequence of a lesion or disease in the brain, the brainstem or the spinal cord (Treede et al. 2005; Costigan et al. 2009). Such a lesion can be caused for example by traumatic injury, multiple sclerosis or stroke. Peripheral neuropathic pain can be caused by polyneuropathy, mononeuropathy, trigeminal neuralgia, traumatic nerve injury, iatrogenic nerve injury, or other defects affecting the peripheral nervous system. Post-herpetic neuralgia and complex regional pain syndrome (CRPS I and II) are combinations of central and peripheral neuropathic pain. Atypical facial pain (AFP) and burning mouth syndrome (BMS) have neurogenic etiology, either peripheral or central (Svensson et al. 1993; Jääskeläinen et al. 1997, 1999; Forssell et al. 2002; Forssell et al. 2007; Lauria et al. 2005, Woda et al. 2009; Balasubramaniam and Klasser 2014). A spinal disk herniation can cause radicular neurogenic pain by pressing the nerve root but rarely leads to chronic neuropathic pain. Thus, a nerve lesion or disease affecting the somatosensory system is needed to develop neuropathic pain, but a nerve lesion does not necessarily lead to a chronic neuropathic pain state. In fact, this occurs only in about 5% of the patients with any peripheral nerve injury and in 13% after an axonal nerve injury (Jääskeläinen et al. 2004; Kehlet et al. 2006). There are contributory mechanisms, both in the peripheral and the central nervous system that can inhibit or facilitate the development of chronic neuropathic pain. Some individuals seem to be more vulnerable in this respect (Jääskeläinen et al. 2004; Kehlet et al. 2006), and genetic risk factors have thus been searched for.

2.2.4. Symptoms of neuropathic pain

Neuropathic pain symptoms follow the nerve lesion usually immediately or within the first weeks after the injury (Kehlet et al. 2006), but they may occur at later stages, too. Pain can be continuous or paroxysmal, and mostly occurs independently of external stimuli. Neuropathic pain is often described as lancinating, burning or an electric shock like. Due to loss of incoming sensory information, negative symptoms, like numbness and hypoesthesia, are typical to neuropathic pain. In addition to these “loss of function” symptoms and signs, positive “gain of function” signs occur. Abnormal sensations, such as stinging, tingling and paresthesia are common. Stimulus-evoked pain has specific features in neuropathic pain: hyperalgesia and allodynia. Hyperalgesia is an overdriven pain response to a suprathreshold noxious stimulus. Allodynia means perceiving an innocuous stimulus as painful. Stimulus-evoked sensory phenomena are classified into subgroups depending on the modality of the stimulus, i.e., mechanical, thermal, or chemical. Altogether, the paradoxical combination of sensory loss and hypersensitivity is a key feature of neuropathic pain.

2.2.5. Risk factors for neuropathic pain

2.2.5.1. Dopamine genetics and pain

Sensitivity to pain and susceptibility to develop chronic pain after injury differs considerably between individuals (Peyron et al. 2000; Jääskeläinen et al. 2004; Kehlet et al. 2006; Haanpää et al. 2011). Genetic factors may influence both the generation and experience of pain (Mogil 1999, 2009; Diatchenko et al. 2005, 2006).

A common single nucleotide polymorphism, valine (Val)-to-methionine (Met) substitution at codon 158 in the gene that codes catechol-O-methyltransferase (COMT) influences COMT enzyme activity and DA metabolism in the PFC (Lotta et al. 1995; Yavich et al. 2007). The Met allele with low enzymatic activity results in high levels of tonic DA release and in turn low phasic DA transmission in extrastriatal brain regions. This leads to DA system stability with impairment of stimulus dependent flexibility. Conversely, Val allele with high enzymatic activity may impair the DA system stability, but promote flexibility (Jarcho et al. 2012). Individuals homozygous for the Met allele have been shown to be more sensitive to pain than those homozygous for the Val allele (Zubieta et al. 2003), and at higher risk to develop certain chronic pain syndromes, such as temporomandibular disorder (Gürsoy et al. 2003; Diatchenko et al. 2005). The same polymorphism has been associated with endogenous opioid analgesia and placebo effects (Diatchenko 2005, 2006; Kim et al. 2004; Klepstad et al. 2005; Zubieta et al. 2003), although some of the results have been partly contradictory (Kim et al. 2006; Lötsch et al. 2006).

Similarly, single nucleotide polymorphism of the DA D2 receptor gene (DRD2) 957C>T has been associated with an increase in DRD2 availability in the human striatum (Hirvonen et al. 2005, 2009), which is involved in sensorimotor control and central pain processing, as discussed earlier in chapter 2.2.4. DRD2 is involved in the reduction of experimental pain (Magnusson and Fisher 2000), and therefore the polymorphism concerned could be one factor explaining the individual differences in pain perception. There is actually some evidence that the striatal DA system and DRD2 are associated with pain sensitivity and modulation (Jääskeläinen et al. 2001; Hagelberg 2004, Pertovaara et al. 2004; Martikainen et al. 2005), and in clinical orofacial pain (Hagelberg et al. 2003 a, b), but the consequences of the genetic variability of the DRD2 are not known.

2.2.5.2. Common risk factor for neuropathic pain

In addition to genetics, there are many other risk factors for neuropathic pain. One common type of neuropathic pain is iatrogenic neuropathic pain that is the most frequent type of persistent postsurgical pain. Since postsurgical pain is a major clinical problem, strategies for identification of patients at high risk of developing persistent pain have been developed. Known risk factors are presented here in Table 1.

Table 1. Risk factors for persistent postsurgical pain (Jääskeläinen et al. 2004, 2005; Kehlet et al. 2006; Gärtner et al. 2009; Niraj and Rowbotham 2011; Teerijoki-Oksa et al. 2011; Johansen et al. 2012; Sipilä et al. 2012; Kaunisto et al. 2013; Kalso 2013; Fong and Schug 2014)

General	Preoperative	Intraoperative	Postoperative
Genetic predisposition	Moderate to severe pain for > 1 month	Surgical site e.g., thoracotomy, amputation, mastectomy -> relative risk of nerve damage	Poorly/uncontrolled pain with high analgesic requirements > 7 days after surgery
Female gender	Preoperative anxiety, fear, catastrophizing, depression	Partial axonal nerve injury	Postoperative anxiety and depression, psychological vulnerability
High Body Mass Index	Surgery performed in previously injured area and reoperations	Extent and duration of surgery	Radiation therapy to area
Younger age (adults)	Low thermal/heat pain detection thresholds	Incision type (laparoscopic vs. open)	Neurotoxic chemotherapy
Workers compensation	Smoking		Pain at 1 month after surgery
Low income			
Lack of education			
Poor self-rating of health			

2.2.6. The comorbid disorders related to chronic neuropathic pain

Pain in general is a common cause of sleep disruption (Pilowsky et al. 1985; Morin et al. 1998; Smith et al. 2000) and disrupted sleep increases pain sensitivity both in healthy subjects (Moldofsky et al. 1975; Lentz et al 1999; Onen et al. 2001; Kundermann et al. 2004; Haack and Mullington 2005; Edwards et al. 2008) and in pain patients (Affleck et al. 1996; Wilson et al. 2002; Smith and Haythorthwaite 2004; Bigatti et al. 2008). The relationship between pain and sleep appears to be bidirectional (Moldofsky 2001; Smith and Haythorthwaite 2004; Lautenbacher et al. 2006; Argoff 2007; O'Brien et al. 2011) as is the relationship between pain and depression (Romano and Turner 1985; Magni et al. 1994; Von Korff and Simon 1996; Fishbain et al. 1997; Morin et al. 1998). The prevalence of lifetime psychiatric disorders has been as high as 75% in patients of a tertiary pain clinic (Knaster et al. 2012). In the same pain patient group, the psychiatric morbidity was associated with increased pain intensity. Altogether, there seems to be a complex and multidirectional relationship between these comorbidities, and together they have a major impact on the quality of life of the patients.

Patients with treatment-resistant neuropathic pain are particularly susceptible to concomitant disorders such as sleep problems and depression (Gore et al. 2005; Poliakov and Toth 2011; Bouhassira et al. 2013). Patients with BMS report a greater degree of sleep problems, anxiety, and depression than controls (Chainani-Wu et al. 2011; Adamo et al. 2013). Sleep disorders may, in turn, increase the risk for BMS (Chainani-Wu et al. 2011; Lee et al. 2014). The negative effect of BMS pain on sleep has been suggested to be at least partly mediated by emotional distress (Riley et al. 2001). Associations between pain intensity, pain interference, distress, and mood have been reported to be very significant in BMS (Forssell et al. 2012). Psychiatric disorders related to low brain DA tone, such as depression, anxiety, and type C personality disorders, have been found to be overrepresented in BMS and AFP patients (Taiminen et al. 2011). Taking into account PET findings in BMS and AFP (Jääskeläinen et al. 2001; Hagelberg et al. 2003, 2004), low brain DA tone has been proposed as a common pathway to shared vulnerability to these psychiatric and pain conditions (Taiminen et al. 2011; Jääskeläinen et al. 2012). The relationships between pain, sleep, and mood have not been thoroughly investigated in patients with other types of neurophysiologically verified neuropathic orofacial pain.

2.3. Dopamine-opioid system and pain

2.3.1. General considerations

While it is well established that endogenous opioids are important in pain modulation, emerging research indicates that the brain dopamine system is another significant modulator of pain perception (Chudler and Dong 1995; Fields 2007; Leknes and Tracey 2008; Wood 2008; Baliki et al. 2010). Animal studies have proposed that drugs which enhance DA neurotransmission have analgesic properties (Lin et al. 1981; Lyerly et al.1988; Paalzow 1992; Pontieri et al. 1995; Shimizu et al. 2004; Gerdelat-Mas et al. 2007; Cobacho et al. 2010, 2014). DRD2 appeared especially important in

this respect as striatal administration of DRD2 agonist suppressed and DRD2 antagonist enhanced pain-related responses in experimental animal models of persistent pain (Lin et al. 1981; Magnusson and Fisher 2000; Ansah et al. 2007). Systemic (Morgan and Franklin 1991; Cobacho et al. 2014) and spinal (Millan et al. 2002) administration of DRD2 agonist also induced analgesia in animals. In animal models of neuropathic pain, mesolimbic and striatal dopaminergic activity was increased in neuropathic pain, and this activation was involved in endogenous descending pain inhibition (Viisanen et al. 2012; Baliki et al. 2014; Taylor et al. 2014; Sagheddu et al. 2015).

2.3.2. Dopamine and clinical pain syndromes

Patients with orofacial pain syndromes, BMS and AFP, have low dopamine tone in the striatum. The first indication of AFP patients having central dopaminergic hypofunction was the finding of diminished levels of dopamine metabolites in the cerebrospinal fluid of the trigeminal cistern of three AFP patients (Bouckoms et al. 1992). Subsequently it was reported that chronic orofacial pain patients had deficient habituation of the R2 component of the blink reflex (Jääskeläinen et al. 1998, 1999; Forssell et al. 2002; Lang et al. 2005), which is a brainstem reflex controlled by dopamine (Evinger et al. 1993; Basso et al. 1996). First neuroimaging indication of striatal hypofunction in BMS was found in a PET study where patients had diminished uptake of fluorodopa F-18 ([^{18}F]FDOPA) in the right putamen (Jääskeläinen et al. 2001). In following PET studies, patients with BMS and AFP had higher DRD2 availability in the putamen compared to healthy controls (Hagelberg 2003 a, b) indicating patients having lower endogenous striatal dopamine tone. Similar low dopamine activity has been seen in patients with another pain syndrome, fibromyalgia (Wood et al. 2007). These findings suggest that patients with orofacial pain and fibromyalgia have low endogenous striatal dopamine, which may be associated to diminished endogenous pain inhibition. Despite these complementary findings, the conclusions should be interpreted with caution, considering the relatively small number of patients in the studies. Still one clinical observation could link BMS to striatal dopamine deficiency; the interesting phenomenon of BMS symptoms being minimal on awakening, similar to “sleep benefit” commonly seen in Parkinson’s disease (Högl et al. 1998; van Gilst et al. 2013).

The prevalence of pain is high in Parkinson’s disease (PD), a disease characterized by a loss of dopaminergic neurons in the substantia nigra. Pain occurs in about 60–80% of PD patients and it is not always related to motor dysfunction (Goetz et al. 1986; Ford et al. 1998; Defazio et al. 2008; Beiske et al. 2009). It has been estimated that 20% of PD patients have peripheral neuropathic pain, and 10% central neuropathic pain (Goetz et al. 1986; Lee et al. 2006; Defazio et al. 2008; Beiske et al. 2009; Ha and Jankovic 2012). The central pain in PD has been associated with impaired modulation of pain caused by dopaminergic deficiency in the BG (Young Blood et al. 2016). Furthermore, some PD patients have burning pain in the mouth typical to BMS (Ford et al. 1996, Clifford et al. 1998).

Patients with schizophrenia have higher pain thresholds and better tolerance to acute noxious stimuli than healthy individuals (Blumensohn et al. 2002; Jochum et al. 2006;

Atik et al. 2007) or patients with bipolar disorder (Atik et al. 2007). According to Jochum et al. study (2006), antipsychotic medication does have an influence on pain perception in schizophrenia**.** Patients with schizophrenia also experience abnormally little pain in usually painful medical conditions, like appendicitis, myocardial infarction, peptic ulcer, and injuries (Dworkin 1994). This hyposensitivity to pain could be related to hyper-responsive or sensitized DA system, as patients with schizophrenia have higher baseline levels of synaptic striatal DA than healthy individuals (Abi-Dargham et al. 2000) and exhibit greater amphetamine-induced striatal DA release than healthy subjects (Laruelle 2000).

Dopaminergic drugs have some analgesic effects. A dopamine reuptake inhibitor, bupropion, demonstrated to produce 30% pain relief in patients with neuropathic pain (Semenchuk et al. 2001). Levodopa has been reported to be superior to placebo in relieving pain in acute herpes zoster infection (Kernbaum and Hauchecorne 1981) and diabetic polyneuropathy (Ertas et al. 1998), however, these two studies were not randomized, and especially the diabetes study had a small number of patients. In a case report, a dopamine agonist, apomorphine, relieved thalamic pain (Miley et al. 1978). Apomorphine has also been reported to relieve pain symptoms in Parkinson's disease (Factor 2004), yet, that may depend on relieving pain caused by primary motor symptoms.

2.3.3. Dopamine-opioid interaction

The interactions between the dopaminergic and opioidergic systems related to pain are not fully understood. Animal studies have demonstrated that endogenous opioids are released almost immediately in DA-rich areas of the brain in response to noxious stimulation (Lapeyre et al. 2001). The μ-opioid receptors are involved in antinociception, and in actions of opiate drugs (Matthes et al. 1996; Wiedenmayer and Barr 2000; Przewłocki and Przewłocka 2001). Administration of exogenous opioids and μ-opioid agonists has consecutively promoted DA release in the striatum (Di Chiara and Imperato 1988; Leone et al. 1991; Maisonneuve et al. 2001; Serra et al. 2003). Opioids have been proposed to enhance DA release for instance by increasing the firing rate of dopaminergic neurons (Johnson and North 1992). Controversially, administration of opioids has also been reported not to alter (Wood et al. 1980; Ahtee et al. 1990) or even decrease (Yonehara and Clouet 1984) striatal DA release. Altogether the dopamine-opioidergic modulation of pain is supposed to derive through the activation of the descending pain modulatory DA pathways (Fields 2007).

2.3.4. Dopamine-opioid system in placebo analgesia

Placebo effect is especially important to be taken into account when assessing subjective outcome measures such as analgesic and antidepressant effects (Hrobjartsson and Gotzsche 2001). Placebo effect is associated with the release of several neurotransmitters, particularly endogenous opioids and dopamine (Petrovic et al. 2002; Kaasinen et al. 2004; Benedetti et al. 2005; Strafella et al. 2006). The individual expectation of analgesia has been shown to correlate with the amount of dopamine release in the nucleus accumbens, and with the amount of endogenous opioid release in nucleus accumbens, ventral putamen, amygdala, insula, and ACC

(Zubieta and Stohler 2009). The placebo effects should, therefore, be carefully controlled and explored when assessing the effects of neurostimulation or drugs that may exert their effects through dopamine-opioid systems.

2.3.5. Positron emission tomography (PET) in human pain research

PET studies with ^{15}O-water to assess neurovascular responses to pain have exhibited substantial overlap between the brain areas involved in pain processing (see Chapter 2.1.3) and brain areas covering the DA system (Leknes and Tracey 2008). [^{11}C]raclopride is a radiotracer most commonly used in PET studies regarding striatal DRD2 and striatal synaptic DA content. The radiotracer binds to postsynaptic D2 receptors and can be used to assess both the tonic levels of striatal DA and the phasic release of DA associated with noxious stimulation. These studies have shown that endogenic DA neurotransmission in the striatum increased (radiotracer binding decreases) during noxious stimulation (Scott et al. 2006, 2007). Furthermore, it has been indicated that individuals with lower baseline tonic DA release are more sensitive to noxious stimulation (Hagelberg et al. 2002; Pertovaara et al. 2004; Martikainen et al. 2005; Scott et al. 2006; Wood et al. 2007).

In PET studies focusing on opioid analgesia, the nonselective opioid receptor antagonist [^{11}C]diprenorphine and μ-receptor agonist [^{11}C]carfentanil are the most commonly used ligands. According to a small [^{11}C]diprenorphine study, the endogenous opioid system is activated during pain attacks related to trigeminal neuralgia (Jones et al. 1999). Several studies with [^{11}C]carfentanil have shown the activation of μ-receptors during tonic pain stimulation (Zubieta 2001, 2002; Bencherif et al. 2002).

2.4. Measuring neuropathic pain and its signs

2.4.1. Clinical examination

Pain and other neuropathic symptoms are highly subjective experiences and therefore a thorough interview of the patient is essential. Standardized neuropathic pain questionnaires can be helpful in identifying neuropathic pain, particularly for non-specialists. Questionnaires include questions about burning pain, paresthesia, hypersensitivity, and numbness (Bennett et al. 2007; Cruccu et al. 2010). Nevertheless, all questionnaires rely on patients' memory and are therefore quite insensitive and unreliable. Clinical neurologic examination is not very sensitive either, but it is specific when abnormal. Clinical examination should include assessment of the following sensory modalities: touch, pin prick, pressure, cool, heat, vibration, and temporal summation (Bouhassira et al. 2004; Haanpää et al. 2004; Cruccu et al. 2010). The responses should be graded as normal, increased, or decreased. The eventual stimulus-evoked pain types should be further classified to hyperalgesic or allodynic. Touch can be assessed by cotton wool, pin-prick sensation by sharp pin, deep pain by gently pressing muscles or joints, vibration by tuning- fork, and temperature sensations by measuring the response to thermal stimuli. For detailed clinical assessment and definition see a comprehensive review by Baron et al. (2010).

2.4.2. Quantitative sensory testing (QST)

QST is a psychophysical method that can be used to assess quantitatively the function of all sensory modalities (vibratory, tactile, and thermal). It requires good patient co-operation, and is thus not objective as clinical neurophysiological investigation. With QST, the anatomical location of damage in the somatosensory system cannot be defined in case of abnormal findings; a lesion at any level along the pathway from the skin receptors to the somatosensory cortices can result in an abnormal QST result. Various measuring algorithms can be applied to track the detection thresholds including method of limits, method of levels, and forced choice. In addition to threshold tracking, QST can be used to assess subjective responses to suprathreshold stimuli for magnitude estimation with stimulus-response curves (Clarke 1974).

Tactile detection thresholds examine the same large myelinated Aβ fibers as sensory electroneurography. Thermal QST investigates cool, warm, heat pain and cold pain detection thresholds separately allowing detailed analysis of the function of small myelinated Aδ and unmyelinated C fibers that cannot be examined with traditional electroneurophysiological techniques (Gruener et al. 1994; Olney 1998, Jääskeläinen 2004). The QST techniques are especially important when exploring exclusively sensory nerves, such as the trigeminal nerve in the facial area. The assessment of hypoesthesia, hyperalgesia and allodynia is more precise and reliable with QST than by clinical examination (Verdugo and Ochoa 1992; Teerijoki-Oksa et al. 2003, 2004; Jääskeläinen et al. 2004). The QST techniques based on the method of limits and levels used in our study are described in detail in the Method section.

2.4.3. Neurophysiological testing

Neurophysiological testing is extremely valuable when assessing neuropathic pain. Electroneuromyography (ENMG) is considered the gold standard of peripheral neuropathy (England et al. 2005; Haanpää et al 2011) examining large myelinated alpha motoneurons and Aβ sensory fibers in the peripheral nervous system. Somatosensory evoked potentials (SEP) to electrical or tactile stimuli give information of the non-nociceptive pathway in the dorsal column - medial lemniscal pathway. Even though these two techniques explore mostly non-nociceptive pathways, they are important in exploring the integrity of the peripheral and central somatosensory systems, because most peripheral nerves are mixed nerves containing both large and small fibers. A lesion in a peripheral nerve may therefore affect both large and small fibers. Contact heat evoked potential (CHEP) and laser evoked potential (LEP) are objective measures of small Aδ and C fiber function and pathways (Truini et al. 2005; Chao et al. 2008). Cerebral responses to heat stimuli conveyed by Aδ and C fiber pathways can be recorded with EEG or MEG. ENMG, SEP, CHEP and LEP are diagnostic tools that can provide objective evidence of a lesion in the somatosensory system crucial for the diagnosis of neuropathic pain (Jääskeläinen 2004, 2009, Garcia-Larrea 2012).

Blink reflex is a brainstem reflex that can be evoked by tactile, light or loud noise stimuli (Rushworth 1962). In clinical practice, responses are usually evoked by electrical stimuli. The stimulation site depends on the nerve investigated, and the intensity of stimulation is adjusted individually to obtain stable responses (Kimura et al.

1969; Shahani 1970). The blink reflex arc is extensive with oligosynaptic and polysynaptic pathways reaching from trigeminal sensory afferents to principal nucleus of the trigeminal nerve in the midpons (R1 component), the trigeminal spinal nucleus in the medulla oblongata (R2 component), motor nucleus of the facial nerve in the lower pons, and to the facial nerve. The R1 and R2 components of the reflex are mediated by different circuits, which together with the possibility of stimulating different branches of the trigeminal nerve, enables localization of the dysfunction (Jääskeläinen 2004). Habituation of the R2 component of blink reflex is supposed to be controlled by the nigrostriatal dopaminergic system (Basso et al. 1993; Evinger et al. 1993). The R2 component habituation is deficient in diseases with dopamine depletion, like Parkinson's disease (Penders and Delwaide 1971; Basso et al. 1996), and also in neuropathic orofacial pain (Jääskeläinen et al. 1998, 1999; Forssell et al. 2002, 2007; Lang et al. 2005). The neurophysiological testing of habituation is carried out with repeated stimulation at 1 Hz or paired stimulation technique (Jääskeläinen 2004). Our protocol of measuring blink reflex habituation is described in the Method section.

2.5. Therapeutic neuromodulation for chronic pain

Drug-resistant pain is a major health problem; hence different neurostimulation techniques for pain alleviation have been investigated. The European Federation of Neurological Societies published the first evidence-based guidelines on neurostimulation for neuropathic pain in 2007 (Cruccu et al. 2007). An update was recently published, and the recommendations were now expanded to cover fibromyalgia pain, CRPS type I pain, and post-surgical chronic back and leg pain, in addition to neuropathic pain (Cruccu et al. 2016). The meta-analysis suggested only moderate efficacy: weak recommendations were given for spinal cord stimulation (SCS), motor cortex stimulation (MCS), rTMS of M1, and transcranial direct electrical stimulation (tDCS) of M1 for the treatment of neuropathic pain. Results for other types of pain were even poorer, except for rTMS in the treatment of fibromyalgia. Deep brain stimulation effects were inconclusive. See Table 2. for the summary of the results. One major reason for these poor results was considered to be the lack of high standard randomized and placebo-controlled trials. A call for future studies with larger sample sizes and multicenter settings was placed. Furthermore, it was proposed that future studies should evaluate patient-reported outcomes of quality of life in addition to mere pain assessment.

Table 2. Summary of the European Federation of Neurological Societies recommendations on neurostimulation for chronic pain (Cruccu et al. 2016).

Stimulation method	Neuropathic pain	Fibromyalgia	CRPS	CBLP
DBS	Inconclusive			
MCS	Weak			
rTMS to DLPFC	Inconclusive	Inconclusive		
rTMS to M1	Weak	Weak		
SCS	Weak		Weak	Weak
tDCS to DLPFC		Inconclusive		
tDCS to M1	Weak	Inconclusive		

Abbreviations: CBLP post-surgical chronic back and leg pain, CRPS complex regional pain syndrome

2.5.1. Invasive neuromodulation – spinal cord stimulation (SCS), deep brain stimulation (DBS) and motor cortex stimulation (MCS)

SCS is an established method for the treatment of intractable pain and it has been in use since 1970's, for example in failed back surgery syndrome and complex regional pain syndrome (Kumar et al. 2008; Mekhail et al. 2011; Sears et al. 2011). There is some evidence that SCS alters local neurochemistry in the dorsal horn leading to suppression of central neuronal hyperexcitability (Linderoth and Foreman 1999; Oakley and Prager 2002), but mechanisms of action are not fully understood. About half of the patients do not respond to SCS (Plow et al. 2012). Therefore, interest in cerebral neuromodulation techniques has been emerging. DBS and MCS are invasive techniques for the treatment of chronic pain. DBS has demonstrated some efficacy both in neuropathic and nociceptive pain, but long term results have been variable and inconsistent (Levy et al. 1987; Coffey 2001; Hamani et al. 2006; Cruccu et al. 2007; Owen et al. 2006). The most effective stimulation targets have also been under debate. Previous evidence indicating that thalamic stimulation would be better for neuropathic pain than periaqueductal/periventricular gray stimulation (Richardson and Akil 1977; Hamani et al. 2006), has been questioned (Owen et al. 2006). Novel, possibly more favorable stimulation targets are under investigation, but for now, DBS is not recommended for the treatment of pain (Cruccu et al. 2016). A less invasive method, epidural stimulation of the motor cortex (MCS), was introduced in the early 1990s by Tsubokawa et al. (1991). Initial results were encouraging for the treatment of central pain, but later on, there have been variable results (Meyerson et al. 1993). Instead, better efficacy has been observed in peripheral neuropathic pain conditions (Saitoh et al. 2000; Nguyen et al. 1997, 2008). Altogether, according to several studies, MCS has been shown to have a significant effect on chronic pain (Cruccu et al. 2007; Lima and Fregni 2008). However, low quality of the studies deteriorates some of the results, and therefore only weak recommendation was given to MCS for pain management in a recent meta-analysis (Cruccu et al. 2016). Patients with severe hemiparesis benefit less of MCS than patients with preserved motor function, indicating that intact corticospinal pathways are important for MCS effectiveness (Katayama et al. 1998; Nuti et al. 2005). Similarly, intact spinothalamic pathways predict better efficacy. In addition to activating the brain networks, MCS probably exerts its analgesic effect by releasing neurotransmitters, like endogenous opioids (Maarrawi et al. 2007, 2013).

2.5.2. Noninvasive neuromodulation – repetitive transcranial magnetic stimulation (rTMS)

rTMS is a noninvasive method to apply magnetic pulses to the scalp, which induces an electrical field sufficient to depolarize cortical neurons and axons of the pyramidal cells and activate neural networks in the brain. Classically, low-frequency (LF) repetitive rTMS (≤ 1 Hz) has been considered as inhibitory and high frequency (HF) stimulation (≥ 5 Hz) as excitatory (Siebner and Rothwell 2003), resembling the effects of long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission in animal models (Hoogendam et al. 2010). This dichotomy is, however, too simplified, as it has been shown that both LF and HF stimulations may have mixed excitatory and inhibitory effects depending on the length of the stimulation and the stimulation target (Houdayer

et al. 2008; Gamboa et al. 2010). It has also been proposed that the excitatory *vs.* inhibitory effects are variable between individuals depending on the baseline cortical excitability (Siebner and Rothwell 2003, Daskalakis et al. 2006) and on the differences in the cortical networks recruited by TMS (Hamada et al. 2013). In addition to activating the local interneuronal circuits, rTMS can activate fibers projecting to distant structures (Fox et al. 1997; Siebner et al. 2008; Di Lazzaro et al. 2011; Lefaucheur et al. 2012). These distant actions have been demonstrated both by functional connectivity studies (Gerschlager et al. 2001; Munchau et al. 2002; Rizzo et al. 2004) and functional imaging studies (Bestman et al. 2005; Siebner et al. 2009; Lee et al. 2009). Several studies have also shown that rTMS can modulate neurotransmission even in deep brain structures, particularly increase dopamine release within BG (Keck et al. 2000, 2002; Strafella et al. 2001, 2003; Kim et al. 2008). There is also indirect evidence of rTMS enhancing endogenous opioid secretion from several brain areas (de Andrade et al. 2011; Taylor et al. 2012, 2013); however, the association between the analgesic effect of rTMS and the brain opioid system has not been directly shown in humans. Furthermore, release of serotonin from the RVM following cortical stimulation has been demonstrated in an experimental animal study (Viisanen and Pertovaara 2010).

The current view is that the analgesic effect induced by a single rTMS session may appear immediately after the session, but the maximum effect is delayed up to three days (Lefaucheur et al. 2001; André-Obadia et al. 2008). It is also quite clear that repeated sessions reinforce the analgesic effects (Khedr et al. 2005; Passard et al. 2007; Mhalla et al. 2011; Hosomi et al. 2013). These long-lasting effects suggest that rTMS could induce neural plasticity, possibly through changes in cortical excitability and reorganization (Lefaucheur et al. 2009; Moisset et al. 2015). Altogether, the mechanisms underlying the analgesic effect are still unclear. The best shape and orientation of the treatment coil are yet to be discovered (André-Obadia et al. 2008; Ciampi de Andrade et al. 2012) along with the most efficient stimulation targets, frequency and the number of pulses (André-Obadia et al. 2006). In any case, neuronavigation-guided rTMS allows more accurate definition of the stimulation site and better reproducibility of the stimulation (Fitzgerald et al. 2009; Ayache et al. 2016).

In pain studies, the most frequently applied target of the rTMS has been the M1 contralateral to pain, as in MCS. The analgesic effects of the M1 stimulation have been approved both in experimental (Summers et al. 2004; Nahmias et al. 2009; de Andrade 2011; Moisset et al. 2015) and clinical pain (André-Obadia et al. 2008; Passard et al 2007; Cruccu et al. 2010; Lefaucheur et al. 2014), although regarding acute and experimental pain, the results have been partly contradictory. The stimulation of the DLPF has also induced analgesia both in experimental and clinical pain (Borckardt et al. 2009, 2014; de Andrade et al. 2011; Brighina et al. 2011; Hou et al. 2016). In a previous study by our group on healthy subjects, a significant decrease in pain sensitivity of the face was found after HF rTMS given to the right S2 (Valmunen et al. 2009). Another study has shown improvement in visceral pain after LF stimulation of the right S2 (Fregni et al. 2011). There is some evidence of rightward lateralization in sensory awareness, interoception, pain processing, and in connections between S2 and the insular cortex as part of the salience network (Coghill et al., 2001; Strafella et

al., 2003; Kucyi et al. 2012 a, b). The S2 as a target for rTMS had not been explored in neuropathic pain earlier.

Recently published guidelines on the therapeutic use of rTMS propose a level A evidence for the analgesic efficacy of high-frequency rTMS of the M1 (Lefaucheur et al. 2014). Similarly, the evidence for the antidepressant efficacy of the high-frequency DLPFC stimulation is considered to be level A (Lefaucheur et al. 2014). However, in another recent meta-analysis covering literature up to December 2014, the recommendation for the clinical use of rTMS was weak, although in the same line as SCS and MCS (Table 2.). Future studies are needed to make firm conclusions about the efficacy and usability of rTMS and other neuromodulation techniques in clinical pain management.

3. AIMS OF THE STUDY

3.1 To investigate if rTMS has an analgesic effect on chronic neuropathic orofacial pain, and to compare the possible analgesic effects of different cortical targets. (Study 1, original article I)

3.2 To investigate whether rTMS treatment has an independent analgesic effect or whether the clinical benefits depend on simultaneous improvement of patients' psychiatric conditions or sleep disturbances. (Study 1, original article II)

3.3 To investigate the role of endogenous dopamine system and its genetics i) in the perception and processing of painful stimuli, ii) in risk for neuropathic pain, and iii) in rTMS efficacy. (Study 2, original article III)

3.4 To evaluate the brain mechanisms and the role of the dopamine-opioid system in rTMS-induced analgesia with neurotransmitter PET (Study 3, original article IV)

Outline of the work

This work consists of three separate Studies (1–3), on which the four Original articles (I–IV) are based. In the following text, the Studies are referred to as Arabic numerals (1–3) and Original articles as Roman numerals (I–IV).

Study 1 investigated the effects of navigated rTMS on neuropathic orofacial pain patients' pain intensity and interference, quality of life, mood, and sleep. The effects of stimulation to different cortical targets were compared. Study 2 examined the role of the dopamine system related genetic polymorphisms in the perception and processing of thermal noxious and nonnoxious stimuli in healthy volunteers and neuropathic orofacial pain patients. The role of the dopamine system was also evaluated regarding the efficacy of rTMS given to different cortical targets. Study 3 elucidated the role of the brain dopamine-opioid systems in rTMS effects with neurotransmitter PET and neurophysiologic recordings in healthy subjects. Dopamine system effects were investigated with [^{11}C]raclopride PET and opioid μ-receptors with [^{11}C]carfentanil PET.

4. SUBJECTS AND METHODS

4.1. Subjects

Table 3. Demographic data of the participants in Studies 1-3

Study #	Original article	Group	Number of subjects (initially recruited)	Age in years mean	Women / men
1	I, II	Patients	16 (20)	59	14 / 2
2	III	Healthy + patients*	29 (31) 16 (20)	23	18 / 11 14 / 2
3	IV	Healthy	11 (12)	26	8 / 3

* Same patients as in study 1

All three studies were performed according to the Declaration of Helsinki and approved by the Ethics Committee of The Intermunicipal Hospital District of Southwest Finland. All participants gave written informed consent.

Study 1 (Original articles I and II)

Initially, 74 patients, who were previously diagnosed and treated for neuropathic orofacial pain in Turku University Hospital, were contacted and interviewed by phone. The main inclusion criterion was chronic daily neuropathic pain with intensity of ≥ 4 using numerical rating scale (NRS) from 0 to 10. Twenty patients, who met the inclusion criterion and were willing to participate, were recruited to the study. Patients (18 women) were all right-handed, and their mean age was 59 (range 37–74). Nine patients had neuropathic pain due to trigeminal nerve lesion i.e. trigeminal neuropathic pain (TNP), six atypical neuropathic pain (AFP) and five burning mouth syndrome (BMS). Diagnoses of the neuropathic orofacial pain were made according to the international criteria for headache disorders that comply with the current diagnostic criteria (ICHD 2013 by International Headache Society), after clinical examinations performed by an orofacial pain specialist and a neurologist. The neuropathic involvement of the trigeminal system was confirmed with neurophysiological and psychophysical tests: ENMG, brainstem reflex recordings (blink and masseter reflexes), CHEP recording, and thermal QST. Patients had no contraindications for MRI or TMS (Rossi et al. 2009). Two patients were excluded after preliminary examinations; one because of significant brain pathology in MRI and one for not meeting the inclusion criterion of pain intensity numerical rating scale (NRS) ≥ 4 at baseline. Two patients dropped out during the study; one because of major depression and the other for starting a new analgesic treatment during the study. Six of the remaining 16 patients had a current psychiatric disorder, two of them depression and four an anxiety disorder. The other four patients had a history of affective disorders but were currently in remission. The co-morbid psychiatric disorders were diagnosed by a specialist in psychiatry on a clinical basis with the aid of structured clinical interview for

axis I disorders, SCID-I (First et al. 1997). Patients' clinical and demographic data including diagnoses and medications are summarized in Table 4.

Table 4. Patients' demographic and clinical data

Gender/ age in years	Dg	Pain side	Duration in years	Lifetime psychiatric disorders	Current psychiatric disorders	Daily treatment
female / 60	AFP	left	10	MDD, GAD*	-	ZOL
female / 64	AFP	right	10	-	-	-
female / 55	AFP	right	20	GAD*, SpP	GAD*, SpP	-
female / 55	AFP	left	30	MDD	-	AMI+CHL, FLU
						TRA, ETO
female / 57	BMS	bilateral	5	MDD, PaD	-	NOR
female / 67	BMS	bilateral	20	MDD, SpP	MDD, SpP	-
female / 61	BMS	bilateral	2	-	-	tCLO, ZOP
female / 74	BMS	bilateral	7	-	-	tCLO, ZOP
female / 69	BMS	bilateral	10	-	-	-
female / 65	TNP	right	15	GAD*, SoP	SoP	LTG
female / 57	TNP	bilateral	5	MDD*	MDD*	PGB, NOR, ESC
female / 47	TNP	left	6	MDD, SpP	SpP	PGB, CIT
female / 70	TNP	right	10	SpP, PaD	SpP	PAR+COD, LOR
female / 69	TNP	right	5	-	-	-
male / 39	TNP	bilateral	7	GAD*, SoP	-	DUL, NOR
male / 50	TNP	right	5	-	-	-

Abbreviations: AMI amitriptyline; AFP Atypical Facial Pain; BMS Burning Mouth Syndrome; CIT citalopram; CHL chlorediazepoxide; COD codeine phosphate hemihydrate; DG Diagnosis; DUL duloxetine; ESC escitalopram; ETO etoricoxib; FLU fluvoxamine; GAD general anxiety disorder; LTG lamotrigin; LOR lorazepam; MDD major depressive disorder; NOR nortriptyline; PaD panic disorder; PAR paracetamol; PGB pregabalin; SoP social phobia; SpP specific phobia; tCLO topical clonazepam; TNP Trigeminal Neuropathic Pain; TRA tramadol; ZOL zolpidem; ZOP zopiclone; * onset after neuropathic pain

Study 2 (Original article III)

Initially, 31 healthy volunteers were recruited to this study group, but two of them were excluded after preliminary tests (EEG abnormal in one, MRI abnormal in another). Thus, 29 healthy subjects with no regular medication, or alcohol or drug abuse, participated in the study. Participants' (18 women) mean age was 23 (range 18–30), and 25 of them were right-handed. Current psychiatric disorders were excluded by Symptom Check-list-90 (SCL-90), which is a widely used and validated screening instrument for various psychiatric disorders. Final participants had no contraindications for MRI or rTMS (Rossi et al. 2009), and their EEG was normal. The 16 patients included in this study were the same subjects as in study 1.

Study 3 (Original article IV)

Twelve healthy subjects were recruited to the study. One of them experienced a panic attack during the first [^{11}C]carfentanil PET scan and did not want to continue participation, and her data was not used in the analyses. Thus, eleven healthy subjects (seven women) with a mean age of 26 (range 21–32) participated in this study. Ten of the patients were right-handed, and one was ambidextrous. One participant was excluded from [^{11}C]carfentanil PET results because of an insufficient injected amount

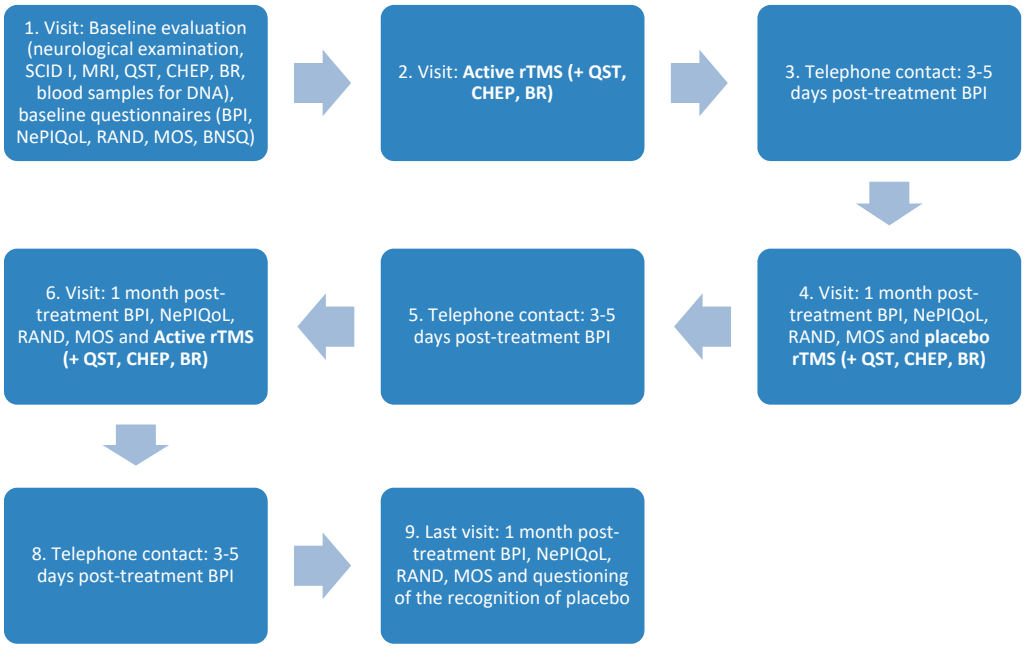
of radiotracer but was included in other parts of the study. All participants went through clinical neurological examination without abnormal findings and filled out the SCL-90 questionnaire to exclude current psychiatric disorders. Participants had neither regular medication nor any history of drug abuse. The subjects were instructed not to use any alcohol, tobacco or caffeine containing drinks during the 12 hours prior to the PET study.

4.2. Study designs

Study 1 (Original articles I, II)

This study with neuropathic orofacial pain patients was conducted in a randomized, single-blind, placebo-controlled, within-subject crossover design. All participants received two active rTMS treatments and one sham (placebo) treatment separated from each other by at least four weeks. The sham treatment was always between the two active treatments, targeted to S1/M1 and S2, which were given in a randomized order. Patients kept pain and sleep diaries throughout the study period beginning four weeks before the first treatment and completing four weeks after the last treatment. The primary outcome measure was pain intensity after each rTMS treatment assessed by using NRS from 0 (no pain) to 10 (worst imaginable pain). Pain and its effects on quality of life were also measured with the Brief Pain Inventory (BPI) (Cleeland and Ryan 1994) and the Neuropathic Pain Impact on Quality-of-Life (NePIQoL) questionnaire (Poole et al. 2009). In addition, the patients' health-related quality of life was measured with a validated Finnish version of the RAND-36 (SF-36) questionnaire (Aalto et al. 1999, Hays et al. 1993, Ware and Sherbourne 1992). Patients' mood was followed weekly with Beck Depression Inventory (BDI) (Beck et al. 1974). The BPI was monitored at baseline, 3 to 5 days after the treatments and one month after the treatments, as well as the NePIQoL and the RAND-36 at baseline and one month after the treatments. Moreover, patients were asked to mark with color pencils on a schematic symptom chart the area and the intensity of pain, and paresthesia or numbness areas immediately before and after each treatment, as well as one and two weeks after the treatments. The extent of the symptomatic area was estimated by using transparent square millimeter sheets. Patients' sleep was evaluated at baseline with the Basic Nordic Sleep Questionnaire (BNSQ) (Partinen and Gislason 1995), and then monitored daily with the sleep diary, and monthly with the Medical Outcomes Study (MOS) Sleep questionnaire (Spritzer and Hays 2003). The MOS Sleep Scale is a 12-item measure assessing six dimensions of sleep: sleep disturbance (SLD), snoring (SNR), awakening with short of breath or a headache (SOB), sleep adequacy (SA), daytime somnolence (SS), and quantity of sleep (QS). Two sleep problem indices, S6 and S9, can be calculated from the subscores.

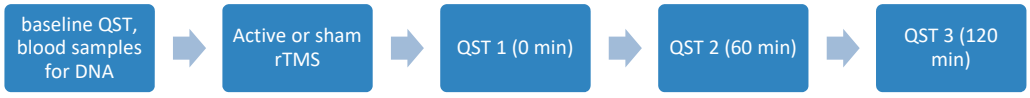
Flowchart of the Study 1



Study 2 (Original article III)

The healthy subjects were divided into two subgroups that received rTMS to different cortical sites in a single-blind, placebo controlled, and crossover design. A group of 15 subjects received stimulation to the right M1, DLPFC and occipital cortex midline (OCC; used as a placebo) in randomized order. Another group of 14 subjects received stimulation targeted to S2 and S1 cortices in randomized order. All sessions were separated from each other by at least three weeks. Before and after each stimulation session, subjects' thermal sensory and pain detection thresholds (method of limits), discriminative capacity, and response criterion (method of levels) were determined. In addition, subjects' vigilance was measured with a 100 mm (0 extremely tired, 100 extremely alert) visual analog scale (VAS) at baseline and before all psychophysical tests.

Flow-chart of the Study 2

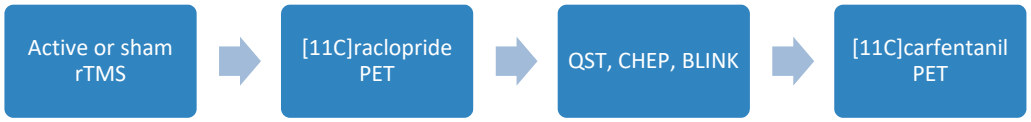


Study 3 (Original article IV)

In the third study, healthy subjects underwent two whole-day sessions including rTMS treatment, two PET scans as well as neurophysiological and psychophysical measurements between the PET scans. Active S1/M1 and sham rTMS were given in randomized order at least four weeks apart in a single-blind crossover design. After the

rTMS, the subjects underwent first the [^{11}C]raclopride PET scan (114 ± 17 min after rTMS) and then just after neurophysiological testing the [^{11}C]carfentanil PET scan (313 ± 45 min after rTMS). Subjects' vigilance was measured with a 100 mm (0 extremely tired, 100 extremely alert) visual analog scale at baseline and before all psychophysical tests.

Flowchart of the Study 3



4.3. Quantitative sensory testing (QST)

Studies 1, 2 and 3

QST was performed at baseline and after rTMS sessions to measure thermal sensory detection and pain thresholds for cold and heat. In healthy subject groups (Studies 2 and 3), thermal sensory measurements were performed at the infraorbital nerve distributions. In the neuropathic orofacial pain patient group, the measurements were done according to clinical symptom distribution. Thermal Sensory Analyzer (TSA-2001) (Medoc Ltd., Rehovet, Israel) (Study 2) and Senselab MSA Termotest (Somedic Sales Ab, Hörby, Sweden) (Studies 1 and 3) devices we used for QST. The size of the contact thermode was 9 x 9 mm in Studies 1 and 3, and 16 x 16 mm in Study 2 healthy subject group. The TSA-computer driven device allowed the use of both the method of limits and the method of levels procedures. In all studies, the increasing and decreasing temperatures were applied at a linear rate of 1 °C/s from the baseline temperature set at 32 °C. For safety reasons, the maximum temperature was set at 50 °C and the minimum at 0 °C. The detection thresholds for cool (CDT), warm (WDT), cold-pain (CPT) and heat-pain (HPT) were determined using the method of limits (Clark 1974; Becser et al. 2004) and always measured in this order. Each threshold was measured three times, and the median was used in analyses. Before the actual tests, the subjects were carefully instructed and went through a short training to make sure that the protocol was correctly understood.

4.4. Determination of the subjects' discriminative capacity and response criterion

Study 2

An elevation of the pain detection threshold can be induced in three ways; by a decrease in subject's discriminative capacity (sensory factor), by an increase in subject's response criterion (non-sensory factor reflecting the subject's response bias or attitude towards painful stimuli), or both. Analysis of psychophysical data by the methods based on the signal detection theory allows separate analysis of these factors (Clark 1974). The assessment of subjects' discriminative capacity and response criterion was done before and after rTMS stimulation with the same TSA-1 device as in

QST, but now using the method of levels (Pertovaara et al. 2004). Briefly, a series of heat stimuli were presented in six different temperatures between 42–47 °C, each stimulus being presented eight times in randomized order. The subjects were asked to estimate the sensation using a verbal rating scale from faintly warm to very painful heat. For assessment of the subjects' discriminative capacity (sensory factor) from this data, a receiver operating characteristics (ROC) curve analysis was performed using MedCalc software (MedCalc, Mariakerke, Belgium). The ROC analysis allowed determining how well the subject was able to discriminate stimulus intensities close to heat pain threshold from each other. To determine the subject's response criterion (non-sensory factor), the probability of rating a stimulus painful, was calculated and converted to a *Z* score. A more negative value of the criterion reflects a bias toward frequent ratings of the stimuli as painful and positive value does the opposite (see Valmunen et al. 2009).

4.5. Blink reflex habituation

Studies 1 and 3

The habituation of the blink reflex R2i component was measured on each side at baseline, and after each rTMS stimulation session, using an eight-channel EMG device (Viking I, Nicolet Biomedical Instruments, Madison, WI, USA) with the standard methodology described earlier in detail (Jääskeläinen et al. 1999, 2004). Electrical stimuli were delivered to the supraorbital nerve using a small bipolar electrode (13L35 Medtronic Functional Diagnostics A/S, Skovlune, Denmark). Stimulus intensity was increased stepwise to evoke both R1 and R2 components of the blink reflex constantly. At this intensity, eight stimuli at the frequency of 1 Hz were applied, and the habituation of the area under the ipsilateral R2 component was calculated. The habituation index was determined to be the ordinal number of the response that first fell below 50% of the original response. Normally, the R2i response habituates at least 50% by the third response and anything above it is considered abnormal.

4.6. Contact heat evoked potential (CHEP) recording

Studies 1 and 3

Subjects' thermal sensory and nociceptive function in the facial area was objectively measured with CHEP at baseline and after the rTMS stimulations. CHEPs were recorded with Medoc PATHWAY thermal stimulator (Medoc Ltd, Ramat Yishai, Israel) and an eight-channel Viking Select ENMG device (Nicolet Biomedical Instruments, Madison, WI, USA). The stimuli were applied with a 27 mm diameter specially constructed thermode that had two layers; an external layer consisting of a heating foil and two thermocouples, and an internal layer consisting of a Peltier element and an active water cooling system. The heating rate of the thermode was 70 °C/s and the cooling rate 40 °C/s. The maximum temperature of the stimulus was set at 54 °C, except in cases where the subject experienced the maximum heat too painful, when the temperature was lowered to 51 °C. In average, 15 stimuli were given with randomly alternating inter-stimulus intervals of 10–20 seconds. After each stimulus, the subjects

were asked to describe the intensity of pain evoked using NRS from 0 to 10. The CHEP responses were recorded with EEG electrodes placed at the Fz, Cz and Pz locations, with a reference at the Fpz, according to the international 10–20 EEG electrode system. The heat stimulations evoked well-defined negative–positive (N–P) waveforms with a maximum at the Cz electrode. The latencies of these peaks, as well as peak-to-peak amplitudes, were measured for the analysis.

4.7. DNA analysis

Studies 1, 2 and 3

All healthy subjects and patients gave a venous blood sample wherefrom the DNA was extracted using standard procedures. The DRD2 957C>T polymorphism (GenBank NM_000795.3:c.957C>T, rs6277) was determined as described previously (Duan et al. 2003, Hirvonen et al. 2009). In brief, PCR amplification of genomic DNA was performed with two forward (5´-ACCACGGTCTCCACAGCACTCT-3´; 5´- ACCATGGTCTCCACAGCACTCT -3´) and a reverse (5-ATGGCGAGCATCTGAGTGGCT-3´) oligonucleotide primer producing a 196 bp fragment. The PCR reaction mix consisted of 100 ng of genomic DNA, 2.5 pmol of each forward primer and 5.0 pmol of reverse primer, 0.2 units of DyNAzyme™ II DNA Polymerase (New England Biolabs GmbH, Frankfurt am Main, Germany), and 0.2 nmol of each dNTP in buffer containing 60 nM Tris-HCl, 15 mM ammonium sulphate and 1.5 nM MgCl2, pH 9.0 (total reaction volume 10 µl). Reaction conditions were 95 °C for 2 min followed by 40 cycles of 95 °C for 30 s, 62 °C for 30 s, 72 °C for 30 s, and a final extension step of 72 °C for 5 min. The DNA fragment was incubated for an hour at 65 °C by adding 4 U Taq^{a}I (New England Biolabs GmbH, Frankfurt am Main, Germany) and 1.0 ng BSA in buffer containing 50 mM Tris-HCl, 100 mM NaCl, 10 mM MgCl2 and 1 mM dithiothreitol, pH 7.9 at 25 °C (total volume 20 µl). Thereby, the C957 allele is cut into two fragments 174 bp and 22 bp long, whereas the 957T allele remains uncut by Tag^{a}I. Finally, digested PCR fragments were electrophorized on a 2.5–3.5% MetaPhor Agarose gel (Cambrex Bio Science Rockland, Unc., Rockland, ME, USA) containing 0.5 µg/ml ethidium bromide, and visualized with UV transillumination.

The COMT enzyme Val158Met polymorphism (GenBank NM_000754.3:c.472G>A, rs4680) was determined using the PCR-RFLP method of Woo et al. (2002). After the digestion the fragments were separated by 2.5% BMA MetaPhor (Oriola, Espoo, Finland), agarose gel electrophoresis containing 0.5 µg/ml ethidium bromide, and documented with UV transillumination as described earlier (Hirvonen et al. 2009).

4.8. Repetitive transcranial magnetic stimulation (rTMS)

Studies 1, 2 and 3

In all studies, the HF rTMS was applied with an E-field navigated TMS device and a biphasic figure-8 coil (eXimia NBS Navigation System and eXimia TMS stimulator, Nextim Ltd., Helsinki, Finland). The navigated device located the optimal coil position and direction using the individual head MRI and infrared tracking unit. With this optimal

placement inducing E-field orthogonal to the stimulated gyrus, the maximum magnetic field reaching the cortex could be up to 2.0 T, corresponding to an electric field of about 150 V/m.

The intensity of stimulation was chosen to be 90% of the individual resting motor threshold (RMT). RMT was determined by single pulse stimulation of the right motor cortex as described earlier (Valmunen et al. 2009). Motor evoked potentials (MEP) were recorded with surface electrodes on the left thenar muscles using the Viking ENMG device (Viking, Nicolet, Madison, WI, USA). The cortex was mapped to find the cortical area giving the largest MEP. The RMT was determined with an automated computerized program. The representation area of the facial muscles in the M1 was determined with single TMS pulses at intensity 10–20% above the previously determined RMT. The elicited MEPs were recorded with surface electrodes on contralateral frontal, nasal and mental muscles, and the cortical area giving the largest response in the nasal muscle was chosen to be the M1 stimulation area. The S1 area of the face was assumed to be in the adjacent postcentral gyrus (Fig. 3). The other cortical targets; the S2 (Fig. 4), the DLPFC (Fig. 5) and the OCC, were defined according to the individual MRI data similarly as described in an earlier study (Valmunen et al. 2009). The S2 stimulation target (Fig.4) did not comply with the exact anatomical location of the S2 cortex that is situated in the parietal operculum inside the sylvian fissure and cannot be reached directly. Instead, we stimulated the area overlying the real S2 and insular cortex on the postcentral gyrus, basing on the fact that focal rTMS can also stimulate the neighboring areas in addition to “hotspot” under the center of the coil (Bestman et al. 2005; Siebner et al. 2009).

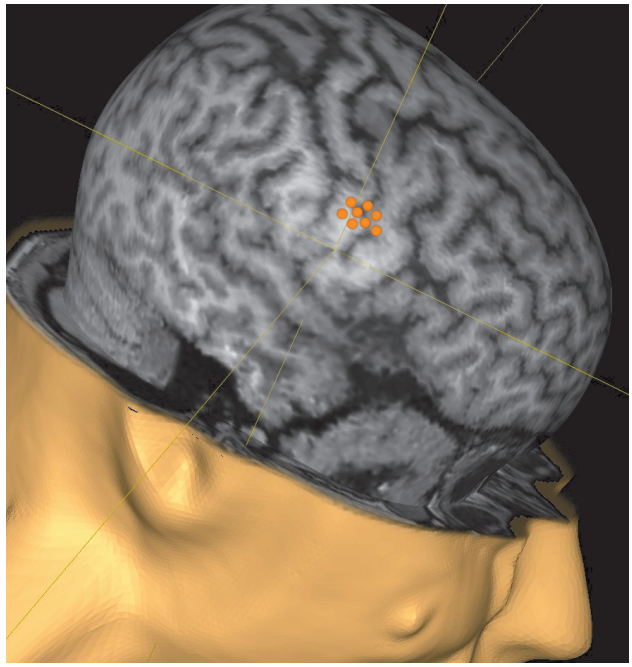


Figure 3. The S1/M1 stimulation area covering the representation area of the face in the pre- and postcentral gyri.

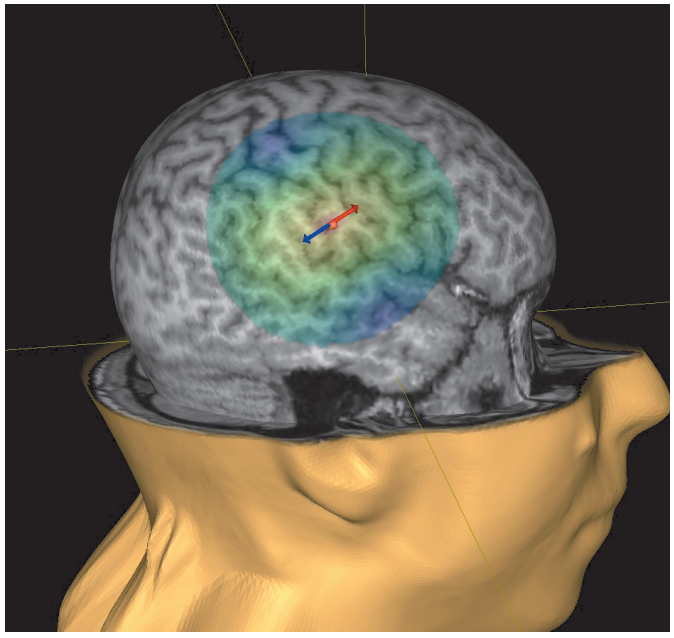


Figure 4. The S2 stimulation target in lateral edge of the postcentral gyrus; the red arrow shows the direction of the main induced electrical field

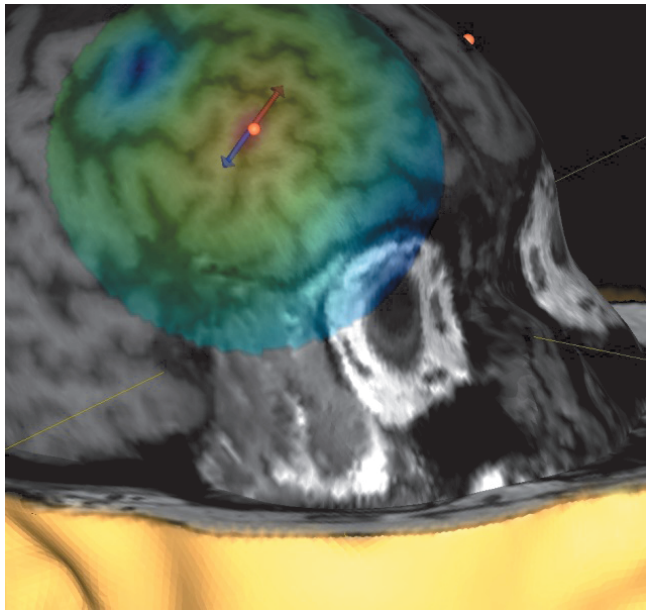


Figure 5. DLPFC stimulation target; the red arrow shows the direction of the main induced electrical field.

In the Study 1 with orofacial pain patients, the rTMS was given to the contralateral S1 and M1 cortices representing the face area when symptoms were unilateral and to the right S1/M1 in the case of bilateral symptoms. The S2 stimulation was always given to the right side. Active stimulations were given in randomized order, but the sham

stimulation was always in the middle to avoid carry-over effects. The sham stimulation was given with the same settings as S1/M1 stimulation, but there was a 75 mm plastic block attached to the coil, which minimized the electric field reaching the cortex negligible (0–4 V/m). Patients could not see the coil during the stimulation session, i.e. they were blinded to the mode of stimulation. The acoustic and sensory effects of the stimulations were similar, except for high stimulation intensities when the active S2-stimulation induced temporal muscle contraction (the location was slightly altered in these cases to minimize the muscle contraction). Other than that there were no side effects during or after the stimulations. Stimulation sessions consisted of 1000 pulses with 10 Hz frequency in trains of 50 pulses at 10-second intervals and a 15-minute break after the first 500 pulses to cool the coil.

The rTMS protocol of the Study 2 has been described in detail previously (Valmunen et al. 2009). Briefly, rTMS stimulation was given to the right M1, DLPFC, and OCC in a cross-over design with at least three weeks intervals to a group of 15 healthy subjects. Another 14 subjects received rTMS targeted to the S1 cortex representing the face and to the right S2 cortex in randomized order. Each stimulation session consisted of 500 biphasic magnetic pulses with 10 Hz frequency in trains of 50 pulses at 10-second intervals.

In the Study 3, the rTMS was given in trains of 50 pulses at 10 Hz to the right S1/M1 cortex representing the face area. The total amount of pulses was 1000 (500+500) per session with a 15-minute break in the middle of the session to cool the coil. The sham stimulation was given with the same settings as the active stimulation at S1/M1, but there was a 75 mm plastic block attached to the coil, which minimized the electric field reaching the cortex close to 0 V/m.

4.9. Positron emission tomography (PET)

Study 3

The radiotracers, [^{11}C]raclopride and [^{11}C]carfentanil, were synthesized using procedures described earlier (Hietala et al. 1994, Hirvonen et al. 2009). PET scans were performed using a high-resolution PET scanner (ECAT HRRT, Siemens Medical Solutions, Knoxville, TN) as previously described (Hirvonen et al. 2008). Briefly, the radiotracers were injected intravenously, and the radioactivity was measured 51 minutes after the [^{11}C]carfentanil IV-bolus and 69 minutes after the [^{11}C]raclopride IV-bolus. The injected masses were 0.7 ± 0.4 μg (308 ± 12 MBq) for sham and 0.8 ± 1.2 μg (301 ± 27 MBq) for active [^{11}C]raclopride , and 1.4 ± 0.6 μg (357 ± 75 MBq) for sham and 1.0 ± 0.5 μg (357 ± 61 MBq) for active [^{11}C] carfentanil. The availability of dopamine D2 receptors and opioid μ-receptors were determined as receptor binding potentials (BP_{ND}) with the simplified reference tissue model (SRTM) (Lammertsmaa and Hume 1996) using cerebellum and the occipital cortex as receptor-free reference regions. The region-of-interest (ROI) was defined with an individually realigned MRI image. A voxel-based statistical parametric mapping (SPM) was used as primary analysis for [^{11}C] carfentanil binding outside the striatum. For the striatum, the ROIs were manually defined for the ventral striatum, dorsal caudate, and dorsal putamen as

previously described (Hirvonen et al. 2008) using Imadeus software (version 1.4, Forima Inc., Turku, Finland).

4.10. Statistical analyses

All statistical analyses were performed by SAS statistical software package for Windows (SAS Institute, Cary, NC, USA).

Study 1

The effects of rTMS on pain, mood and the quality of life were determined by repeated measures analysis of variance (rmANOVA) with time as the within-subject factor, and diagnosis (AFP, BMS, TNP) and genotype as between subject factors. As regards rmANOVA analyses and results, estimates of mean (EM) +/- standard errors (SE) are given. P-values less than 0.05 were considered to be significant. Post-hoc comparisons between the MOS scores at baseline and after the treatments were made with paired Student's t-test. Correlations between RAND, NePIQoL, MOS, BPI and pain/sleep diary scores were tested using Pearson's correlation coefficient. A logistic regression analysis was run to find out if there were any baseline factors influencing the treatment outcome.

Study 2

The effects of the rTMS on the psychophysical measures were determined by mixed rmANOVA with time as the within subject factor, sex and genotypes as the between subjects factors, age as a fixed covariate, and vigilance as a varying covariate. In the case of multiple tests, the Tukey-Kramer method was used to adjust P values for the individual alpha level (0.05). Post hoc comparisons were done with Student's t test for independent variables. The frequencies of genotypes were compared between the neuropathic pain patients and the Finnish population using the binomial tests.

Study 3

The primary hypothesis of rTMS-induced opioid and dopamine releases was tested with the paired samples t-test at the voxel level. Correlations between the changes in binding potentials and other variables were tested using Pearson's correlation coefficients. Evaluation of significant changes in QST and CHEP after rTMS was done with rmANOVA. The rTMS effects on the habituation of the blink reflex were analyzed with the non-parametric Cochra-Mantel-Haenszel statistics. The validity of all models was checked by residual analysis, and P-values of less than 0.05 were considered statistically significant.

5. RESULTS

rTMS effects on pain perception, clinical pain, mood and sleep (I, II, III, IV)

In healthy subjects (N = 29; III), rTMS to the right S1 cortex increased heat pain detection thresholds in subjects homozygous for the 957T allele ($F_{6,24}$ = 3.78, p = 0.009 for the interaction effect of time and genotype), whose mean heat pain detection thresholds were initially lower than 957C allele carriers (p < 0.05 after adjusting for multiple comparisons). The S1 stimulation did not change the pain detection thresholds in 957C allele carriers. For complete results see Fig. 6.

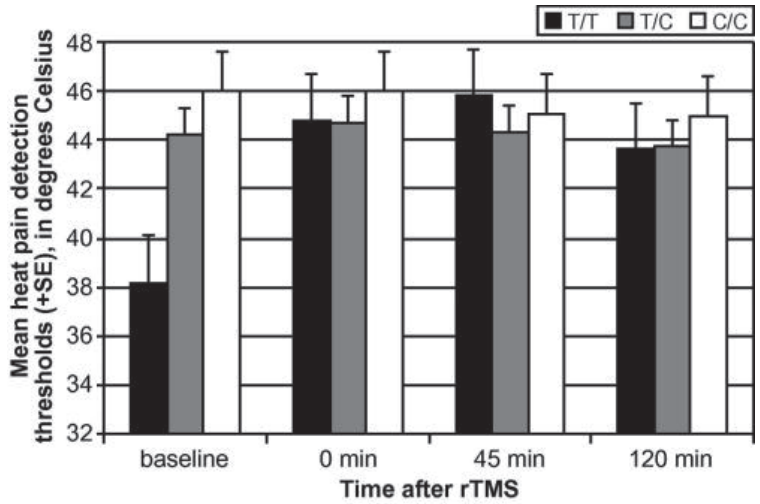


Figure 6. Initially low heat pain detection thresholds in subjects homozygous for 957TT rose to same level as in other genotype carriers after rTMS to the right S1.

In the smaller group of healthy subjects (N = 11; IV), the right S1/M1 stimulation did not have an effect on pain detection thresholds or heat pain evoked potentials.

In neuropathic orofacial pain patients (N = 16; I, II), only rTMS targeted to the right S2 alleviated otherwise intractable pain. Daily pain intensity in NRS was lowest three days after the S2 stimulation (EM 3.8, SE 0.6) being significantly lower than after the S1/M1 stimulation (EM 5.4, SE 0.6, p = 0.007) or placebo stimulation (EM 5.3, SE 0.6, p = 0.019) as shown in Fig. 7.

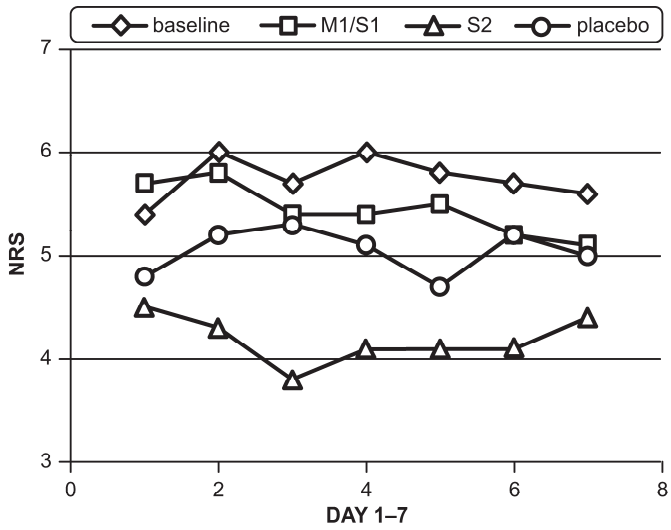


Figure 7. Mean pain intensity (NRS) for 7 concecutive days at baseline and after the rTMS treatments starting in the evening of the treatment day.

The rTMS targeted to S2 was effective compared to the placebo with an effect size (Cohen's d) of 0.6. When compared to the baseline level of pain (mean NRS 5.7, SD 1.9), the effect size for S2 stimulation (mean NRS 3.8, SD 2.0) was 1.0, for S1/M1 stimulation 0.1 (mean NRS 5.4, SD 2.0) and for placebo stimulation 0.4 (mean NRS 5.0, SD 2.0).

The BPI intensity of pain scores were significantly lower 3–5 days after the rTMS targeted to S2 (EM 4.5, SE 0.4) than at baseline (EM 5.4, SE 0.4; p = 0.013) or after the S1/M1 stimulation (EM 6.2, SE 0.4; p = 0.001) and the placebo stimulation (EM 5.1, SE 0.4; p = 0.049) (Fig 8).

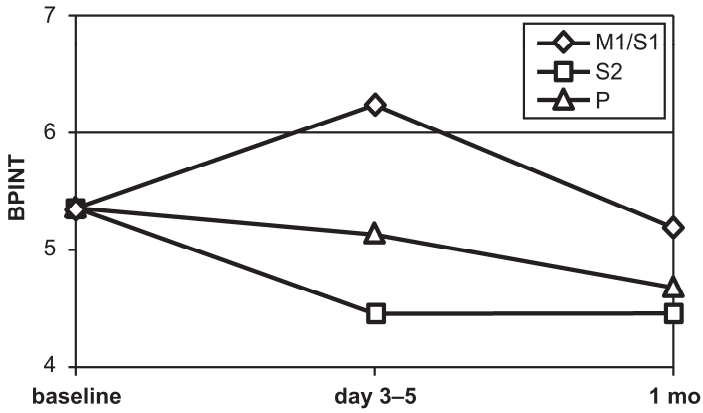


Figure 8. BPI Intensity of pain (BPINT) scores at baseline and after the stimulation sessions.

The BPI interference of pain scores were also lower after the rTMS targeted to S2 (EM 2.7, SE 0.5) than before the treatments (EM 3.6, SE 0.5; p = 0.007) or after the S1/M1 (EM 0.4, SE 0.5; p = 0.000) and placebo (EM 3.4, SE 0.5, p = 0.036) treatments (Fig. 9).

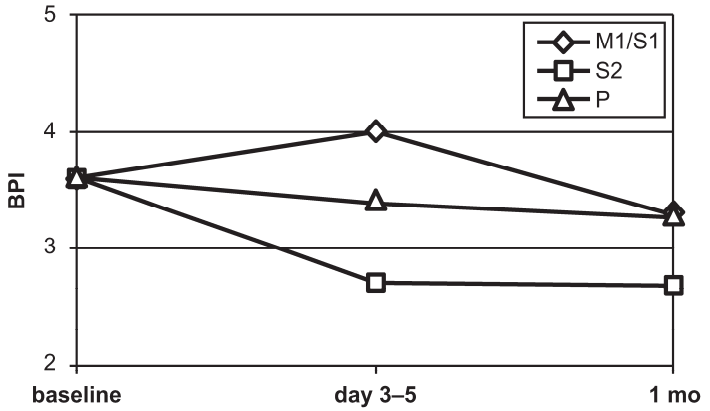


Figure 9. BPI Interference of pain scores at baseline and after the stimulation sessions.

There was a small but significant reduction in NePIQoL total score still a month after the S2 treatment (ES 79.8 vs. 86.6; p = 0.003), indicating less interference of pain in daily life. No significant changes were seen in NePIQoL scores after the S1/M1 (ES 85.5, SE 5.7; p = 0.608) or the placebo (ES 87.0, SE 5.7; p = 0.856) treatments. There were no significant changes in the questionnaire assessing more general quality of life, the RAND-36.

There were no alterations in the BDI scores measuring mood, or in the sleep diary measurements concerning the amount and the quality of sleep before and after the rTMS treatments (I, II).

In the pairwise, posthoc comparisons (II), only the MOS Sleep Scale SOB subscore describing shortness of breath or headache was lower (p = 0.027) after the rTMS targeted to S2 than at baseline. The SLD (sleep disturbance) subscore (p = 0.046), and both S6 (p = 0.040) and S9 (p = 0.013) index scores describing overall sleep problems, were lower after the S1/M1 stimulation, even though that stimulation had no analgesic effect. Nonetheless, after correction for multiple comparisons, only the difference in S9 sleep index score remained significant. The placebo treatment did not have any influence on the MOS sleep scores.

The effects of individual features on rTMS treatment outcome (I, II, III)

In pain patients (I, II), the baseline psychiatric disorders (depression, general anxiety disorder, social phobia, specific phobia), sleep disorders (poor quality of sleep, restless legs), or notable medications (opioids, gabaergic drugs) had no predictive value for the treatment outcome in any of the stimulation conditions. Patients' diagnoses or genotypes related to brain dopamine system did not have an influence on the treatment effect, either. On the contrary, analgesic efficacy of S1 rTMS in healthy subject depended on DRD2 gene 957C>T genotype (Fig 6).

The quality of life and sleep in neuropathic orofacial pain patients (I, II)

Patients' quality of life at baseline was very variable according to the RAND questionnaire. In older age group (≥ 65 years), scores did not differ from the general

population. Younger patients (18–64 years) were clearly more painful than the general population. Otherwise, scores differed so much between individual patients that the results of the statistical analyses remained non-significant, and no firm conclusions could be made.

Sleep disturbances were common among patients. According to the BNSQ questionnaire at baseline, 11 of 15 patients experienced their sleep being usually poor, and 9 (/15) suffered from daytime somnolence and early awakenings more than three times a week. 11 of 16 patients experienced trouble falling asleep more than three times a week, and 6 (/16) suffered from awakening more than three times per night. Almost half of the patients (7/16) used sleep medicine more than three times a week. 14 (/16) had sometimes snored, but none of them snored more than three times per week. Only 2 (/16) had experienced sleep apnea, which in these cases occurred less than once a week.

Patients reported worse scores on three of five MOS Sleep Scale scores (SLD p = 0.000, SOB p = 0.000, SS p = 0.001) and on the 9-item index score (p = 0.000) compared to the US general population. Comparison of the MOS scores between the patients and healthy population is shown in Fig. 10.

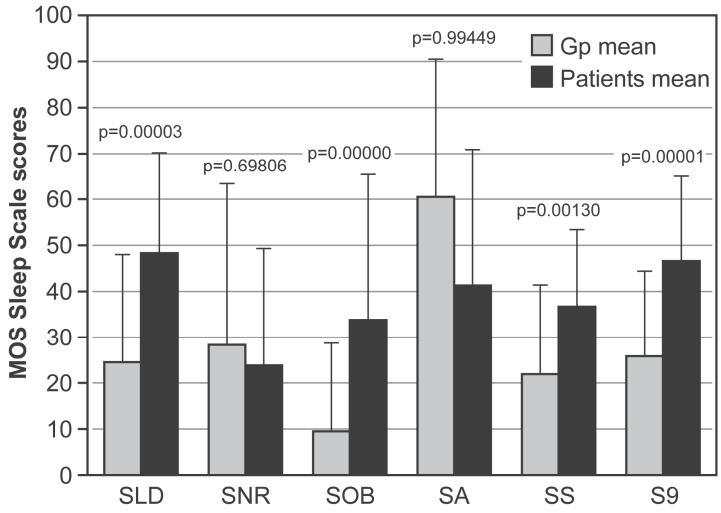


Figure 10. Comparison of the MOS Sleep Scale Scores between the neuropathic orofacial pain patients and the US general population. Patients reported worse scores on sleep disturbance, awakening with short of breath or headache, daytime somnolence, and 9-item sleep problem index total score.

According to SCID-I interviews, six (38%) of the patients had a present and ten (63%) a lifetime axis I psychiatric disorder. The lifetime rates of depressive and anxiety disorders were higher in patients than in general population (Pirkola et al. 2005) but comparable to those reported earlier for a larger sample of Finnish orofacial pain patients (Taiminen et al. 2011). Patients' current and lifetime psychiatric diagnoses along with current medications are presented in Table 4.

The role of endogenous dopamine-opioid system in pain perception, modulation, and vulnerability, and in rTMS mechanisms and efficacy (I, II, III, IV)

Healthy subjects homozygous for DRD2 957T allele (957TT) had lower detection thresholds for all four thermal sensory modalities than subjects with 957CC genotype ($p < 0.05$ after adjusting for multiple comparisons), indicating that 957TT carriers were most sensitive to both innocuous and noxious thermal stimuli (Fig. 11).

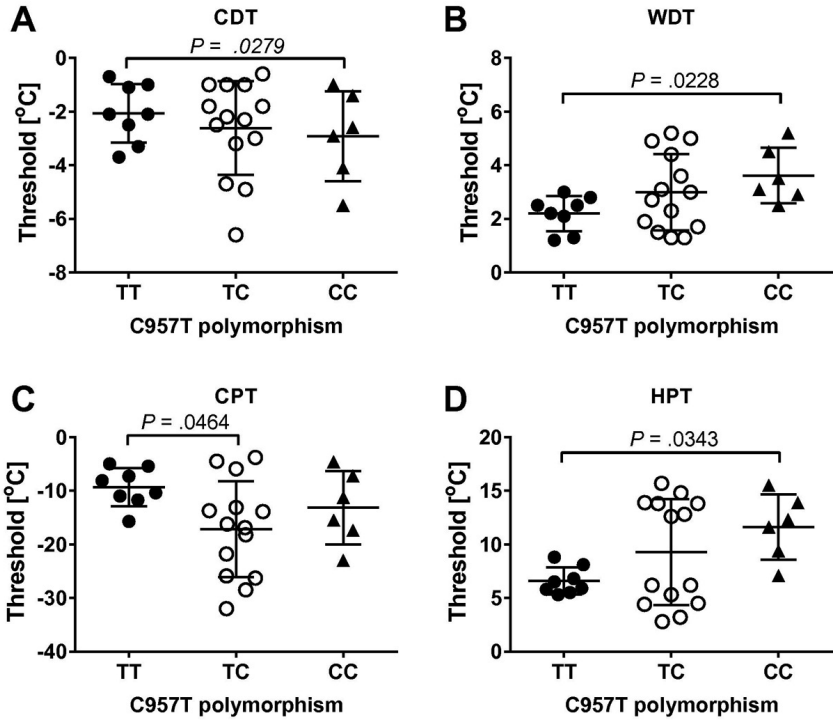


Figure 11. Thermal sensory detection thresholds depend on DRDT gene 957C>T polymorphism.

The initially low heat pain detection thresholds in subjects with 957TT genotype increased to the same level with other genotype carriers after rTMS given to S1, whereas there were no changes in thermal thresholds seen in other genotype carriers (time by DRD2 957C>T genotype interaction effect in rmANOVA $p = 0.009$) (Fig. 6). The cold pain thresholds were lowest in subjects concurrently homozygous for 957TT and 158MetMet ($F_{4,14} = 4.13$, $p = 0.020$).

The prevalence of DRD2 957TT genotype was higher within the neuropathic orofacial pain patient group (50%) than in Finnish general population (27%, $p = 0.019$). Patients with 957TT genotype had also higher pain intensity scores at baseline (mean NRS 5.8, SE 0.5) than patients with 957CT (mean NRS 2.9, SE 0.9) or 957CC (mean 4.4, SE 0.7) genotypes ($p = 0.035$ for main effect of 957C>T genotype). The prevalence of 158MetMet genotype did not differ significantly between the patients (37%) and the general population (27%). Neither did the Val145Met polymorphism impact the pain severity at baseline. The genotypes did not have an influence on the rTMS treatment response in the patients (I).

In the neurotransmitter PET study on healthy subjects (IV), [^{11}C]carfentanil PET imaging showed significantly lower μ-opioid receptor binding after active rTMS to the right S1/M1 in all right-handed subjects compared to placebo ($p \leq 0.000$), but not in the one ambidextrous subject. The μ-opioid receptor availability was lower in the right ventral striatum, medial orbitofrontal cortex, prefrontal cortex, ACC, left insula, superior temporal gyrus, DLPFC and precentral gyrus indicating endogenous opioid release from this wide brain network as a result of active rTMS (Figs. 12–13).

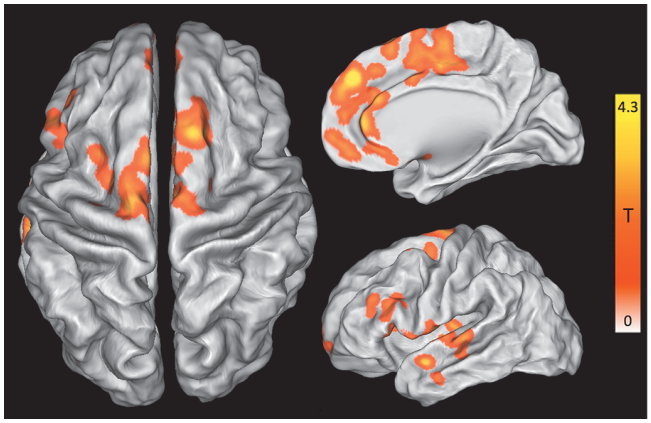


Figure 12. Statistical parametric mapping (SPM) analysis shows lower [^{11}C]carfentanil BP_{ND} after active rTMS treatment compared with sham in multiple brain regions. Colour bar represent t value in each voxel within the significant cluster.

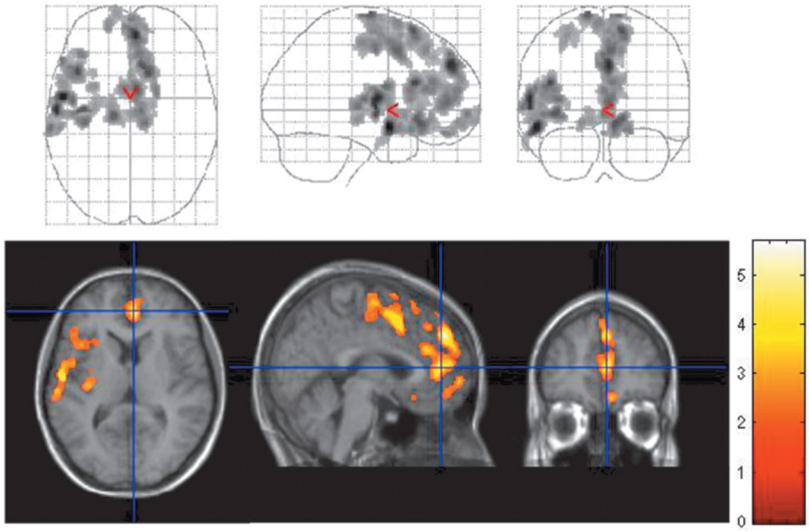


Figure 13. Results of voxel-wise SPM analysis.

There were no differences in striatal dopamine D2 receptor availability between active and sham rTMS in [11C]raclopride PET, but active rTMS potentiated the habituation of the blink reflex compared to sham ($p = 0.02$) suggesting possible activation of the nigrostriatal dopamine system as well (IV).

6. DISCUSSION

Considerations of the effects of rTMS to different cortical targets

Posterior operculo-insular cortex, which is specifically involved in the processing of nociceptive information (Peyron et al. 2000, Garcia-Larrea 2012), could be an interesting novel target for therapeutic analgesic rTMS. As the deeply situated insular cortex cannot be directly stimulated with rTMS, we chose to stimulate a site on the postcentral gyrus overlying the right S2 and insular cortex, calling it here S2 (Fig. 4), based on the fact that the neighboring areas can also be stimulated with focal rTMS (Bestman et al. 2005, Siebner et al. 2009). Supporting our hypothesis, rTMS targeted to this novel area seemed to have an independent analgesic effect on neuropathic orofacial pain (I). The rTMS targeted to the right S2 had no effect on depressive symptoms, or sleep disturbances indicating that analgesic effect did not depend on simultaneous improvement of comorbid disorders (I, II). Baseline psychiatric or sleep comorbidities did not predict the treatment outcome either (II). The rTMS targeted to the right S2 induced hypoalgesic effects regardless of the painful side. The right side was chosen based on previous findings of decrease in thermal pain sensitivity (Valmunen et al. 2009) after similar stimulation. There was also some earlier evidence of rightward lateralization in sensory awareness, interoception, pain processing, and in connections between S2 and the insular cortex as part of the salience network (Coghill et al., 2001; Strafella et al., 2003). It would have been interesting to investigate the effects of the rTMS targeted to the left S2 as well, but additional stimulation targets would have made the study protocol even more demanding. The discovered analgesic effect of the rTMS targeted to the right S2 complies with findings in healthy subject suggesting this type of stimulation both impairs the subjective appraisal of painful stimuli and reduces the perceived pain intensity (Valmunen et al. 2009; Lockwood et al. 2013; Uglem et al. 2016).

The effectiveness of the rTMS targeted to the right S2 may depend on the location of the target close to the insular cortex, which is known to be important in pain perception (Peyron et al. 1999, 2000; Treede et al. 1999, 2000; Apkarian et al. 2005; Baumgärtner et al. 2010; García-Larrea 2012; Wiech et al. 2010; Ploner et al. 2011). The functional connection between the S2 and the insular cortex has been proposed to be especially strong during painful stimulation (Peltz et al. 2011). Altered baseline functional connectivity during chronic pain could, therefore, influence the rTMS effect, which has been suggested to depend on subject-specific cortical excitability and connectivity (Lefaucheur et al. 2014; Nettekoven et al. 2015). It could be possible that rTMS to somatosensory cortices is effective only when there is something to normalize, such as baseline hypersensitivity or plastic cortical reorganization in response to chronic pain. Results of our study with healthy subjects (III) support this concept, because rTMS to the right S1 cortex increased heat pain detection thresholds only in subjects whose baseline detection thresholds were low, i.e. in subjects who were hypersensitive. Actually, in a recent rTMS study, it was suggested that rTMS could modulate pathologically sensitized networks and cognitive appraisal of chronic pain, rather than

change the physiological transmission within an intact nervous system (Bradley et al. 2016). It has been previously demonstrated that plastic cortical reorganization correlates to perceived pain and for example, in phantom limb pain, this reorganization can be (re)normalized by successful therapy, like regional anesthesia (Birbaumer et al. 1997) or somatosensory training (Flor et al. 2001, Huse et al. 2001).

In the neuropathic pain patient group (I), the S1/M1 stimulation induced variable effects from analgesia to hyperalgesia, leaving the group level efficacy non-significant. This stimulation target was chosen because S1 stimulation had shown DRD2 genotype-related efficacy in our healthy subjects group, and because of already established analgesic effect of M1 stimulation (Hirayama et al. 2006; Leo and Latif 2007, André-Obadia et al. 2008; Cruccu et al. 2010). However, earlier studies have presented negligible (Hirayama et al. 2006) or even hyperalgesic (Tsubokawa et al. 1993) effects of S1 stimulation, which our findings now support. Our plan was to search for novel efficient stimulation targets, but considering it now afterwards, it would have been interesting to compare the rTMS targeted to the right S2 with the most commonly used M1 instead of the controversial S1/M1. Nevertheless, these results emphasize the importance of precise anatomical navigation in rTMS treatment, as it has recently been reported (Ayache et al. 2016). In that study, navigated HF rTMS delivered to the M1 representation of pain region relieved upper and lower limb pain, but not facial or hemibody pain. However, the neuronavigation was done according to classical homunculus anatomy (the actual representation areas of painful region were not mapped), and possible plastic changes in the representation areas following chronic pain were not considered.

The role of endogenous dopamine and opioid systems in rTMS-induced analgesia and pain perception

In the group of neuropathic orofacial pain patients, the genotypes related to dopamine system did not have an influence on rTMS treatment outcome (I). Instead, the variation in dopamine D2 receptor gene had a clear effect on thermal perception and rTMS effects in healthy subjects (III). More closely, the DRD2 957TT homozygotes were originally more sensitive to heat pain, and this oversensitivity was normalized by rTMS given to S1 cortex. This “pain sensitive” TT genotype was overrepresented (50%) in our unselected group of neuropathic pain patients, which may have rendered the results of genetic association analyses non-significant in this small group of patients. These results support the earlier findings indicating that the dopamine system and DRD2 are important in adjusting baseline pain sensitivity and modulating pain responses both in healthy people and in orofacial pain patients (Jääskeläinen et al. 2001; Hagelberg et al. 2002, 2003 a,b, 2004; Pertovaara et al. 2004; Martikainen et al. 2005). In line, several animal studies have shown that the striatal DRD2 mediate analgesic effects especially in persistent pain models (Chudler and Dong 1995; Magnusson and Fisher 2000; Ansah et al. 2007). There is also earlier evidence that rTMS given to M1 induces striatal dopamine release in humans (Strafella et al. 2003). We could not confirm this finding with PET imaging, but the differences seen in habituation of the blink reflex might indirectly represent activation of the striatal dopamine system (IV). There could have been a possibility in missing the initial fast

phasic dopamine release because of the delay between the rTMS and PET scanning (114 min compared to 5 min in Strafella et al. 2003). Nonetheless, opioids were released in the right NAc, which is one of the primary sites of interaction between brain dopamine and opioid systems (Zubieta et al., 2001).

According to the PET study on healthy subjects (IV), right S1/M1 rTMS seems to activate the endogenous opioid system in the brain network known to be involved in the processing of pain and other salient information. In the right-handed subjects, the opioid system was activated in operculoinsular structures and DLPFC contralateral to stimulation, and in ACC, medial orbitofrontal cortex and striatum ipsilateral to stimulation. Thus, homologous regions of the non-dominant and dominant hemispheres seem to have different roles in the modulation of pain. This finding supports the hemispheric lateralization of pain processing presented previously (Coghill et al., 2001; Strafella et al., 2003; Kucyi et al. 2012 a, b). Endogenous opioid system activation has earlier been shown to be one of the mechanisms of analgesia induced by invasive MCS (Maarrawi et al. 2007, 2013). The present results indicate the same mechanism to be active also in rTMS-induced analgesia. No alterations were seen in thermal QST and CHEP compared to sham stimulation. Together these findings may indicate that rTMS affects the cognitive-evaluative and affective-motivational dimensions of pain rather than the sensory-discriminative dimension. This theory is supported by the earlier findings suggesting that rTMS effects could be due to a change in the subjective appraisal of pain, which occurs with a delay after rTMS targeted to the right S2 (Valmunen et al. 2009).

There is some contradiction in these results concerning S1/M1 stimulation effects. Considering the opioid system activation induced by S1/M1 rTMS, one could expect it to be analgesic in neuropathic orofacial pain. However, that was not the case in our treatment study (I). Unfortunately, we did not include the S2 target in the PET study (IV). Future studies on patients with neuropathic pain are definitely needed to make any firmer conclusions about the mechanisms of action of therapeutic rTMS, and to discover the most efficient stimulation settings.

Placebo effects and limitations of the study

If rTMS-induced analgesia is a result of a top-down dopamine-opioidergic system activation, it is crucial to bear in mind the placebo effects. During placebo effect, the amount of dopamine and opioid release has been found to correlate positively with the individual expectation of analgesia (Zubieta and Stohler 2009). In our PET study (IV), the placebo effect and expectation were controlled by a credible sham control and a study design accounting for anticipation. There were no baseline measurements, but only comparison between results after active and sham rTMS. Furthermore, healthy subjects had no expectations of any benefit from the stimulations, and they knew that one of the two stimulations was a sham. In the study with clinical pain patients, the expectation could not be eliminated. When the pain intensities at baseline and after the treatments were compared, the effect size for the placebo treatment was 0.4 and for rTMS targeted to the right S2 1.0 (I). Nevertheless, the effect size of the rTMS targeted to the right S2 compared to the placebo was still remarkable, 0.6, and can be

considered clinically relevant. Patients knew that one of the three treatments was placebo and after finishing the study, the majority of the patients could not recognize the placebo treatment correctly. Yet, 6 out of 16 patients recognized the placebo, two because of temporal muscle contraction during active stimulation and four because of a distinct positive response to the active treatment. The placebo stimulation was thus far from optimal, but that is, unfortunately, the case in most rTMS studies. Nevertheless, in our study, the effects of the previous active stimulation did not have an influence on the following placebo session as was found in an earlier rTMS study (André-Obadia et al. 2011).

Another common limitation concerning both rTMS and PET studies is the small sample size that must be recognized in our studies, too. Thus, the novel results of our studies with small sample sizes must be considered preliminary but still of value in the field of pain treatment with central neuromodulation. Study protocols were challenging, especially in the study of clinical patients, which complicated recruitment. However, according to the power analysis, the sample size of the neuropathic orofacial patient group was considered sufficient to detect clinically meaningful changes in pain intensity, as was shown for rTMS targeted to the right S2 (I).

Heterogeneity of the patient group with three different diagnoses was a limitation too, but pathophysiologically, the group was still homogeneous as all patients had a neurophysiologically confirmed i.e. definite neuropathic orofacial pain.

Possible shared vulnerability behind comorbidities in neuropathic pain patients

Neuropathic pain patients having comorbidities like mood and sleep disorders is nothing new, but still, the amount of these comorbid disorders in our group of orofacial pain patients was remarkable (I, II). Depressive disorders mostly preceded the onset of pain, which is consistent with other studies concerning orofacial pain (Lascelles 1966; Lamey and Lamb 1988; Taiminen et al. 2011). The shared vulnerability through hypofunctional brain dopamine activity could be a possible underlying predisposing factor both to depression and chronic pain (Jääskeläinen et al. 1997, 2001, 2014; Hagelberg et al. 2003 a, b; Zubieta et al. 2003). This hypothesis is supported by the fact that the pain vulnerable DRD2 gene genotype 957TT carriers with low striatal dopamine content were overrepresented in the study group of neuropathic orofacial pain patients (III). The occurrence of the anxiety disorder at and after the onset of pain could also be explained by the hypofunctional dopamine activity related to a specific personality trait of harm avoidance (Kim et al. 2011). The personality trait of harm avoidance (type C personality disorder) predisposes to worrying and catastrophizing about the pain and is associated with pain-related anxiety (Knaster et al. 2012). General anxiety disorder, in turn, is shown to be associated with low striatal dopamine synthesis capacity (Laakso et al. 2003). This hypothesis is of course highly speculative, especially as we did not analyze the possible axis II personality disorders in this group of patients. However, in a larger sample of Finnish orofacial pain patients, neurotic and fearful personality (type C) disorders were strikingly higher than in general population (Taiminen et al. 2011).

Sleep disorders were also significantly more common in our group of neuropathic orofacial pain patients than in general population (II), which is in line with earlier reports on BMS patients (Chainani-Wu et al. 2011; Adamo et al. 2013) and neuropathic pain patients on average (Gore et al. 2005; Poliakov and Toth 2011, Bouhassira et al. 2013). Sleep disorders were associated with the interference of pain in daily life (NePIQoL and BPI), but not with the intensity of pain (II). The same tendency was seen with depressive symptoms that were more common in patients reporting more interference of pain in daily life (NePIQoL and BPI) and poorer quality of sleep (II). It could be concluded that not the pain intensity itself but the coping with the pain is important in relation to mood and sleep disturbances. It has been shown earlier that a negative cognitive and affective response to pain, so called pain catastrophizing, might contribute to sleep disturbance in chronic pain (Smith et al. 2001; Buenaver et al. 2012). Altogether, the relationship between chronic pain, sleep disorders, and psychiatric disorders is obvious and to optimize the overall treatment outcome, these comorbidities should be adequately assessed and treated (Nicholson and Verma 2004, Argoff 2007).

7. CONCLUSIONS

The right S2 seems to be a promising novel target for the rTMS treatment of drug-resistant neuropathic orofacial pain. The analgesic effect of the rTMS targeted to the right S2 is not mediated or predicted by comorbid psychiatric or sleep disorders. Orofacial pain patients have more psychiatric and sleep disorders than the general population, and there are associations between these comorbid disorders, which may be explained by shared vulnerability via low striatal brain dopamine tone.

Our results suggest that the top-down endogenous dopamine-opioid system is important in the perception and modulation of pain, and in rTMS-induced analgesia. Yet, it must be acknowledged that dopamine-opioid system is just one of the mediators in the complex brain system associated with salient stimuli like pain.

Considering the burden of resistant neuropathic pain, novel treatments are needed and worth examining. rTMS holds promise as an effective therapy for drug-resistant neuropathic orofacial pain. Accurate targeting with neuronavigated devices as well as setting novel targets, such as the right S2, will probably further increase its efficacy.

ACKNOWLEDGEMENTS

This thesis was carried out at the Department of Clinical Neurophysiology, Turku University Hospital and the University of Turku during 2009-2017.

I wish to express my deepest gratitude to my supervisor Professor Satu Jääskeläinen for introducing me to the interesting word of neuromodulation and pain research. Your enthusiasm for research and amazing knowledge has been most inspiring. Without your kind guidance and understanding for my other commitments, I would not have been able to finish this project.

I warmly thank my other supervisor Salla Lamusuo M.D., Ph.D. for her encouragements, never failing support and guidance to neuroscience and sleep medicine. Our “way to work” conversations were of irreplaceable value, especially when things were not going so smooth. I will never forget us trying to figure out wonders of statistics in the Wiklund cafeteria. Well, we are just neurologists.

I gratefully acknowledge the official reviewers, Adjunct Professor Erika Kirveskari and Adjunct Professor Jyrki Mäkelä for their careful review of this thesis. Your constructive comments and advice really improved the outcome.

My sincere gratitude goes to Professor Antti Pertovaara, a member of the study group and my supervisory committee, for his guidance and encouragement throughout this work. Your knowledge of neuroscience and neuromodulation is truly admirable. I also appreciatively acknowledge Adjunct Professor Aki Hietaharju, another member of my supervisory committee, for giving his valuable time to my thesis.

I thankfully acknowledge the members of our research team, who all participated in designing the study as experts of their fields. I thank Adjunct Professor Tero Taiminen and Ari Lahti M.D., Ph.D. for the psychiatric evaluations and participation in the rTMS sessions, Adjunct Professor Heli Forssell for contribution to patient recruitment and valuable advice throughout the project, Adjunct Professor Nora Hagelberg for great advice and encouragement, Professor Jarmo Hietala and Adjunct Professor Ullamari Pesonen for sharing their expertise of dopamine system genetics, Arja Virtanen Ph.D., MSc for statistical analyses, and Professor Riitta Parkkola for MRI analyses. I also thank co-writers, Tanja Valmunen M.D., Jussi Hirvonen Ph.D., M.D., Ilkka K. Martikainen Ph.D., M.D. and Semi Helin Ph.D., MSc for their contributions. I warmly thank Eeva Kärpijoki, Tuula Jokela, and Pia Aalto for their excellent and flexible work with QST, CHEP and BLINK measurements. The expert staff at Turku PET Center and the Centre for Cognitive Neuroscience are gratefully acknowledged for their expertise and collaboration, especially planning officer Maria Ek for her kind help with arranging the schedules and other practical things.

I am truly thankful for the healthy subjects and patients who participated in this study.

I warmly thank the former Head of the Salo Hospital Neurology, Kari Koski Ph.D., M.D., for his positive attitude towards my research project, and for sharing with me his wide

knowledge in neurology. I also sincerely thank Professor Risto O. Roine, the Head of the Department of Neurology in Turku University Hospital, Professor Seppo Soinila and Adjunct Professor Merja Soilu-Hänninen for their support to my interdisciplinary thesis. Especially Adjunct Professor Merja Soilu-Hänninen and my supervisor, and Head of the Salo Hospital Neurology, Salla Lamusuo M.D., Ph.D. are thanked for arranging me valuable time off from my daily work to complete this thesis. I am deeply appreciative to the former Head of the Department of Neurology in Turku University Hospital, Professor Emeritus Reijo Marttila for introducing me to the fascinating word of neurology, and for guiding and supporting me during my specialization years in neurology. I warmly thank all my colleagues and friends at the Department of Neurology in Turku University Hospital for their companionship in and outside work. Special thanks go to my dear Sisters in neurology, Jaana, Ninni and Anna. Your peer support is irreplaceable. Talking about peer support, if I could do it, Miia, you can do it.

I warmly thank all my dear friends for relaxing times that have given me strength to accomplish this thesis among other things in life. Special thanks to my precious friends Pia and Wera, to whose friendship and support I can count at all times. With you it has never been a problem to seize the day.

I have been blessed with an amazing family, the Kariniemi people, as my sister-in-law says. I owe my heartfelt thanks to my parents Marja-Leena and Matti Kariniemi; sister Ikka; brothers Jukka and Matti; in-laws Leona, Auli and Timo; and nephews and nieces Aleksi, Ruija, Arttu-Kalle, Iiris, and Kare. Your unfailing support and friendship give me strength and spirit. Special thanks go to my sister-in-law, Adjunct Professor Leona Gilbert for inspiring conversations regarding scientific work and beyond, and for checking the language of this thesis.

As silly as it appears, Remu must be acknowledged for keeping me constant company during the long hours of this writing process, and for taking me out regularly.

Finally, my deepest loving thanks go to my main men, Johan and Aron. Without your unlimited support, love, and encouragement, this thesis would have never been completed.

Financial support from the Turku University Hospital, the Turku University Foundation, the Finnish Medical Foundation, the Sigrid Jusélius Foundation, and the Finnish Association for the Study of Pain is greatly acknowledged.

REFERENCES

Aalto A-M, Aro AR, Teperi J. 1999, RAND-36 as a measure of health-related quality of life. reliability, construct validity and reference values in the Finnish general population. Helsinki: Stakes, Res Rep 101; 49–50.

Adamo, D., Schiavone, V., Aria, M., Leuci, S., Ruoppo, E., Dell'Aversana, G. & Mignogna, M.D. 2013, "Sleep disturbance in patients with burning mouth syndrome: a case-control study", *Journal of orofacial pain,* vol. 27, no. 4, pp. 304-313.

Affleck, G., Urrows, S., Tennen, H., Higgins, P. & Abeles, M. 1996, "Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia", *Pain,* vol. 68, no. 2-3, pp. 363-368.

Ahtee, L., Attila, L.M. & Carlson, K.R. 1990, "Augmentation of morphine-induced changes in brain monoamine metabolism after chronic naltrexone treatment", *The Journal of pharmacology and experimental therapeutics,* vol. 255, no. 2, pp. 803-808.

Al Quran, F.A. 2004, "Psychological profile in burning mouth syndrome", *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics,* vol. 97, no. 3, pp. 339-344.

Ali, Z., Raja, S.N., Wesselmann, U., Fuchs, P.N., Meyer, R.A. & Campbell, J.N. 2000, "Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain", *Pain,* vol. 88, no. 2, pp. 161-168.

Altier, N. & Stewart, J. 1999, "The role of dopamine in the nucleus accumbens in analgesia", *Life Sciences,* vol. 65, no. 22, pp. 2269-2287.

Amir, R., Kocsis, J.D. & Devor, M. 2005, "Multiple interacting sites of ectopic spike electrogenesis in primary sensory neurons", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 25, no. 10, pp. 2576-2585.

Andre-Obadia, N., Magnin, M. & Garcia-Larrea, L. 2011, "On the importance of placebo timing in rTMS studies for pain relief", *Pain,* vol. 152, no. 6, pp. 1233-1237.

Andre-Obadia, N., Mertens, P., Gueguen, A., Peyron, R. & Garcia-Larrea, L. 2008, "Pain relief by rTMS: differential effect of current flow but no specific action on pain subtypes", *Neurology,* vol. 71, no. 11, pp. 833-840.

Andre-Obadia, N., Peyron, R., Mertens, P., Mauguiere, F., Laurent, B. & Garcia-Larrea, L. 2006, "Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 117, no. 7, pp. 1536-1544.

Ansah, O.B., Leite-Almeida, H., Wei, H. & Pertovaara, A. 2007, "Striatal dopamine D2 receptors attenuate neuropathic hypersensitivity in the rat", *Experimental neurology,* vol. 205, no. 2, pp. 536-546.

Antal, A., Kincses, T.Z., Nitsche, M.A. & Paulus, W. 2003, "Manipulation of phosphene thresholds by transcranial direct current stimulation in man", *Experimental brain research,* vol. 150, no. 3, pp. 375-378.

Antal, A., Terney, D., Kuhnl, S. & Paulus, W. 2010, "Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition", *Journal of pain and symptom management,* vol. 39, no. 5, pp. 890-903.

Apkarian, A.V., Bushnell, M.C., Treede, R.D. & Zubieta, J.K. 2005, "Human brain mechanisms of pain perception and regulation in health and disease", *European journal of pain (London, England),* vol. 9, no. 4, pp. 463-484.

Apkarian, A.V. & Hodge, C.J. 1989, "Primate spinothalamic pathways: III. Thalamic terminations of the dorsolateral and ventral spinothalamic pathways", *The Journal of comparative neurology,* vol. 288, no. 3, pp. 493-511.

Argoff, C.E. 2007, "The coexistence of neuropathic pain, sleep, and psychiatric disorders: a novel treatment approach", *The Clinical journal of pain,* vol. 23, no. 1, pp. 15-22.

Attal, N., Cruccu, G., Haanpaa, M., Hansson, P., Jensen, T.S., Nurmikko, T., Sampaio, C., Sindrup, S., Wiffen, P. & EFNS Task Force 2006, "EFNS guidelines on pharmacological treatment of neuropathic pain", *European journal of neurology,* vol. 13, no. 11, pp. 1153-1169.

Ayache, S.S., Ahdab, R., Chalah, M.A., Farhat, W.H., Mylius, V., Goujon, C., Sorel, M. & Lefaucheur, J.P. 2016, "Analgesic effects of navigated motor cortex rTMS in patients with chronic neuropathic pain", *European journal of pain (London, England),* vol. 20, no. 9, pp. 1413-1422.

Balasubramaniam, R. & Klasser, G.D. 2014, "Orofacial pain syndromes: evaluation and management", *The Medical clinics of North America,* vol. 98, no. 6, pp. 1385-1405.

Baliki, M.N., Chang, P.C., Baria, A.T., Centeno, M.V. & Apkarian, A.V. 2014, "Resting-sate functional reorganization of the rat limbic system following neuropathic injury", *Scientific reports,* vol. 4, pp. 6186.

Barasi, S. & Duggal, K.N. 1985, "The effect of local and systemic application of dopaminergic agents on tail flick latency in the rat", *European journal of pharmacology,* vol. 117, no. 3, pp. 287-294.

Barker, R.A. 1988, "The basal ganglia and pain", *The International journal of neuroscience,* vol. 41, no. 1-2, pp. 29-34.

Baron, R. 2006, "Mechanisms of disease: neuropathic pain--a clinical perspective", *Nature clinical practice.Neurology,* vol. 2, no. 2, pp. 95-106.

Baron, R., Binder, A. & Wasner, G. 2010, "Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment", *The Lancet.Neurology,* vol. 9, no. 8, pp. 807-819.

Baron, R., Schattschneider, J., Binder, A., Siebrecht, D. & Wasner, G. 2002, "Relation between sympathetic vasoconstrictor activity and pain and hyperalgesia in complex regional pain syndromes: a case-control study", *Lancet (London, England),* vol. 359, no. 9318, pp. 1655-1660.

Basbaum, A.I. & Fields, H.L. 1978, "Endogenous pain control mechanisms: review and hypothesis", *Annals of Neurology,* vol. 4, no. 5, pp. 451-462.

Basso, M.A., Powers, A.S. & Evinger, C. 1996, "An explanation for reflex blink hyperexcitability in Parkinson's disease. I. Superior colliculus", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 16, no. 22, pp. 7308-7317.

Basso, M.A., Strecker, R.E. & Evinger, C. 1993, "Midbrain 6-hydroxydopamine lesions modulate blink reflex excitability", *Experimental brain research,* vol. 94, no. 1, pp. 88-96.

Baumgartner, U., Buchholz, H.G., Bellosevich, A., Magerl, W., Siessmeier, T., Rolke, R., Hohnemann, S., Piel, M., Rosch, F., Wester, H.J., Henriksen, G., Stoeter, P., Bartenstein, P., Treede, R.D. & Schreckenberger, M. 2006, "High opiate receptor binding potential in the human lateral pain system", *NeuroImage,* vol. 30, no. 3, pp. 692-699.

Baumgartner, U., Iannetti, G.D., Zambreanu, L., Stoeter, P., Treede, R.D. & Tracey, I. 2010, "Multiple somatotopic representations of heat and mechanical pain in the operculo-insular cortex: a high-resolution fMRI study", *Journal of neurophysiology,* vol. 104, no. 5, pp. 2863-2872.

Beck, A.T., Rial, W.Y. & Rickels, K. 1974, "Short form of depression inventory: cross-validation", *Psychological reports,* vol. 34, no. 3, pp. 1184-1186.

Becser, N., Sand, T. & Zwart, J.A. 1998, "Reliability of cephalic thermal thresholds in healthy subjects", *Cephalalgia : an international journal of headache,* vol. 18, no. 8, pp. 574-582.

Beiske, A.G., Loge, J.H., Ronningen, A. & Svensson, E. 2009, "Pain in Parkinson's disease: Prevalence and characteristics", *Pain,* vol. 141, no. 1-2, pp. 173-177.

Bencherif, B., Fuchs, P.N., Sheth, R., Dannals, R.F., Campbell, J.N. & Frost, J.J. 2002, "Pain activation of human supraspinal opioid pathways as demonstrated by [11C]-carfentanil and positron emission tomography (PET)", *Pain,* vol. 99, no. 3, pp. 589-598.

Benedetti, F., Mayberg, H.S., Wager, T.D., Stohler, C.S. & Zubieta, J.K. 2005, "Neurobiological mechanisms of the placebo effect", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 25, no. 45, pp. 10390-10402.

Bennett, M.I., Attal, N., Backonja, M.M., Baron, R., Bouhassira, D., Freynhagen, R., Scholz, J., Tolle, T.R., Wittchen, H.U. & Jensen, T.S. 2007, "Using screening tools to identify neuropathic pain", *Pain,* vol. 127, no. 3, pp. 199-203.

Bernard, J.F., Huang, G.F. & Besson, J.M. 1992, "Nucleus centralis of the amygdala and the globus pallidus ventralis: electrophysiological evidence for an involvement in pain processes", *Journal of neurophysiology,* vol. 68, no. 2, pp. 551-569.

Bestmann, S., Baudewig, J., Siebner, H.R., Rothwell, J.C. & Frahm, J. 2005, "BOLD MRI responses to repetitive TMS over human dorsal premotor cortex", *NeuroImage,* vol. 28, no. 1, pp. 22-29.

Bigatti, S.M., Hernandez, A.M., Cronan, T.A. & Rand, K.L. 2008, "Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression", *Arthritis and Rheumatism,* vol. 59, no. 7, pp. 961-967.

Birbaumer, N., Lutzenberger, W., Montoya, P., Larbig, W., Unertl, K., Topfner, S., Grodd, W., Taub, E. & Flor, H. 1997, "Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 17, no. 14, pp. 5503-5508.

Borckardt, J.J., Smith, A.R., Reeves, S.T., Madan, A., Shelley, N., Branham, R., Nahas, Z. & George, M.S. 2009, "A pilot study investigating the effects of fast left prefrontal rTMS on chronic neuropathic pain", *Pain medicine (Malden, Mass.),* vol. 10, no. 5, pp. 840-849.

Borsook, D., Upadhyay, J., Chudler, E.H. & Becerra, L. 2010, "A key role of the basal ganglia in pain and analgesia--insights gained through human functional imaging", *Molecular pain,* vol. 6, pp. 27-8069-6-27.

Bouckoms, A.J., Sweet, W.H., Poletti, C., Lavori, P., Carr, D., Matson, W., Gamache, P. & Aronin, N. 1992, "Monoamines in the brain cerebrospinal fluid of facial pain patients", *Anesthesia Progress,* vol. 39, no. 6, pp. 201-208.

Bouhassira, D., Attal, N., Fermanian, J., Alchaar, H., Gautron, M., Masquelier, E., Rostaing, S., Lanteri-Minet, M., Collin, E., Grisart, J. & Boureau, F. 2004, "Development and validation of the Neuropathic Pain Symptom Inventory", *Pain,* vol. 108, no. 3, pp. 248-257.

Bouhassira, D., Gall, O., Chitour, D. & Le Bars, D. 1995, "Dorsal horn convergent neurones: negative feedback triggered by spatial summation of nociceptive afferents", *Pain,* vol. 62, no. 2, pp. 195-200.

Bouhassira, D., Lanteri-Minet, M., Attal, N., Laurent, B. & Touboul, C. 2008, "Prevalence of chronic pain with neuropathic characteristics in the general population", *Pain,* vol. 136, no. 3, pp. 380-387.

Bouhassira, D., Letanoux, M. & Hartemann, A. 2013, "Chronic pain with neuropathic characteristics in diabetic patients: a French cross-sectional study", *PloS one,* vol. 8, no. 9, pp. e74195.

Bradley, C., Perchet, C., Lelekov-Boissard, T., Magnin, M. & Garcia-Larrea, L. 2016, "Not an Aspirin: No Evidence for Acute Anti-Nociception to Laser-Evoked Pain After Motor Cortex rTMS in Healthy Humans", *Brain stimulation,* vol. 9, no. 1, pp. 48-57.

Braz, J.M., Nassar, M.A., Wood, J.N. & Basbaum, A.I. 2005, "Parallel "pain" pathways arise from subpopulations of primary afferent nociceptor", *Neuron,* vol. 47, no. 6, pp. 787-793.

Brighina, F., De Tommaso, M., Giglia, F., Scalia, S., Cosentino, G., Puma, A., Panetta, M., Giglia, G. & Fierro, B. 2011, "Modulation of pain perception by transcranial magnetic stimulation of left prefrontal cortex", *The journal of headache and pain,* vol. 12, no. 2, pp. 185-191.

Bushnell, M.C., Duncan, G.H., Hofbauer, R.K., Ha, B., Chen, J.I. & Carrier, B. 1999, "Pain perception: is there a role for primary somatosensory cortex?", *Proceedings of the National Academy of Sciences of the United States of America,* vol. 96, no. 14, pp. 7705-7709.

Chainani-Wu, N., Madden, E. & Silverman, S.,Jr 2011, "A case-control study of burning mouth syndrome and sleep dysfunction", *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics,* vol. 112, no. 2, pp. 203-208.

Chao, C.C., Hsieh, S.C., Tseng, M.T., Chang, Y.C. & Hsieh, S.T. 2008, "Patterns of contact heat evoked potentials (CHEP) in neuropathy with skin denervation: correlation of CHEP amplitude with intraepidermal nerve fiber density", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 119, no. 3, pp. 653-661.

Choi, B. & Rowbotham, M.C. 1997, "Effect of adrenergic receptor activation on post-herpetic neuralgia pain and sensory disturbances", *Pain,* vol. 69, no. 1-2, pp. 55-63.

Chudler, E.H. & Dong, W.K. 1995, "The role of the basal ganglia in nociception and pain", *Pain,* vol. 60, no. 1, pp. 3-38.

Ciampi de Andrade, D., Galhardoni, R., Pinto, L.F., Lancelotti, R., Rosi, J.,Jr, Marcolin, M.A. & Teixeira, M.J. 2012, "Into the island: a new technique of non-invasive cortical stimulation of the insula", *Neurophysiologie clinique = Clinical neurophysiology,* vol. 42, no. 6, pp. 363-368.

Clark, W.C. 1974, "Pain sensitivity and the report of pain: an introduction to sensory decision theory", *Anesthesiology,* vol. 40, no. 3, pp. 272-287.

Cleeland, C.S. & Ryan, K.M. 1994, "Pain assessment: global use of the Brief Pain Inventory", *Annals of the Academy of Medicine, Singapore,* vol. 23, no. 2, pp. 129-138.

Clifford, T.J., Warsi, M.J., Burnett, C.A. & Lamey, P.J. 1998, "Burning mouth in Parkinson's disease sufferers", *Gerodontology,* vol. 15, no. 2, pp. 73-78.

Cobacho, N., De la Calle, J.L., Gonzalez-Escalada, J.R. & Paino, C.L. 2010, "Levodopa analgesia in experimental neuropathic pain", *Brain research bulletin,* vol. 83, no. 6, pp. 304-309.

Cobacho, N., de la Calle, J.L. & Paino, C.L. 2014, "Dopaminergic modulation of neuropathic pain: analgesia in rats by a D2-type receptor agonist", *Brain research bulletin,* vol. 106, pp. 62-71.

Coffey, R.J. 2001, "Deep brain stimulation for chronic pain: results of two multicenter trials and a structured review", *Pain medicine (Malden, Mass.),* vol. 2, no. 3, pp. 183-192.

Coghill, R.C., Gilron, I. & Iadarola, M.J. 2001, "Hemispheric lateralization of somatosensory processing", *Journal of neurophysiology,* vol. 85, no. 6, pp. 2602-2612.

Coghill, R.C., Sang, C.N., Maisog, J.M. & Iadarola, M.J. 1999, "Pain intensity processing within the human brain: a bilateral, distributed mechanism", *Journal of neurophysiology,* vol. 82, no. 4, pp. 1934-1943.

Costigan, M., Scholz, J. & Woolf, C.J. 2009, "Neuropathic pain: a maladaptive response of the nervous system to damage", *Annual Review of Neuroscience,* vol. 32, pp. 1-32.

Craig, A.D., Chen, K., Bandy, D. & Reiman, E.M. 2000, "Thermosensory activation of insular cortex", *Nature neuroscience,* vol. 3, no. 2, pp. 184-190.

Craig, A.D., Reiman, E.M., Evans, A. & Bushnell, M.C. 1996, "Functional imaging of an illusion of pain", *Nature,* vol. 384, no. 6606, pp. 258-260.

Cross, A.J., Hille, C. & Slater, P. 1987, "Subtraction autoradiography of opiate receptor subtypes in human brain", *Brain research,* vol. 418, no. 2, pp. 343-348.

Cruccu, G., Aziz, T.Z., Garcia-Larrea, L., Hansson, P., Jensen, T.S., Lefaucheur, J.P., Simpson, B.A. & Taylor, R.S. 2007, "EFNS guidelines on neurostimulation therapy for neuropathic pain", *European journal of neurology,* vol. 14, no. 9, pp. 952-970.

Cruccu, G., Garcia-Larrea, L., Hansson, P., Keindl, M., Lefaucheur, J.P., Paulus, W., Taylor, R., Tronnier, V., Truini, A. & Attal, N. 2016, "EAN guidelines on central neurostimulation therapy in chronic pain conditions", *European journal of neurology,* vol. 23, no. 10, pp. 1489-1499.

Cruccu, G., Sommer, C., Anand, P., Attal, N., Baron, R., Garcia-Larrea, L., Haanpaa, M., Jensen, T.S., Serra, J. & Treede, R.D. 2010, "EFNS guidelines on neuropathic pain assessment: revised 2009", *European journal of neurology,* vol. 17, no. 8, pp. 1010-1018.

Cummins, T.R., Sheets, P.L. & Waxman, S.G. 2007, "The roles of sodium channels in nociception: Implications for mechanisms of pain", *Pain,* vol. 131, no. 3, pp. 243-257.

Daskalakis, Z.J., Moller, B., Christensen, B.K., Fitzgerald, P.B., Gunraj, C. & Chen, R. 2006, "The effects of repetitive transcranial magnetic stimulation on cortical inhibition in healthy human subjects", *Experimental brain research,* vol. 174, no. 3, pp. 403-412.

de Andrade, D.C., Mhalla, A., Adam, F., Texeira, M.J. & Bouhassira, D. 2011, "Neuropharmacological basis of rTMS-induced analgesia: the role of endogenous opioids", *Pain,* vol. 152, no. 2, pp. 320-326.

Defazio, G., Berardelli, A., Fabbrini, G., Martino, D., Fincati, E., Fiaschi, A., Moretto, G., Abbruzzese, G., Marchese, R., Bonuccelli, U., Del Dotto, P., Barone, P., De Vivo, E., Albanese, A., Antonini, A., Canesi, M., Lopiano, L., Zibetti, M., Nappi, G., Martignoni, E., Lamberti, P. & Tinazzi, M. 2008, "Pain as a nonmotor symptom of Parkinson disease: evidence from a case-control study", *Archives of Neurology,* vol. 65, no. 9, pp. 1191-1194.

Derbyshire, S.W. 1999, "Meta-Analysis of Thirty-Four Independent Samples Studied Using PET Reveals a

Significantly Attenuated Central Response to Noxious Stimulation in Clinical Pain Patients", *Current review of pain,* vol. 3, no. 4, pp. 265-280.

Derbyshire, S.W., Jones, A.K., Collins, M., Feinmann, C. & Harris, M. 1999, "Cerebral responses to pain in patients suffering acute post-dental extraction pain measured by positron emission tomography (PET)", *European journal of pain (London, England),* vol. 3, no. 2, pp. 103-113.

Derbyshire, S.W., Jones, A.K., Devani, P., Friston, K.J., Feinmann, C., Harris, M., Pearce, S., Watson, J.D. & Frackowiak, R.S. 1994, "Cerebral responses to pain in patients with atypical facial pain measured by positron emission tomography", *Journal of neurology, neurosurgery, and psychiatry,* vol. 57, no. 10, pp. 1166-1172.

Di Chiara, G. & Imperato, A. 1988, "Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats", *The Journal of pharmacology and experimental therapeutics,* vol. 244, no. 3, pp. 1067-1080.

Diatchenko, L., Nackley, A.G., Slade, G.D., Bhalang, K., Belfer, I., Max, M.B., Goldman, D. & Maixner, W. 2006, "Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli", *Pain,* vol. 125, no. 3, pp. 216-224.

Diatchenko, L., Slade, G.D., Nackley, A.G., Bhalang, K., Sigurdsson, A., Belfer, I., Goldman, D., Xu, K., Shabalina, S.A., Shagin, D., Max, M.B., Makarov, S.S. & Maixner, W. 2005, "Genetic basis for individual variations in pain perception and the development of a chronic pain condition", *Human molecular genetics,* vol. 14, no. 1, pp. 135-143.

Dworkin, R.H., O'Connor, A.B., Backonja, M., Farrar, J.T., Finnerup, N.B., Jensen, T.S., Kalso, E.A., Loeser, J.D., Miaskowski, C., Nurmikko, T.J., Portenoy, R.K., Rice, A.S., Stacey, B.R., Treede, R.D., Turk, D.C. & Wallace, M.S. 2007, "Pharmacologic management of neuropathic pain: evidence-based recommendations", *Pain,* vol. 132, no. 3, pp. 237-251.

Edwards, R.R., Almeida, D.M., Klick, B., Haythornthwaite, J.A. & Smith, M.T. 2008, "Duration of sleep contributes to next-day pain report in the general population", *Pain,* vol. 137, no. 1, pp. 202-207.

England, J.D., Gronseth, G.S., Franklin, G., Miller, R.G., Asbury, A.K., Carter, G.T., Cohen, J.A., Fisher, M.A., Howard, J.F., Kinsella, L.J., Latov, N., Lewis, R.A., Low, P.A., Sumner, A.J., American Academy of Neurology, American Association of Electrodiagnostic Medicine & American Academy of Physical Medicine and Rehabilitation 2005, "Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation", *Neurology,* vol. 64, no. 2, pp. 199-207.

Ertas, M., Sagduyu, A., Arac, N., Uludag, B. & Ertekin, C. 1998, "Use of levodopa to relieve pain from painful symmetrical diabetic polyneuropathy", *Pain,* vol. 75, no. 2-3, pp. 257-259.

Evinger, C., Basso, M.A., Manning, K.A., Sibony, P.A., Pellegrini, J.J. & Horn, A.K. 1993, "A role for the basal ganglia in nicotinic modulation of the blink reflex", *Experimental brain research,* vol. 92, no. 3, pp. 507-515.

Fields, H.L. 2007, "Understanding how opioids contribute to reward and analgesia", *Regional anesthesia and pain medicine,* vol. 32, no. 3, pp. 242-246.

Finnerup, N.B., Attal, N., Haroutounian, S., McNicol, E., Baron, R., Dworkin, R.H., Gilron, I., Haanpaa, M., Hansson, P., Jensen, T.S., Kamerman, P.R., Lund, K., Moore, A., Raja, S.N., Rice, A.S., Rowbotham, M., Sena, E., Siddall, P., Smith, B.H. & Wallace, M. 2015, "Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis", *The Lancet.Neurology,* vol. 14, no. 2, pp. 162-173.

First, M.B., Spritzer, R.L., Gibbon M., Williams J.B.W. 1994, Structured clinical interview for DSM-IV axis I disorders (SCID-I, 4/97 version). New York, NY: Biometrics Research Department, New York State Psychiatric Institute.

Fishbain, D.A., Cutler, R., Rosomoff, H.L. & Rosomoff, R.S. 1997, "Chronic pain-associated depression: antecedent or consequence of chronic pain? A review", *The Clinical journal of pain,* vol. 13, no. 2, pp. 116-137.

Fitzgerald, P.B., Hoy, K., McQueen, S., Maller, J.J., Herring, S., Segrave, R., Bailey, M., Been, G., Kulkarni, J. & Daskalakis, Z.J. 2009, "A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression", *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology,* vol. 34, no. 5, pp. 1255-1262.

Fleetwood-Walker, S.M., Hope, P.J. & Mitchell, R. 1988, "Antinociceptive actions of descending dopaminergic tracts on cat and rat dorsal horn somatosensory neurones", *The Journal of physiology,* vol. 399, pp. 335-348.

Flor, H., Denke, C., Schaefer, M. & Grusser, S. 2001, "Effect of sensory discrimination training on cortical reorganisation and phantom limb pain", *Lancet (London, England),* vol. 357, no. 9270, pp. 1763-1764.

Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumer, N., Larbig, W. & Taub, E. 1995, "Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation", *Nature,* vol. 375, no. 6531, pp. 482-484.

Fong, A. & Schug, S.A. 2014, "Pathophysiology of pain: a practical primer", *Plastic and Reconstructive Surgery,* vol. 134, no. 4 Suppl 2, pp. 8S-14S.

Ford, B. 1998, "Pain in Parkinson's disease", *Clinical neuroscience (New York, N.Y.),* vol. 5, no. 2, pp. 63-72.

Ford, B., Louis, E.D., Greene, P. & Fahn, S. 1996, "Oral and genital pain syndromes in Parkinson's disease", *Movement disorders : official journal of the Movement Disorder Society,* vol. 11, no. 4, pp. 421-426.

Forss, N., Raij, T.T., Seppa, M. & Hari, R. 2005, "Common cortical network for first and second pain", *NeuroImage,* vol. 24, no. 1, pp. 132-142.

Forssell, H., Jaaskelainen, S., Tenovuo, O. & Hinkka, S. 2002, "Sensory dysfunction in burning mouth syndrome", *Pain,* vol. 99, no. 1-2, pp. 41-47.

Forssell, H., Teerijoki-Oksa, T., Kotiranta, U., Kantola, R., Back, M., Vuorjoki-Ranta, T.R., Siponen, M., Leino, A., Puukka, P. & Estlander, A.M. 2012, "Pain and pain behavior in burning mouth syndrome: a pain diary study", *Journal of orofacial pain,* vol. 26, no. 2, pp. 117-125.

Forssell, H., Tenovuo, O., Silvoniemi, P. & Jaaskelainen, S.K. 2007, "Differences and similarities between atypical facial pain and trigeminal neuropathic pain", *Neurology,* vol. 69, no. 14, pp. 1451-1459.

Fregni, F., Boggio, P.S., Lima, M.C., Ferreira, M.J., Wagner, T., Rigonatti, S.P., Castro, A.W., Souza, D.R., Riberto, M., Freedman, S.D., Nitsche, M.A. & Pascual-Leone, A. 2006, "A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury", *Pain,* vol. 122, no. 1-2, pp. 197-209.

Fregni, F., Potvin, K., Dasilva, D., Wang, X., Lenkinski, R.E., Freedman, S.D. & Pascual-Leone, A. 2011, "Clinical effects and brain metabolic correlates in non-invasive cortical neuromodulation for visceral pain", *European journal of pain (London, England),* vol. 15, no. 1, pp. 53-60.

Frot, M., Magnin, M., Mauguiere, F. & Garcia-Larrea, L. 2013, "Cortical representation of pain in primary sensory-motor areas (S1/M1)--a study using intracortical recordings in humans", *Human brain mapping,* vol. 34, no. 10, pp. 2655-2668.

Frot, M., Rambaud, L., Guenot, M. & Mauguiere, F. 1999, "Intracortical recordings of early pain-related CO2-laser evoked potentials in the human second somatosensory (SII) area", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 110, no. 1, pp. 133-145.

Fukumoto, M., Ushida, T., Zinchuk, V.S., Yamamoto, H. & Yoshida, S. 1999, "Contralateral thalamic perfusion in patients with reflex sympathetic dystrophy syndrome", *Lancet (London, England),* vol. 354, no. 9192, pp. 1790-1791.

Garcia-Larrea, L. 2012, "Objective pain diagnostics: clinical neurophysiology", *Neurophysiologie clinique = Clinical neurophysiology,* vol. 42, no. 4, pp. 187-197.

Garcia-Larrea, L. 2012, "The posterior insular-opercular region and the search of a primary cortex for pain", *Neurophysiologie clinique = Clinical neurophysiology,* vol. 42, no. 5, pp. 299-313.

Gartner, R., Jensen, M.B., Nielsen, J., Ewertz, M., Kroman, N. & Kehlet, H. 2009, "Prevalence of and factors associated with persistent pain following breast cancer surgery", *Jama,* vol. 302, no. 18, pp. 1985-1992.

Gerdelat-Mas, A., Simonetta-Moreau, M., Thalamas, C., Ory-Magne, F., Slaoui, T., Rascol, O. & Brefel-Courbon, C. 2007, "Levodopa raises objective pain threshold in Parkinson's disease: a RIII reflex study", *Journal of neurology, neurosurgery, and psychiatry,* vol. 78, no. 10, pp. 1140-1142.

Gerschlager, W., Siebner, H.R. & Rothwell, J.C. 2001, "Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex", *Neurology,* vol. 57, no. 3, pp. 449-455.

Goetz, C.G., Tanner, C.M., Levy, M., Wilson, R.S. & Garron, D.C. 1986, "Pain in Parkinson's disease", *Movement disorders : official journal of the Movement Disorder Society,* vol. 1, no. 1, pp. 45-49.

Gore, M., Brandenburg, N.A., Dukes, E., Hoffman, D.L., Tai, K.S. & Stacey, B. 2005, "Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep", *Journal of pain and symptom management,* vol. 30, no. 4, pp. 374-385.

Gracely, R.H., Petzke, F., Wolf, J.M. & Clauw, D.J. 2002, "Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia", *Arthritis and Rheumatism,* vol. 46, no. 5, pp. 1333-1343.

Gruener, G. & Dyck, P.J. 1994, "Quantitative sensory testing: methodology, applications, and future directions", *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society,* vol. 11, no. 6, pp. 568-583.

Grusser, S.M., Winter, C., Muhlnickel, W., Denke, C., Karl, A., Villringer, K. & Flor, H. 2001, "The relationship of perceptual phenomena and cortical reorganization in upper extremity amputees", *Neuroscience,* vol. 102, no. 2, pp. 263-272.

Gursoy, S., Erdal, E., Herken, H., Madenci, E., Alasehirli, B. & Erdal, N. 2003, "Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome", *Rheumatology international,* vol. 23, no. 3, pp. 104-107.

Ha, A.D. & Jankovic, J. 2012, "Pain in Parkinson's disease", *Movement disorders : official journal of the Movement Disorder Society,* vol. 27, no. 4, pp. 485-491.

Haack, M. & Mullington, J.M. 2005, "Sustained sleep restriction reduces emotional and physical well-being", *Pain,* vol. 119, no. 1-3, pp. 56-64.

Haanpaa, M., Attal, N., Backonja, M., Baron, R., Bennett, M., Bouhassira, D., Cruccu, G., Hansson, P., Haythornthwaite, J.A., Iannetti, G.D., Jensen, T.S., Kauppila, T., Nurmikko, T.J., Rice, A.S., Rowbotham, M., Serra, J., Sommer, C., Smith, B.H. & Treede, R.D. 2011, "NeuPSIG guidelines on neuropathic pain assessment", *Pain,* vol. 152, no. 1, pp. 14-27.

Haanpaa, M.L., Backonja, M.M., Bennett, M.I., Bouhassira, D., Cruccu, G., Hansson, P.T., Jensen, T.S., Kauppila, T., Rice, A.S., Smith, B.H., Treede, R.D. & Baron, R. 2009, "Assessment of neuropathic pain in primary care", *The American Journal of Medicine,* vol. 122, no. 10 Suppl, pp. S13-21.

Hagelberg, N., Forssell, H., Aalto, S., Rinne, J.O., Scheinin, H., Taiminen, T., Nagren, K., Eskola, O. & Jaaskelainen, S.K. 2003, "Altered dopamine D2 receptor binding in atypical facial pain", *Pain,* vol. 106, no. 1-2, pp. 43-48.

Hagelberg, N., Forssell, H., Rinne, J.O., Scheinin, H., Taiminen, T., Aalto, S., Luutonen, S., Nagren, K. & Jaaskelainen, S. 2003, "Striatal dopamine D1 and D2

receptors in burning mouth syndrome", *Pain,* vol. 101, no. 1-2, pp. 149-154.

Hagelberg, N., Jaaskelainen, S.K., Martikainen, I.K., Mansikka, H., Forssell, H., Scheinin, H., Hietala, J. & Pertovaara, A. 2004, "Striatal dopamine D2 receptors in modulation of pain in humans: a review", *European journal of pharmacology,* vol. 500, no. 1-3, pp. 187-192.

Hagelberg, N., Martikainen, I.K., Mansikka, H., Hinkka, S., Nagren, K., Hietala, J., Scheinin, H. & Pertovaara, A. 2002, "Dopamine D2 receptor binding in the human brain is associated with the response to painful stimulation and pain modulatory capacity", *Pain,* vol. 99, no. 1-2, pp. 273-279.

Hains, B.C., Saab, C.Y., Klein, J.P., Craner, M.J. & Waxman, S.G. 2004, "Altered sodium channel expression in second-order spinal sensory neurons contributes to pain after peripheral nerve injury", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 24, no. 20, pp. 4832-4839.

Hamada, M., Murase, N., Hasan, A., Balaratnam, M. & Rothwell, J.C. 2013, "The role of interneuron networks in driving human motor cortical plasticity", *Cerebral cortex (New York, N.Y.: 1991),* vol. 23, no. 7, pp. 1593-1605.

Hamani, C., Schwalb, J.M., Rezai, A.R., Dostrovsky, J.O., Davis, K.D. & Lozano, A.M. 2006, "Deep brain stimulation for chronic neuropathic pain: long-term outcome and the incidence of insertional effect", *Pain,* vol. 125, no. 1-2, pp. 188-196.

Hays, R.D., Sherbourne, C.D. & Mazel, R.M. 1993, "The RAND 36-Item Health Survey 1.0", *Health Economics,* vol. 2, no. 3, pp. 217-227.

Hietala, J., West, C., Syvalahti, E., Nagren, K., Lehikoinen, P., Sonninen, P. & Ruotsalainen, U. 1994, "Striatal D2 dopamine receptor binding characteristics in vivo in patients with alcohol dependence", *Psychopharmacology,* vol. 116, no. 3, pp. 285-290.

Hirayama, A., Saitoh, Y., Kishima, H., Shimokawa, T., Oshino, S., Hirata, M., Kato, A. & Yoshimine, T. 2006, "Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex", *Pain,* vol. 122, no. 1-2, pp. 22-27.

Hirvonen, J., Aalto, S., Hagelberg, N., Maksimow, A., Ingman, K., Oikonen, V., Virkkala, J., Nagren, K. & Scheinin, H. 2009, "Measurement of central mu-opioid receptor binding in vivo with PET and [11C]carfentanil: a test-retest study in healthy subjects", *European journal of nuclear medicine and molecular imaging,* vol. 36, no. 2, pp. 275-286.

Hirvonen, J., Johansson, J., Teras, M., Oikonen, V., Lumme, V., Virsu, P., Roivainen, A., Nagren, K., Halldin, C., Farde, L. & Hietala, J. 2008, "Measurement of striatal and extrastriatal dopamine transporter binding with high-resolution PET and [11C]PE2I: quantitative modeling and test-retest reproducibility", *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism,* vol. 28, no. 5, pp. 1059-1069.

Hirvonen, M.M., Laakso, A., Nagren, K., Rinne, J.O., Pohjalainen, T. & Hietala, J. 2009, "C957T polymorphism of dopamine D2 receptor gene affects striatal DRD2 in vivo availability by changing the receptor affinity", *Synapse (New York, N.Y.),* vol. 63, no. 10, pp. 907-912.

Hogl, B.E., Gomez-Arevalo, G., Garcia, S., Scipioni, O., Rubio, M., Blanco, M. & Gershanik, O.S. 1998, "A clinical, pharmacologic, and polysomnographic study of sleep benefit in Parkinson's disease", *Neurology,* vol. 50, no. 5, pp. 1332-1339.

Hoogendam, J.M., Ramakers, G.M. & Di Lazzaro, V. 2010, "Physiology of repetitive transcranial magnetic stimulation of the human brain", *Brain stimulation,* vol. 3, no. 2, pp. 95-118.

Horvitz, J.C. 2000, "Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events", *Neuroscience,* vol. 96, no. 4, pp. 651-656.

Hosomi, K., Shimokawa, T., Ikoma, K., Nakamura, Y., Sugiyama, K., Ugawa, Y., Uozumi, T., Yamamoto, T. & Saitoh, Y. 2013, "Daily repetitive transcranial magnetic stimulation of primary motor cortex for neuropathic pain: a randomized, multicenter, double-blind, crossover, sham-controlled trial", *Pain,* vol. 154, no. 7, pp. 1065-1072.

Hou, W.H., Wang, T.Y. & Kang, J.H. 2016, "The effects of add-on non-invasive brain stimulation in fibromyalgia: a meta-analysis and meta-regression of randomized controlled trials", *Rheumatology (Oxford, England),* vol. 55, no. 8, pp. 1507-1517.

Hrobjartsson, A. & Gotzsche, P.C. 2001, "Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment", *The New England journal of medicine,* vol. 344, no. 21, pp. 1594-1602.

Hucho, T. & Levine, J.D. 2007, "Signaling pathways in sensitization: toward a nociceptor cell biology", *Neuron,* vol. 55, no. 3, pp. 365-376.

Huse, E., Preissl, H., Larbig, W. & Birbaumer, N. 2001, "Phantom limb pain", *Lancet (London, England),* vol. 358, no. 9286, pp. 1015.

Isnard, J., Magnin, M., Jung, J., Mauguiere, F. & Garcia-Larrea, L. 2011, "Does the insula tell our brain that we are in pain?", *Pain,* vol. 152, no. 4, pp. 946-951.

Jaaskelainen, S.K. 2012, "Pathophysiology of primary burning mouth syndrome", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 123, no. 1, pp. 71-77.

Jaaskelainen, S.K. 2004, "Clinical neurophysiology and quantitative sensory testing in the investigation of orofacial pain and sensory function", *Journal of orofacial pain,* vol. 18, no. 2, pp. 85-107.

Jaaskelainen, S.K. 2004, "The utility of clinical neurophysiological and quantitative sensory testing for trigeminal neuropathy", *Journal of orofacial pain,* vol. 18, no. 4, pp. 355-359.

Jaaskelainen, S.K., Forssell, H. & Tenovuo, O. 1999, "Electrophysiological testing of the trigeminofacial system: aid in the diagnosis of atypical facial pain", *Pain,* vol. 80, no. 1-2, pp. 191-200.

Jaaskelainen, S.K., Forssell, H. & Tenovuo, O. 1997, "Abnormalities of the blink reflex in burning mouth syndrome", *Pain,* vol. 73, no. 3, pp. 455-460.

Jaaskelainen, S.K., Rinne, J.O., Forssell, H., Tenovuo, O., Kaasinen, V., Sonninen, P. & Bergman, J. 2001, "Role of the dopaminergic system in chronic pain -- a fluorodopa-PET study", *Pain,* vol. 90, no. 3, pp. 257-260.

Jaaskelainen, S.K., Teerijoki-Oksa, T., Virtanen, A., Tenovuo, O. & Forssell, H. 2004, "Sensory regeneration following intraoperatively verified trigeminal nerve injury", *Neurology,* vol. 62, no. 11, pp. 1951-1957.

Jarcho, J.M., Mayer, E.A., Jiang, Z.K., Feier, N.A. & London, E.D. 2012, "Pain, affective symptoms, and cognitive deficits in patients with cerebral dopamine dysfunction", *Pain,* vol. 153, no. 4, pp. 744-754.

Johansen, A., Romundstad, L., Nielsen, C.S., Schirmer, H. & Stubhaug, A. 2012, "Persistent postsurgical pain in a general population: prevalence and predictors in the Tromso study", *Pain,* vol. 153, no. 7, pp. 1390-1396.

Johnson, S.W., Seutin, V. & North, R.A. 1992, "Burst firing in dopamine neurons induced by N-methyl-D-aspartate: role of electrogenic sodium pump", *Science (New York, N.Y.),* vol. 258, no. 5082, pp. 665-667.

Jones, A.K. & Derbyshire, S.W. 1997, "Reduced cortical responses to noxious heat in patients with rheumatoid arthritis", *Annals of the Rheumatic Diseases,* vol. 56, no. 10, pp. 601-607.

Jones, S.L. 1991, "Descending noradrenergic influences on pain", *Progress in brain research,* vol. 88, pp. 381-394.

Julius, D. & Basbaum, A.I. 2001, "Molecular mechanisms of nociception", *Nature,* vol. 413, no. 6852, pp. 203-210.

Juottonen, K., Gockel, M., Silen, T., Hurri, H., Hari, R. & Forss, N. 2002, "Altered central sensorimotor processing in patients with complex regional pain syndrome", *Pain,* vol. 98, no. 3, pp. 315-323.

Kaasinen, V., Aalto, S., Nagren, K. & Rinne, J.O. 2004, "Expectation of caffeine induces dopaminergic responses in humans", *The European journal of neuroscience,* vol. 19, no. 8, pp. 2352-2356.

Kalso, E. 2013, "IV. Persistent post-surgery pain: research agenda for mechanisms, prevention, and treatment", *British journal of anaesthesia,* vol. 111, no. 1, pp. 9-12.

Karl, A., Birbaumer, N., Lutzenberger, W., Cohen, L.G. & Flor, H. 2001, "Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 21, no. 10, pp. 3609-3618.

Katayama, Y., Fukaya, C. & Yamamoto, T. 1998, "Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response", *Journal of neurosurgery,* vol. 89, no. 4, pp. 585-591.

Kaunisto, M.A., Jokela, R., Tallgren, M., Kambur, O., Tikkanen, E., Tasmuth, T., Sipila, R., Palotie, A., Estlander, A.M., Leidenius, M., Ripatti, S. & Kalso, E.A. 2013, "Pain in 1,000 women treated for breast cancer: a prospective study of pain sensitivity and postoperative pain", *Anesthesiology,* vol. 119, no. 6, pp. 1410-1421.

Keck, M.E., Sillaber, I., Ebner, K., Welt, T., Toschi, N., Kaehler, S.T., Singewald, N., Philippu, A., Elbel, G.K., Wotjak, C.T., Holsboer, F., Landgraf, R. & Engelmann, M. 2000, "Acute transcranial magnetic stimulation of frontal brain regions selectively modulates the release of vasopressin, biogenic amines and amino acids in the rat brain", *The European journal of neuroscience,* vol. 12, no. 10, pp. 3713-3720.

Keck, M.E., Welt, T., Muller, M.B., Erhardt, A., Ohl, F., Toschi, N., Holsboer, F. & Sillaber, I. 2002, "Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system", *Neuropharmacology,* vol. 43, no. 1, pp. 101-109.

Kehlet, H., Jensen, T.S. & Woolf, C.J. 2006, "Persistent postsurgical pain: risk factors and prevention", *Lancet (London, England),* vol. 367, no. 9522, pp. 1618-1625.

Kernbaum, S. & Hauchecorne, J. 1981, "Administration of levodopa for relief of herpes zoster pain", *Jama,* vol. 246, no. 2, pp. 132-134.

Khedr, E.M., Kotb, H., Kamel, N.F., Ahmed, M.A., Sadek, R. & Rothwell, J.C. 2005, "Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain", *Journal of neurology, neurosurgery, and psychiatry,* vol. 76, no. 6, pp. 833-838.

Kim, H., Lee, H., Rowan, J., Brahim, J. & Dionne, R.A. 2006, "Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans", *Molecular pain,* vol. 2, pp. 24.

Kim, H., Neubert, J.K., San Miguel, A., Xu, K., Krishnaraju, R.K., Iadarola, M.J., Goldman, D. & Dionne, R.A. 2004, "Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament", *Pain,* vol. 109, no. 3, pp. 488-496.

Kim, J.H., Son, Y.D., Kim, H.K., Lee, S.Y., Cho, S.E., Kim, Y.B. & Cho, Z.H. 2011, "Association of harm avoidance with dopamine D2/3 receptor availability in striatal subdivisions: a high resolution PET study", *Biological psychology,* vol. 87, no. 1, pp. 164-167.

Kim, J.Y., Chung, E.J., Lee, W.Y., Shin, H.Y., Lee, G.H., Choe, Y.S., Choi, Y. & Kim, B.J. 2008, "Therapeutic effect of repetitive transcranial magnetic stimulation in Parkinson's disease: analysis of [11C] raclopride PET study", *Movement disorders : official journal of the Movement Disorder Society,* vol. 23, no. 2, pp. 207-211.

Kimura, J., Powers, J.M. & Van Allen, M.W. 1969, "Reflex response of orbicularis oculi muscle to supraorbital nerve stimulation. Study in normal subjects and in peripheral facial paresis", *Archives of Neurology,* vol. 21, no. 2, pp. 193-199.

Kirveskari, E., Vartiainen, N.V., Gockel, M. & Forss, N. 2010, "Motor cortex dysfunction in complex regional pain syndrome", *Clinical neurophysiology : official*

journal of the International Federation of Clinical Neurophysiology, vol. 121, no. 7, pp. 1085-1091.

Kirveskari, E., Vartiainen, N.V., Kallio-Laine, K., Kalso, E. & Forss, N. 2015, "Normal laser-evoked cortical responses in patients with chronic hemibody pain", *European journal of pain (London, England),* vol. 19, no. 8, pp. 1168-1176.

Klepstad, P., Dale, O., Skorpen, F., Borchgrevink, P.C. & Kaasa, S. 2005, "Genetic variability and clinical efficacy of morphine", *Acta Anaesthesiologica Scandinavica,* vol. 49, no. 7, pp. 902-908.

Knaster, P., Estlander, A.M., Karlsson, H., Kaprio, J. & Kalso, E. 2012, "Temperament traits and chronic pain: the association of harm avoidance and pain-related anxiety", *PloS one,* vol. 7, no. 10, pp. e45672.

Knaster, P., Karlsson, H., Estlander, A.M. & Kalso, E. 2012, "Psychiatric disorders as assessed with SCID in chronic pain patients: the anxiety disorders precede the onset of pain", *General hospital psychiatry,* vol. 34, no. 1, pp. 46-52.

Knecht, S., Henningsen, H., Hohling, C., Elbert, T., Flor, H., Pantev, C. & Taub, E. 1998, "Plasticity of plasticity? Changes in the pattern of perceptual correlates of reorganization after amputation", *Brain : a journal of neurology,* vol. 121 (Pt 4), no. Pt 4, pp. 717-724.

Kreitzer, A.C. & Malenka, R.C. 2008, "Striatal plasticity and basal ganglia circuit function", *Neuron,* vol. 60, no. 4, pp. 543-554.

Kucyi, A., Hodaie, M. & Davis, K.D. 2012, "Lateralization in intrinsic functional connectivity of the temporoparietal junction with salience- and attention-related brain networks", *Journal of neurophysiology,* vol. 108, no. 12, pp. 3382-3392.

Kucyi, A., Moayedi, M., Weissman-Fogel, I., Hodaie, M. & Davis, K.D. 2012, "Hemispheric asymmetry in white matter connectivity of the temporoparietal junction with the insula and prefrontal cortex", *PloS one,* vol. 7, no. 4, pp. e35589.

Kumar, K., Taylor, R.S., Jacques, L., Eldabe, S., Meglio, M., Molet, J., Thomson, S., O'Callaghan, J., Eisenberg, E., Milbouw, G., Buchser, E., Fortini, G., Richardson, J. & North, R.B. 2008, "The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation", *Neurosurgery,* vol. 63, no. 4, pp. 762-70; discussion 770.

Kundermann, B., Krieg, J.C., Schreiber, W. & Lautenbacher, S. 2004, "The effect of sleep deprivation on pain", *Pain research & management,* vol. 9, no. 1, pp. 25-32.

Laakso, A., Wallius, E., Kajander, J., Bergman, J., Eskola, O., Solin, O., Ilonen, T., Salokangas, R.K., Syvalahti, E. & Hietala, J. 2003, "Personality traits and striatal dopamine synthesis capacity in healthy subjects", *The American Journal of Psychiatry,* vol. 160, no. 5, pp. 904-910.

Lai, J., Hunter, J.C. & Porreca, F. 2003, "The role of voltage-gated sodium channels in neuropathic pain", *Current opinion in neurobiology,* vol. 13, no. 3, pp. 291-297.

Lamey, P.J. & Lamb, A.B. 1988, "Prospective study of aetiological factors in burning mouth syndrome", *British medical journal (Clinical research ed.),* vol. 296, no. 6631, pp. 1243-1246.

Lammertsma, A.A. & Hume, S.P. 1996, "Simplified reference tissue model for PET receptor studies", *NeuroImage,* vol. 4, no. 3 Pt 1, pp. 153-158.

Lang, E., Kaltenhauser, M., Seidler, S., Mattenklodt, P. & Neundorfer, B. 2005, "Persistent idiopathic facial pain exists independent of somatosensory input from the painful region: findings from quantitative sensory functions and somatotopy of the primary somatosensory cortex", *Pain,* vol. 118, no. 1-2, pp. 80-91.

Lapeyre, S., Mauborgne, A., Becker, C., Benoliel, J.J., Cesselin, F., Hamon, M. & Bourgoin, S. 2001, "Subcutaneous formalin enhances outflow of met-enkephalin- and cholecystokinin-like materials in the rat nucleus accumbens", *Naunyn-Schmiedeberg's archives of pharmacology,* vol. 363, no. 4, pp. 399-406.

Lapirot, O., Melin, C., Modolo, A., Nicolas, C., Messaoudi, Y., Monconduit, L., Artola, A., Luccarini, P. & Dallel, R. 2011, "Tonic and phasic descending dopaminergic controls of nociceptive transmission in the medullary dorsal horn", *Pain,* vol. 152, no. 8, pp. 1821-1831.

Lascelles, R.G. 1966, "Atypical facial pain and depression", *The British journal of psychiatry : the journal of mental science,* vol. 112, no. 488, pp. 651-659.

Lauria, G., Majorana, A., Borgna, M., Lombardi, R., Penza, P., Padovani, A. & Sapelli, P. 2005, "Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome", *Pain,* vol. 115, no. 3, pp. 332-337.

Le Moal, M. & Simon, H. 1991, "Mesocorticolimbic dopaminergic network: functional and regulatory roles", *Physiological Reviews,* vol. 71, no. 1, pp. 155-234.

Lee, C.F., Lin, K.Y., Lin, M.C., Lin, C.L., Chang, S.N. & Kao, C.H. 2014, "Sleep disorders increase the risk of burning mouth syndrome: a retrospective population-based cohort study", *Sleep medicine,* vol. 15, no. 11, pp. 1405-1410.

Lee, M., Kim, S.E., Kim, W.S., Han, J., Kim, H.J., Kim, B.S., Kim, J.Y., Hong, S.B., Kim, B.G. & Lee, H.W. 2013, "Cortico-cortical modulation induced by 1-Hz repetitive transcranial magnetic stimulation of the temporal cortex", *Journal of clinical neurology (Seoul, Korea),* vol. 9, no. 2, pp. 75-82.

Lee, M.A., Walker, R.W., Hildreth, T.J. & Prentice, W.M. 2006, "A survey of pain in idiopathic Parkinson's disease", *Journal of pain and symptom management,* vol. 32, no. 5, pp. 462-469.

Lefaucheur, J.P. 2009, "Methods of therapeutic cortical stimulation", *Neurophysiologie clinique = Clinical neurophysiology,* vol. 39, no. 1, pp. 1-14.

Lefaucheur, J.P., Andre-Obadia, N., Antal, A., Ayache, S.S., Baeken, C., Benninger, D.H., Cantello, R.M., Cincotta, M., de Carvalho, M., De Ridder, D., Devanne, H., Di Lazzaro, V., Filipovic, S.R., Hummel, F.C., Jaaskelainen, S.K., Kimiskidis, V.K., Koch, G., Langguth, B., Nyffeler, T., Oliviero, A., Padberg, F.,

Poulet, E., Rossi, S., Rossini, P.M., Rothwell, J.C., Schonfeldt-Lecuona, C., Siebner, H.R., Slotema, C.W., Stagg, C.J., Valls-Sole, J., Ziemann, U., Paulus, W. & Garcia-Larrea, L. 2014, "Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 125, no. 11, pp. 2150-2206.

Lefaucheur, J.P., Drouot, X. & Nguyen, J.P. 2001, "Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex", *Neurophysiologie clinique = Clinical neurophysiology,* vol. 31, no. 4, pp. 247-252.

Leknes, S. & Tracey, I. 2008, "A common neurobiology for pain and pleasure", *Nature reviews.Neuroscience,* vol. 9, no. 4, pp. 314-320.

Lentz, M.J., Landis, C.A., Rothermel, J. & Shaver, J.L. 1999, "Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women", *The Journal of rheumatology,* vol. 26, no. 7, pp. 1586-1592.

Lenz, F.A., Rios, M., Zirh, A., Chau, D., Krauss, G. & Lesser, R.P. 1998, "Painful stimuli evoke potentials recorded over the human anterior cingulate gyrus", *Journal of neurophysiology,* vol. 79, no. 4, pp. 2231-2234.

Leo, R.J. & Latif, T. 2007, "Repetitive transcranial magnetic stimulation (rTMS) in experimentally induced and chronic neuropathic pain: a review", *The journal of pain : official journal of the American Pain Society,* vol. 8, no. 6, pp. 453-459.

Leone, P., Pocock, D. & Wise, R.A. 1991, "Morphine-dopamine interaction: ventral tegmental morphine increases nucleus accumbens dopamine release", *Pharmacology, biochemistry, and behavior,* vol. 39, no. 2, pp. 469-472.

Levy, R.M., Lamb, S. & Adams, J.E. 1987, "Treatment of chronic pain by deep brain stimulation: long term follow-up and review of the literature", *Neurosurgery,* vol. 21, no. 6, pp. 885-893.

Lin, M.T., Wu, J.J., Chandra, A. & Tsay, B.L. 1981, "Activation of striatal dopamine receptors induces pain inhibition in rats", *Journal of neural transmission,* vol. 51, no. 3-4, pp. 213-222.

Linderoth, B. & Foreman, R.D. 1999, "Physiology of spinal cord stimulation: review and update", *Neuromodulation : journal of the International Neuromodulation Society,* vol. 2, no. 3, pp. 150-164.

Lockwood, P.L., Iannetti, G.D. & Haggard, P. 2013, "Transcranial magnetic stimulation over human secondary somatosensory cortex disrupts perception of pain intensity", *Cortex; a journal devoted to the study of the nervous system and behavior,* vol. 49, no. 8, pp. 2201-2209.

Lorenz, J., Cross, D.J., Minoshima, S., Morrow, T.J., Paulson, P.E. & Casey, K.L. 2002, "A unique representation of heat allodynia in the human brain", *Neuron,* vol. 35, no. 2, pp. 383-393.

Lotsch, J. & Geisslinger, G. 2006, "Current evidence for a genetic modulation of the response to analgesics", *Pain,* vol. 121, no. 1-2, pp. 1-5.

Lotta, T., Vidgren, J., Tilgmann, C., Ulmanen, I., Melen, K., Julkunen, I. & Taskinen, J. 1995, "Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme", *Biochemistry,* vol. 34, no. 13, pp. 4202-4210.

Lumpkin, E.A. & Caterina, M.J. 2007, "Mechanisms of sensory transduction in the skin", *Nature,* vol. 445, no. 7130, pp. 858-865.

Lyerly, M.A., Rossitch, E.,Jr, Ovelmen-Levitt, J. & Nashold, B.S.,Jr 1988, "The deafferentation syndrome in the rat: effects of intraventricular apomorphine", *Experimental neurology,* vol. 100, no. 1, pp. 188-202.

Maarrawi, J., Peyron, R., Mertens, P., Costes, N., Magnin, M., Sindou, M., Laurent, B. & Garcia-Larrea, L. 2013, "Brain opioid receptor density predicts motor cortex stimulation efficacy for chronic pain", *Pain,* vol. 154, no. 11, pp. 2563-2568.

Maarrawi, J., Peyron, R., Mertens, P., Costes, N., Magnin, M., Sindou, M., Laurent, B. & Garcia-Larrea, L. 2007, "Motor cortex stimulation for pain control induces changes in the endogenous opioid system", *Neurology,* vol. 69, no. 9, pp. 827-834.

Magni, G., Moreschi, C., Rigatti-Luchini, S. & Merskey, H. 1994, "Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain", *Pain,* vol. 56, no. 3, pp. 289-297.

Magnusson, J.E. & Fisher, K. 2000, "The involvement of dopamine in nociception: the role of D(1) and D(2) receptors in the dorsolateral striatum", *Brain research,* vol. 855, no. 2, pp. 260-266.

Maihofner, C., Kaltenhauser, M., Neundorfer, B. & Lang, E. 2002, "Temporo-spatial analysis of cortical activation by phasic innocuous and noxious cold stimuli--a magnetoencephalographic study", *Pain,* vol. 100, no. 3, pp. 281-290.

Maina, G., Albert, U., Gandolfo, S., Vitalucci, A. & Bogetto, F. 2005, "Personality disorders in patients with burning mouth syndrome", *Journal of personality disorders,* vol. 19, no. 1, pp. 84-93.

Maisonneuve, I.M., Warner, L.M. & Glick, S.D. 2001, "Biphasic dose-related effects of morphine on dopamine release", *Drug and alcohol dependence,* vol. 65, no. 1, pp. 55-63.

Martikainen, I.K., Hagelberg, N., Mansikka, H., Hietala, J., Nagren, K., Scheinin, H. & Pertovaara, A. 2005, "Association of striatal dopamine D2/D3 receptor binding potential with pain but not tactile sensitivity or placebo analgesia", *Neuroscience letters,* vol. 376, no. 3, pp. 149-153.

Matthes, H.W., Maldonado, R., Simonin, F., Valverde, O., Slowe, S., Kitchen, I., Befort, K., Dierich, A., Le Meur, M., Dolle, P., Tzavara, E., Hanoune, J., Roques, B.P. & Kieffer, B.L. 1996, "Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene", *Nature,* vol. 383, no. 6603, pp. 819-823.

Mazzola, L., Isnard, J., Peyron, R. & Mauguiere, F. 2012, "Stimulation of the human cortex and the experience of pain: Wilder Penfield's observations

revisited", *Brain : a journal of neurology,* vol. 135, no. Pt 2, pp. 631-640.

Mekhail, N.A., Mathews, M., Nageeb, F., Guirguis, M., Mekhail, M.N. & Cheng, J. 2011, "Retrospective review of 707 cases of spinal cord stimulation: indications and complications", *Pain practice : the official journal of World Institute of Pain,* vol. 11, no. 2, pp. 148-153.

Melzack, R. 1999, "From the gate to the neuromatrix", *Pain,* vol. Suppl 6, pp. S121-6.

Melzack, R. & Casey, K.L. 1967, "Localized temperature changes evoked in the brain by somatic stimulation", *Experimental neurology,* vol. 17, no. 3, pp. 276-292.

Melzack, R. & Wall, P.D. 1965, "Pain mechanisms: a new theory", *Science (New York, N.Y.),* vol. 150, no. 3699, pp. 971-979.

Meyerson, B.A., Lindblom, U., Linderoth, B., Lind, G. & Herregodts, P. 1993, "Motor cortex stimulation as treatment of trigeminal neuropathic pain", *Acta neurochirurgica.Supplementum,* vol. 58, pp. 150-153.

Mhalla, A., Baudic, S., Ciampi de Andrade, D., Gautron, M., Perrot, S., Teixeira, M.J., Attal, N. & Bouhassira, D. 2011, "Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia", *Pain,* vol. 152, no. 7, pp. 1478-1485.

Miley, D.P., Abrams, A.A., Atkinson, J.H. & Janowsky, D.S. 1978, "Successful treatment of thalamic pain with apomorphine", *The American Journal of Psychiatry,* vol. 135, no. 10, pp. 1230-1232.

Millan, M.J. 2002, "Descending control of pain", *Progress in neurobiology,* vol. 66, no. 6, pp. 355-474.

Mogil, J.S. 2009, "Are we getting anywhere in human pain genetics?", *Pain,* vol. 146, no. 3, pp. 231-232.

Mogil, J.S. 1999, "The genetic mediation of individual differences in sensitivity to pain and its inhibition", *Proceedings of the National Academy of Sciences of the United States of America,* vol. 96, no. 14, pp. 7744-7751.

Moisset, X., de Andrade, D.C. & Bouhassira, D. 2016, "From pulses to pain relief: an update on the mechanisms of rTMS-induced analgesic effects", *European journal of pain (London, England),* vol. 20, no. 5, pp. 689-700.

Moldofsky, H. 2001, "Sleep and pain", *Sleep medicine reviews,* vol. 5, no. 5, pp. 385-396.

Montoya, P., Ritter, K., Huse, E., Larbig, W., Braun, C., Topfner, S., Lutzenberger, W., Grodd, W., Flor, H. & Birbaumer, N. 1998, "The cortical somatotopic map and phantom phenomena in subjects with congenital limb atrophy and traumatic amputees with phantom limb pain", *The European journal of neuroscience,* vol. 10, no. 3, pp. 1095-1102.

Moore, K.A., Kohno, T., Karchewski, L.A., Scholz, J., Baba, H. & Woolf, C.J. 2002, "Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 22, no. 15, pp. 6724-6731.

Morgan, M.J. & Franklin, K.B. 1991, "Dopamine receptor subtypes and formalin test analgesia", *Pharmacology, biochemistry, and behavior,* vol. 40, no. 2, pp. 317-322.

Mori, F., Codeca, C., Kusayanagi, H., Monteleone, F., Buttari, F., Fiore, S., Bernardi, G., Koch, G. & Centonze, D. 2010, "Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis", *The journal of pain : official journal of the American Pain Society,* vol. 11, no. 5, pp. 436-442.

Morin, C.M., Gibson, D. & Wade, J. 1998, "Self-reported sleep and mood disturbance in chronic pain patients", *The Clinical journal of pain,* vol. 14, no. 4, pp. 311-314.

Munchau, A., Orth, M., Rothwell, J.C., Di Lazzaro, V., Oliviero, A., Profice, P., Tonali, P., Pramstaller, P.P. & Bhatia, K.P. 2002, "Intracortical inhibition is reduced in a patient with a lesion in the posterolateral thalamus", *Movement disorders : official journal of the Movement Disorder Society,* vol. 17, no. 1, pp. 208-212.

Nahmias, F., Debes, C., de Andrade, D.C., Mhalla, A. & Bouhassira, D. 2009, "Diffuse analgesic effects of unilateral repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers", *Pain,* vol. 147, no. 1-3, pp. 224-232.

Nettekoven, C., Volz, L.J., Leimbach, M., Pool, E.M., Rehme, A.K., Eickhoff, S.B., Fink, G.R. & Grefkes, C. 2015, "Inter-individual variability in cortical excitability and motor network connectivity following multiple blocks of rTMS", *NeuroImage,* vol. 118, pp. 209-218.

Nguyen, J.P., Keravel, Y., Feve, A., Uchiyama, T., Cesaro, P., Le Guerinel, C. & Pollin, B. 1997, "Treatment of deafferentation pain by chronic stimulation of the motor cortex: report of a series of 20 cases", *Acta neurochirurgica.Supplement,* vol. 68, pp. 54-60.

Nguyen, J.P., Velasco, F., Brugieres, P., Velasco, M., Keravel, Y., Boleaga, B., Brito, F. & Lefaucheur, J.P. 2008, "Treatment of chronic neuropathic pain by motor cortex stimulation: results of a bicentric controlled crossover trial", *Brain stimulation,* vol. 1, no. 2, pp. 89-96.

Nicholson, B. & Verma, S. 2004, "Comorbidities in chronic neuropathic pain", *Pain medicine (Malden, Mass.),* vol. 5 Suppl 1, pp. S9-S27.

Nickel, F.T., Seifert, F., Lanz, S. & Maihofner, C. 2012, "Mechanisms of neuropathic pain", *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology,* vol. 22, no. 2, pp. 81-91.

Niraj, G. & Rowbotham, D.J. 2011, "Persistent postoperative pain: where are we now?", *British journal of anaesthesia,* vol. 107, no. 1, pp. 25-29.

Nitsche, M.A., Liebetanz, D., Antal, A., Lang, N., Tergau, F. & Paulus, W. 2003, "Modulation of cortical excitability by weak direct current stimulation--technical, safety and functional aspects", *Supplements to Clinical neurophysiology,* vol. 56, pp. 255-276.

Nitsche, M.A. & Paulus, W. 2000, "Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation", *The Journal of physiology,* vol. 527 Pt 3, pp. 633-639.

Nuti, C., Peyron, R., Garcia-Larrea, L., Brunon, J., Laurent, B., Sindou, M. & Mertens, P. 2005, "Motor cortex stimulation for refractory neuropathic pain: four year outcome and predictors of efficacy", *Pain,* vol. 118, no. 1-2, pp. 43-52.

Oakley, J.C. & Prager, J.P. 2002, "Spinal cord stimulation: mechanisms of action", *Spine,* vol. 27, no. 22, pp. 2574-2583.

O'Brien, E.M., Waxenberg, L.B., Atchison, J.W., Gremillion, H.A., Staud, R.M., McCrae, C.S. & Robinson, M.E. 2011, "Intraindividual variability in daily sleep and pain ratings among chronic pain patients: bidirectional association and the role of negative mood", *The Clinical journal of pain,* vol. 27, no. 5, pp. 425-433.

Olney, R.K. 1998, "Clinical trials for polyneuropathy: the role of nerve conduction studies, quantitative sensory testing, and autonomic function testing", *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society,* vol. 15, no. 2, pp. 129-137.

Onen, S.H., Alloui, A., Gross, A., Eschallier, A. & Dubray, C. 2001, "The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects", *Journal of sleep research,* vol. 10, no. 1, pp. 35-42.

Owen, S.L., Green, A.L., Stein, J.F. & Aziz, T.Z. 2006, "Deep brain stimulation for the alleviation of post-stroke neuropathic pain", *Pain,* vol. 120, no. 1-2, pp. 202-206.

Paalzow, G.H. 1992, "L-dopa induces opposing effects on pain in intact rats: (-)-sulpiride, SCH 23390 or alpha-methyl-DL-p-tyrosine methylester hydrochloride reveals profound hyperalgesia in large antinociceptive doses", *The Journal of pharmacology and experimental therapeutics,* vol. 263, no. 2, pp. 470-479.

Partinen, M. & Gislason, T. 1995, "Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints", *Journal of sleep research,* vol. 4, no. S1, pp. 150-155.

Passard, A., Attal, N., Benadhira, R., Brasseur, L., Saba, G., Sichere, P., Perrot, S., Januel, D. & Bouhassira, D. 2007, "Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia", *Brain : a journal of neurology,* vol. 130, no. Pt 10, pp. 2661-2670.

Peltz, E., Seifert, F., DeCol, R., Dorfler, A., Schwab, S. & Maihofner, C. 2011, "Functional connectivity of the human insular cortex during noxious and innocuous thermal stimulation", *NeuroImage,* vol. 54, no. 2, pp. 1324-1335.

Penders, C.A. & Delwaide, P.J. 1971, "Blink reflex studies in patients with Parkinsonism before and during therapy", *Journal of neurology, neurosurgery, and psychiatry,* vol. 34, no. 6, pp. 674-678.

Pertovaara, A. 1999, "The influence of stimulus temperature rise rate, adapting temperature, and stimulus duration on suprathreshold responses evoked by noxious heat in the glabrous skin of the limb. Comparison of neuronal discharge in the rat spinal dorsal horn with human sensations", *Experimental brain research,* vol. 126, no. 4, pp. 482-494.

Pertovaara, A. & Almeida, A. 2006, "Chapter 13 Descending inhibitory systems", *Handbook of clinical neurology,* vol. 81, pp. 179-192.

Pertovaara, A., Martikainen, I.K., Hagelberg, N., Mansikka, H., Nagren, K., Hietala, J. & Scheinin, H. 2004, "Striatal dopamine D2/D3 receptor availability correlates with individual response characteristics to pain", *The European journal of neuroscience,* vol. 20, no. 6, pp. 1587-1592.

Petrovic, P., Kalso, E., Petersson, K.M. & Ingvar, M. 2002, "Placebo and opioid analgesia-- imaging a shared neuronal network", *Science (New York, N.Y.),* vol. 295, no. 5560, pp. 1737-1740.

Peyron, R., Garcia-Larrea, L., Gregoire, M.C., Costes, N., Convers, P., Lavenne, F., Mauguiere, F., Michel, D. & Laurent, B. 1999, "Haemodynamic brain responses to acute pain in humans: sensory and attentional networks", *Brain : a journal of neurology,* vol. 122 (Pt 9), no. Pt 9, pp. 1765-1780.

Peyron, R., Laurent, B. & Garcia-Larrea, L. 2000, "Functional imaging of brain responses to pain. A review and meta-analysis (2000)", *Neurophysiologie clinique = Clinical neurophysiology,* vol. 30, no. 5, pp. 263-288.

Pezet, S. & McMahon, S.B. 2006, "Neurotrophins: mediators and modulators of pain", *Annual Review of Neuroscience,* vol. 29, pp. 507-538.

Pfaffenrath, V., Rath, M., Pollmann, W. & Keeser, W. 1993, "Atypical facial pain--application of the IHS criteria in a clinical sample", *Cephalalgia : an international journal of headache,* vol. 13 Suppl 12, pp. 84-88.

Pilowsky, I., Crettenden, I. & Townley, M. 1985, "Sleep disturbance in pain clinic patients", *Pain,* vol. 23, no. 1, pp. 27-33.

Ploner, M., Lee, M.C., Wiech, K., Bingel, U. & Tracey, I. 2011, "Flexible cerebral connectivity patterns subserve contextual modulations of pain", *Cerebral cortex (New York, N.Y.: 1991),* vol. 21, no. 3, pp. 719-726.

Poliakov, I. & Toth, C. 2011, "The impact of pain in patients with polyneuropathy", *European journal of pain (London, England),* vol. 15, no. 10, pp. 1015-1022.

Pontieri, F.E., Tanda, G. & Di Chiara, G. 1995, "Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens", *Proceedings of the National Academy of Sciences of the United States of America,* vol. 92, no. 26, pp. 12304-12308.

Poole, H.M., Murphy, P. & Nurmikko, T.J. 2009, "Development and preliminary validation of the NePIQoL: a quality-of-life measure for neuropathic pain", *Journal of pain and symptom management,* vol. 37, no. 2, pp. 233-245.

Potvin, S., Grignon, S. & Marchand, S. 2009, "Human evidence of a supra-spinal modulating role of dopamine on pain perception", *Synapse (New York, N.Y.),* vol. 63, no. 5, pp. 390-402.

Przewlocki, R. & Przewlocka, B. 2001, "Opioids in chronic pain", *European journal of pharmacology,* vol. 429, no. 1-3, pp. 79-91.

Purves, D., Augustine, G., Fitzpatrick D., Hall, W., LaMantia A-S., White, L. 2012, *Neuroscience*, Fifth Edition, published by Sinauer Associates.

Rainville, P., Duncan, G.H., Price, D.D., Carrier, B. & Bushnell, M.C. 1997, "Pain affect encoded in human anterior cingulate but not somatosensory cortex", *Science (New York, N.Y.),* vol. 277, no. 5328, pp. 968-971.

Richardson, D.E. & Akil, H. 1977, "Long term results of periventricular gray self-stimulation", *Neurosurgery,* vol. 1, no. 2, pp. 199-202.

Riley, J.L.,3rd, Benson, M.B., Gremillion, H.A., Myers, C.D., Robinson, M.E., Smith, C.L.,Jr & Waxenberg, L.B. 2001, "Sleep disturbance in orofacial pain patients: pain-related or emotional distress?", *Cranio : the journal of craniomandibular practice,* vol. 19, no. 2, pp. 106-113.

Rizzo, V., Siebner, H.R., Modugno, N., Pesenti, A., Munchau, A., Gerschlager, W., Webb, R.M. & Rothwell, J.C. 2004, "Shaping the excitability of human motor cortex with premotor rTMS", *The Journal of physiology,* vol. 554, no. Pt 2, pp. 483-495.

Romano, J.M. & Turner, J.A. 1985, "Chronic pain and depression: does the evidence support a relationship?", *Psychological bulletin,* vol. 97, no. 1, pp. 18-34.

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A. & Safety of TMS Consensus Group 2009, "Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 120, no. 12, pp. 2008-2039.

Ruda, M.A., Bennett, G.J. & Dubner, R. 1986, "Neurochemistry and neural circuitry in the dorsal horn", *Progress in brain research,* vol. 66, pp. 219-268.

Rushworth, G. 1962, "Observations on blink reflexes", *Journal of neurology, neurosurgery, and psychiatry,* vol. 25, pp. 93-108.

Sagheddu, C., Aroni, S., De Felice, M., Lecca, S., Luchicchi, A., Melis, M., Muntoni, A.L., Romano, R., Palazzo, E., Guida, F., Maione, S. & Pistis, M. 2015, "Enhanced serotonin and mesolimbic dopamine transmissions in a rat model of neuropathic pain", *Neuropharmacology,* vol. 97, pp. 383-393.

Saitoh, Y., Shibata, M., Hirano, S., Hirata, M., Mashimo, T. & Yoshimine, T. 2000, "Motor cortex stimulation for central and peripheral deafferentation pain. Report of eight cases", *Journal of neurosurgery,* vol. 92, no. 1, pp. 150-155.

Scala, A., Checchi, L., Montevecchi, M., Marini, I. & Giamberardino, M.A. 2003, "Update on burning mouth syndrome: overview and patient management", *Critical reviews in oral biology and medicine : an official publication of the American Association of Oral Biologists,* vol. 14, no. 4, pp. 275-291.

Schiavone, V., Adamo, D., Ventrella, G., Morlino, M., De Notaris, E.B., Ravel, M.G., Kusmann, F., Piantadosi, M., Pollio, A., Fortuna, G. & Mignogna, M.D. 2012, "Anxiety, depression, and pain in burning mouth syndrome: first chicken or egg?", *Headache,* vol. 52, no. 6, pp. 1019-1025.

Schweinhardt, P. & Bushnell, M.C. 2010, "Pain imaging in health and disease--how far have we come?", *The Journal of clinical investigation,* vol. 120, no. 11, pp. 3788-3797.

Schweinhardt, P. & Bushnell, M.C. 2010, "Pain imaging in health and disease--how far have we come?", *The Journal of clinical investigation,* vol. 120, no. 11, pp. 3788-3797.

Scott, D.J., Heitzeg, M.M., Koeppe, R.A., Stohler, C.S. & Zubieta, J.K. 2006, "Variations in the human pain stress experience mediated by ventral and dorsal basal ganglia dopamine activity", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 26, no. 42, pp. 10789-10795.

Scott, D.J., Stohler, C.S., Koeppe, R.A. & Zubieta, J.K. 2007, "Time-course of change in [11C]carfentanil and [11C]raclopride binding potential after a nonpharmacological challenge", *Synapse (New York, N.Y.),* vol. 61, no. 9, pp. 707-714.

Sears, N.C., Machado, A.G., Nagel, S.J., Deogaonkar, M., Stanton-Hicks, M., Rezai, A.R. & Henderson, J.M. 2011, "Long-term outcomes of spinal cord stimulation with paddle leads in the treatment of complex regional pain syndrome and failed back surgery syndrome", *Neuromodulation : journal of the International Neuromodulation Society,* vol. 14, no. 4, pp. 312-8; discussion 318.

Semenchuk, M.R., Sherman, S. & Davis, B. 2001, "Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain", *Neurology,* vol. 57, no. 9, pp. 1583-1588.

Serra, P.A., Susini, G., Rocchitta, G., Migheli, R., Dessanti, G., Miele, E., Desole, M.S. & Miele, M. 2003, "Effects of sufentanil on the release and metabolism of dopamine and ascorbic acid and glutamate release in the striatum of freely moving rats", *Neuroscience letters,* vol. 344, no. 1, pp. 9-12.

Shahani, B. 1970, "The human blink reflex", *Journal of neurology, neurosurgery, and psychiatry,* vol. 33, no. 6, pp. 792-800.

Shimizu, T., Iwata, S., Morioka, H., Masuyama, T., Fukuda, T. & Nomoto, M. 2004, "Antinociceptive mechanism of L-DOPA", *Pain,* vol. 110, no. 1-2, pp. 246-249.

Siebner, H.R., Bergmann, T.O., Bestmann, S., Massimini, M., Johansen-Berg, H., Mochizuki, H., Bohning, D.E., Boorman, E.D., Groppa, S., Miniussi, C., Pascual-Leone, A., Huber, R., Taylor, P.C., Ilmoniemi, R.J., De Gennaro, L., Strafella, A.P., Kahkonen, S., Kloppel, S., Frisoni, G.B., George, M.S., Hallett, M., Brandt, S.A., Rushworth, M.F., Ziemann, U., Rothwell, J.C., Ward, N., Cohen, L.G., Baudewig, J., Paus, T., Ugawa, Y. & Rossini, P.M. 2009, "Consensus paper: combining transcranial stimulation with neuroimaging", *Brain stimulation,* vol. 2, no. 2, pp. 58-80.

Siebner, H.R. & Rothwell, J. 2003, "Transcranial magnetic stimulation: new insights into

representational cortical plasticity", *Experimental brain research,* vol. 148, no. 1, pp. 1-16.

Sipila, R., Estlander, A.M., Tasmuth, T., Kataja, M. & Kalso, E. 2012, "Development of a screening instrument for risk factors of persistent pain after breast cancer surgery", *British journal of cancer,* vol. 107, no. 9, pp. 1459-1466.

Smith, M.T. & Haythornthwaite, J.A. 2004, "How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature", *Sleep medicine reviews,* vol. 8, no. 2, pp. 119-132.

Smith, M.T., Perlis, M.L., Smith, M.S., Giles, D.E. & Carmody, T.P. 2000, "Sleep quality and presleep arousal in chronic pain", *Journal of Behavioral Medicine,* vol. 23, no. 1, pp. 1-13.

Sommer, C. & Kress, M. 2004, "Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia", *Neuroscience letters,* vol. 361, no. 1-3, pp. 184-187.

Spanagel, R. & Weiss, F. 1999, "The dopamine hypothesis of reward: past and current status", *Trends in neurosciences,* vol. 22, no. 11, pp. 521-527.

Spritzer KL, Hays RD. (2003, November). MOS Sleep Scale: A Manual for Use and Scoring, Version 1.0. Los Angeles, CA.

Stone, L.S., Broberger, C., Vulchanova, L., Wilcox, G.L., Hokfelt, T., Riedl, M.S. & Elde, R. 1998, "Differential distribution of alpha2A and alpha2C adrenergic receptor immunoreactivity in the rat spinal cord", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 18, no. 15, pp. 5928-5937.

Strafella, A.P., Ko, J.H. & Monchi, O. 2006, "Therapeutic application of transcranial magnetic stimulation in Parkinson's disease: the contribution of expectation", *NeuroImage,* vol. 31, no. 4, pp. 1666-1672.

Strafella, A.P., Paus, T., Barrett, J. & Dagher, A. 2001, "Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 21, no. 15, pp. RC157.

Strafella, A.P., Paus, T., Fraraccio, M. & Dagher, A. 2003, "Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex", *Brain : a journal of neurology,* vol. 126, no. Pt 12, pp. 2609-2615.

Sugimoto, T., Bennett, G.J. & Kajander, K.C. 1990, "Transsynaptic degeneration in the superficial dorsal horn after sciatic nerve injury: effects of a chronic constriction injury, transection, and strychnine", *Pain,* vol. 42, no. 2, pp. 205-213.

Summers, J., Johnson, S., Pridmore, S. & Oberoi, G. 2004, "Changes to cold detection and pain thresholds following low and high frequency transcranial magnetic stimulation of the motor cortex", *Neuroscience letters,* vol. 368, no. 2, pp. 197-200.

Svensson, P., Bjerring, P., Arendt-Nielsen, L. & Kaaber, S. 1993, "Sensory and pain thresholds to orofacial argon laser stimulation in patients with chronic burning mouth syndrome", *The Clinical journal of pain,* vol. 9, no. 3, pp. 207-215.

Taiminen, T., Kuusalo, L., Lehtinen, L., Forssell, H., Hagelberg, N., Tenovuo, O., Luutonen, S., Pertovaara, A., Jääskeläinen, S. 2011, "Psychiatric (axis I) and personality (axis II) disorders in patients with burning mouth syndrome or atypical facial pain", Scandinavian Journal of Pain, vol. 2, pp. 155-160.

Tal, M., Wall, P.D. & Devor, M. 1999, "Myelinated afferent fiber types that become spontaneously active and mechanosensitive following nerve transection in the rat", *Brain research,* vol. 824, no. 2, pp. 218-223.

Tamae, A., Nakatsuka, T., Koga, K., Kato, G., Furue, H., Katafuchi, T. & Yoshimura, M. 2005, "Direct inhibition of substantia gelatinosa neurones in the rat spinal cord by activation of dopamine D2-like receptors", *The Journal of physiology,* vol. 568, no. Pt 1, pp. 243-253.

Taylor, A.M., Murphy, N.P., Evans, C.J. & Cahill, C.M. 2014, "Correlation between ventral striatal catecholamine content and nociceptive thresholds in neuropathic mice", *The journal of pain : official journal of the American Pain Society,* vol. 15, no. 8, pp. 878-885.

Taylor, J.J., Borckardt, J.J., Canterberry, M., Li, X., Hanlon, C.A., Brown, T.R. & George, M.S. 2013, "Naloxone-reversible modulation of pain circuitry by left prefrontal rTMS", *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology,* vol. 38, no. 7, pp. 1189-1197.

Taylor, J.J., Borckardt, J.J. & George, M.S. 2012, "Endogenous opioids mediate left dorsolateral prefrontal cortex rTMS-induced analgesia", *Pain,* vol. 153, no. 6, pp. 1219-1225.

Teerijoki-Oksa, T., Jaaskelainen, S., Forssell, K., Virtanen, A. & Forssell, H. 2003, "An evaluation of clinical and electrophysiologic tests in nerve injury diagnosis after mandibular sagittal split osteotomy", *International journal of oral and maxillofacial surgery,* vol. 32, no. 1, pp. 15-23.

Teerijoki-Oksa, T., Jaaskelainen, S.K., Forssell, K. & Forssell, H. 2004, "Recovery of nerve injury after mandibular sagittal split osteotomy. Diagnostic value of clinical and electrophysiologic tests in the follow-up", *International journal of oral and maxillofacial surgery,* vol. 33, no. 2, pp. 134-140.

Teerijoki-Oksa, T., Jaaskelainen, S.K., Soukka, T., Virtanen, A. & Forssell, H. 2011, "Subjective sensory symptoms associated with axonal and demyelinating nerve injuries after mandibular sagittal split osteotomy", *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons,* vol. 69, no. 6, pp. e208-13.

Tolle, T.R., Kaufmann, T., Siessmeier, T., Lautenbacher, S., Berthele, A., Munz, F., Zieglgansberger, W., Willoch, F., Schwaiger, M., Conrad, B. & Bartenstein, P. 1999, "Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission

tomography correlation analysis", *Annals of Neurology,* vol. 45, no. 1, pp. 40-47.

Torrance, N., Smith, B.H., Bennett, M.I. & Lee, A.J. 2006, "The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey", *The journal of pain : official journal of the American Pain Society,* vol. 7, no. 4, pp. 281-289.

Treede, R.D., Jensen, T.S., Campbell, J.N., Cruccu, G., Dostrovsky, J.O., Griffin, J.W., Hansson, P., Hughes, R., Nurmikko, T. & Serra, J. 2008, "Neuropathic pain: redefinition and a grading system for clinical and research purposes", *Neurology,* vol. 70, no. 18, pp. 1630-1635.

Treede, R.D., Kenshalo, D.R., Gracely, R.H. & Jones, A.K. 1999, "The cortical representation of pain", *Pain,* vol. 79, no. 2-3, pp. 105-111.

Truini, A., Galeotti, F., Romaniello, A., Virtuoso, M., Iannetti, G.D. & Cruccu, G. 2005, "Laser-evoked potentials: normative values", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 116, no. 4, pp. 821-826.

Tsubokawa, T., Katayama, Y., Yamamoto, T., Hirayama, T. & Koyama, S. 1993, "Chronic motor cortex stimulation in patients with thalamic pain", *Journal of neurosurgery,* vol. 78, no. 3, pp. 393-401.

Tsubokawa, T., Katayama, Y., Yamamoto, T., Hirayama, T. & Koyama, S. 1991, "Chronic motor cortex stimulation for the treatment of central pain", *Acta neurochirurgica.Supplementum,* vol. 52, pp. 137-139.

Tsubokawa, T., Katayama, Y., Yamamoto, T., Hirayama, T. & Koyama, S. 1991, "Treatment of thalamic pain by chronic motor cortex stimulation", *Pacing and clinical electrophysiology : PACE,* vol. 14, no. 1, pp. 131-134.

Uglem, M., Omland, P.M., Engstrom, M., Gravdahl, G.B., Linde, M., Hagen, K. & Sand, T. 2016, "Non-invasive cortical modulation of experimental pain in migraine", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 127, no. 6, pp. 2362-2369.

Ultenius, C., Linderoth, B., Meyerson, B.A. & Wallin, J. 2006, "Spinal NMDA receptor phosphorylation correlates with the presence of neuropathic signs following peripheral nerve injury in the rat", *Neuroscience letters,* vol. 399, no. 1-2, pp. 85-90.

Valmunen, T., Pertovaara, A., Taiminen, T., Virtanen, A., Parkkola, R. & Jaaskelainen, S.K. 2009, "Modulation of facial sensitivity by navigated rTMS in healthy subjects", *Pain,* vol. 142, no. 1-2, pp. 149-158.

van Gilst, M.M., Bloem, B.R. & Overeem, S. 2013, ""Sleep benefit" in Parkinson's disease: a systematic review", *Parkinsonism & related disorders,* vol. 19, no. 7, pp. 654-659.

Vartiainen, N., Kallio-Laine, K., Hlushchuk, Y., Kirveskari, E., Seppanen, M., Autti, H., Jousmaki, V., Forss, N., Kalso, E. & Hari, R. 2009, "Changes in brain function and morphology in patients with recurring herpes simplex virus infections and chronic pain", *Pain,* vol. 144, no. 1-2, pp. 200-208.

Vartiainen, N., Kirveskari, E., Kallio-Laine, K., Kalso, E. & Forss, N. 2009, "Cortical reorganization in primary somatosensory cortex in patients with unilateral chronic pain", *The journal of pain : official journal of the American Pain Society,* vol. 10, no. 8, pp. 854-859.

Verdugo, R. & Ochoa, J.L. 1992, "Quantitative somatosensory thermotest. A key method for functional evaluation of small calibre afferent channels", *Brain : a journal of neurology,* vol. 115 (Pt 3), no. Pt 3, pp. 893-913.

Viisanen, H., Ansah, O.B. & Pertovaara, A. 2012, "The role of the dopamine D2 receptor in descending control of pain induced by motor cortex stimulation in the neuropathic rat", *Brain research bulletin,* vol. 89, no. 3-4, pp. 133-143.

Viisanen, H. & Pertovaara, A. 2010, "Roles of the rostroventromedial medulla and the spinal 5-HT(1A) receptor in descending antinociception induced by motor cortex stimulation in the neuropathic rat", *Neuroscience letters,* vol. 476, no. 3, pp. 133-137.

Vogt, B.A. & Sikes, R.W. 2000, "The medial pain system, cingulate cortex, and parallel processing of nociceptive information", *Progress in brain research,* vol. 122, pp. 223-235.

Von Korff, M. & Simon, G. 1996, "The relationship between pain and depression", *The British journal of psychiatry.Supplement,* vol. (30), no. 30, pp. 101-108.

Ware, J.E.,Jr & Sherbourne, C.D. 1992, "The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection", *Medical care,* vol. 30, no. 6, pp. 473-483.

Westlund, K.N., Carlton, S.M., Zhang, D. & Willis, W.D. 1990, "Direct catecholaminergic innervation of primate spinothalamic tract neurons", *The Journal of comparative neurology,* vol. 299, no. 2, pp. 178-186.

Wiech, K., Lin, C.S., Brodersen, K.H., Bingel, U., Ploner, M. & Tracey, I. 2010, "Anterior insula integrates information about salience into perceptual decisions about pain", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 30, no. 48, pp. 16324-16331.

Wiedenmayer, C.P. & Barr, G.A. 2000, "Mu opioid receptors in the ventrolateral periaqueductal gray mediate stress-induced analgesia but not immobility in rat pups", *Behavioral neuroscience,* vol. 114, no. 1, pp. 125-136.

Wilson, K.G., Eriksson, M.Y., D'Eon, J.L., Mikail, S.F. & Emery, P.C. 2002, "Major depression and insomnia in chronic pain", *The Clinical journal of pain,* vol. 18, no. 2, pp. 77-83.

Woda, A. 2009, "A "dysfunctional" pain group in addition to the "neuropathic" and "nociception/inflammatory" groups of orofacial pain entities?", *Journal of orofacial pain,* vol. 23, no. 2, pp. 89-90.

Woda, A. & Pionchon, P. 1999, "A unified concept of idiopathic orofacial pain: clinical features", *Journal of orofacial pain,* vol. 13, no. 3, pp. 172-84; discussion 185-95.

Wood, P.B. 2008, "Role of central dopamine in pain and analgesia", *Expert review of neurotherapeutics,* vol. 8, no. 5, pp. 781-797.

Wood, P.B., Schweinhardt, P., Jaeger, E., Dagher, A., Hakyemez, H., Rabiner, E.A., Bushnell, M.C. & Chizh, B.A. 2007, "Fibromyalgia patients show an abnormal dopamine response to pain", *The European journal of neuroscience,* vol. 25, no. 12, pp. 3576-3582.

Wood, P.L. & Rao, T.S. 1991, "Morphine stimulation of mesolimbic and mesocortical but not nigrostriatal dopamine release in the rat as reflected by changes in 3-methoxytyramine levels", *Neuropharmacology,* vol. 30, no. 4, pp. 399-401.

Woolf, C.J. & Mannion, R.J. 1999, "Neuropathic pain: aetiology, symptoms, mechanisms, and management", *Lancet (London, England),* vol. 353, no. 9168, pp. 1959-1964.

Wu, G., Ringkamp, M., Murinson, B.B., Pogatzki, E.M., Hartke, T.V., Weerahandi, H.M., Campbell, J.N., Griffin, J.W. & Meyer, R.A. 2002, "Degeneration of myelinated efferent fibers induces spontaneous activity in uninjured C-fiber afferents", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 22, no. 17, pp. 7746-7753.

Yavich, L., Forsberg, M.M., Karayiorgou, M., Gogos, J.A. & Mannisto, P.T. 2007, "Site-specific role of catechol-O-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 27, no. 38, pp. 10196-10209.

Yonehara, N. & Clouet, D.H. 1984, "Effects of delta and mu opiopeptides on the turnover and release of dopamine in rat striatum", *The Journal of pharmacology and experimental therapeutics,* vol. 231, no. 1, pp. 38-42.

Young Blood, M.R., Ferro, M.M., Munhoz, R.P., Teive, H.A. & Camargo, C.H. 2016, "Classification and Characteristics of Pain Associated with Parkinson's Disease", *Parkinson's disease,* vol. 2016, pp. 6067132.

Zubieta, J.K., Heitzeg, M.M., Smith, Y.R., Bueller, J.A., Xu, K., Xu, Y., Koeppe, R.A., Stohler, C.S. & Goldman, D. 2003, "COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor", *Science (New York, N.Y.),* vol. 299, no. 5610, pp. 1240-1243.

Zubieta, J.K., Smith, Y.R., Bueller, J.A., Xu, Y., Kilbourn, M.R., Jewett, D.M., Meyer, C.R., Koeppe, R.A. & Stohler, C.S. 2002, "Mu-Opioid Receptor-Mediated Antinociceptive Responses Differ in Men and Women", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 22, no. 12, pp. 5100-5107.

Zubieta, J.K., Smith, Y.R., Bueller, J.A., Xu, Y., Kilbourn, M.R., Jewett, D.M., Meyer, C.R., Koeppe, R.A. & Stohler, C.S. 2001, "Regional mu opioid receptor regulation of sensory and affective dimensions of pain", *Science (New York, N.Y.),* vol. 293, no. 5528, pp. 311-315.

Zubieta, J.K. & Stohler, C.S. 2009, "Neurobiological mechanisms of placebo responses", *Annals of the New York Academy of Sciences,* vol. 1156, pp. 198-210.