Original Article

The Effects of Transcranial Direct Current Stimulation on Metabolite Changes at the Thalamus in Neuropathic Pain after Spinal Cord Injury: A Pilot Study

Auvichayapat P, MD[1]*, Keeratitanont K, MD[2]*, Aneksan B, PhD[3], Jensen MP, PhD[4]*, Tammaroj J, MD[2], Arayawichanon P, MD[5], Tunkamnerdthai O, PhD[1], Boonphongsathian W, BSc[2], Auvichayapat N, MD[6]*

[1] Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[2] Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[3] Department of Physical Therapy, Mahidol University, Nakhon Pathom, Thailand

[4] Department of Rehabilitation Medicine, University of Washington, USA

[5] Department of Rehabilitation Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[6] Division of Pediatric Neurology, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

* Member of Noninvasive Brain Stimulation Research Group of Thailand

Objective: To evaluate the pain intensity and brain metabolites, N-acetyl aspartate (NAA), myo-inositol (ml), choline (Cho), and glutamine combined glutamate (Glx) levels in the thalami after transcranial direct current stimulation (tDCS) treatment.

Materials and Methods: Ten spinal cord injury (SCI) with neuropathic pain (NP) patients were given 20 minutes, 2 mA anodal tDCS over the left primary motor cortex for five consecutive days. Measures of numerical rating scales (NRS) and concentration of brain metabolites were performed before and immediately after treatment.

Results: The results showed significant reduction between pre- and immediately post-treatment in NRS (–2.213, 95% CI –0.836 to –3.570; p=0.005), significant decrease in Glx/Cr concentration (–0.025, 95% CI –0.004 to –0.045; p=0.022), and significant increased in ml/Cr (0.049, 95% CI 0.014 to 0.083; p=0.012) after tDCS treatment. No statistically significant pre- to post-treatment differences in NAA/Cr or and Cho/Cr were found in the present study.

Conclusion: The findings suggest that abnormal Glx/Cr and mI/Cr levels in the thalami would cause NP after SCI. The tDCS may be useful in NP reduction by returning the abnormal brain metabolites to normal. Additional research with larger sample size is warranted to evaluate this possibility.

Keywords: Magnetic resonance spectroscopy, Neuropathic pain, Spinal cord injury, Transcranial direct current stimulation

J Med Assoc Thai 2019;102(1):71-7
Website: http://www.jmatonline.com

One of the most common refractory neuropathic pain (NP) is caused by spinal cord injury (SCI)[1]. There is a significant need to develop and identify effective treatments for NP. The beneficial effects of transcranial direct current stimulation (tDCS) in patients with NP may be related to the up-regulation of motor cortex excitability in pain-modulating areas, such as thalamic nuclei[2,3]. However, these mechanisms are not yet fully understood.

Proton magnetic resonance spectroscopy (1HMRS) is a brain imaging method that can assess the concentrations of specific metabolites in different brain regions, including N-acetyl aspartate (NAA), choline (Cho), creatine (Cr), myo-inositol (mI), glutamate (Glu), glutamine (Gln), glutamine combined glutamate (Glx), and gamma-aminobutyric acid (GABA). Concentration changes of these metabolites are associated with numerous neurological diseases and symptoms, including SCI-related NP[4].

The thalamus serves as a relay center that receives information from multiple ascending

Correspondence to:
Auvichayapat N.
Division of Pediatric Neurology, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
Phone: +66-89-6222624
Email: anaron@kku.ac.th

How to cite this article: Auvichayapat P, Keeratitanont K, Aneksan B, Jensen MP, Tammaroj J, Arayawichanon P, et al. The Effects of Transcranial Direct Current Stimulation on Metabolite Changes at the Thalamus in Neuropathic Pain after Spinal Cord Injury: A Pilot Study. J Med Assoc Thai 2019;102:71-7.

pathways, and then sends information related to this input to and from other cortical areas. Thus, it is a key structure involved in the processing of pain[5]. Moreover, some researches have shown that measures of metabolite concentrations in the thalamus are related to pain. For example, pain intensity has been shown to be associated with lower levels of neuronal metabolites e.g., NAA/Cr in the thalamus[6-8]. Greater concentrations of the glial marker mI have also been shown to be commonly associated with SCI-related NP[9]. Elevated levels of Glx/Cr have also been found in a number of brain regions in individuals with chronic pain, relative to those who do not have chronic pain[10,11]. Consistent with these findings, it has been hypothesized that alterations in brain metabolites, specifically a reduction in the concentrations of NAA and an increase in concentration of mI, in the thalamus may result in increases in pain intensity[4,5,11].

It is reasonable to speculate that the analgesic effects of tDCS in SCI-related NP may be related to the effects of tDCS on metabolite concentrations. Preliminary studies support this idea[12,13]. For example, changes of mI concentrations were found following a single session of tDCS[12]. Another preliminary study showed decrease in NAA/Cr in the primary motor cortex in nine individuals with chronic pelvic pain patients after 10 sessions of tDCS[13]. However, to the best of the authors' knowledge, there is no study that examined brain metabolite change in the thalamus following tDCS.

The purpose of the present study was to evaluate the concentrations of brain metabolite in the thalami and association between pain intensity and brain metabolite changes.

Materials and Methods

Study design

The present study was performed over five weeks consisting of 1) a 1-week baseline assessment, 2) five consecutive days of 2 mA anodal tDCS for 20 minutes, and 3) a 3-week follow-up period. The numerical rating scale was assessed during baseline and treatment, and then again weekly during the follow-up period. Brain metabolites were assessed before and immediately after tDCS. Participants were asked to continue their routine analgesic medication regimen throughout the duration of the 5-week study.

Participant recruitment and informed consent

The study enlisted participants who expressed an interest in participating in the present study that would match the inclusion and exclusion criteria of our previous study[2]. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Khon Kaen University (Identifier number: HE561320). Written informed consents were obtained from all participants before participation. This protocol had been approved for registration at the TCTR (Identification number: TCTR20170822003).

Measures

The primary outcomes of the present study were the concentrations of brain metabolite in the thalami and association between pain intensity and brain metabolite changes.

Pain intensity

The 0 to 10 numerical rating scale (NRS) was used to assess average pain intensity in the past 24 hours on a 0 to 10 scale, where 0=no pain, and 10=pain as intense as they can imagine.

Brain metabolite level assessment

A 1-hour MRS assessment was used to measure baseline and post-treatment levels of NAA, Glx, Cho, mI, and Cr in the left and right thalamus, The MRS voxels ($2\times2\times2$ cm^3) were positioned on the coronal, sagittal, and axial images from the thalami. The MR equipment, techniques, shimming, and metabolites calculating were the same as the previous study[14].

Transcranial direct current stimulation (tDCS)

The anode electrode was placed over the left M1, which was located by single-pulse transcranial magnetic stimulation. The cathode (reference) electrode was placed on the right shoulder. Direct current of 2 mA for 20 minutes was administered once a day for five consecutive days during the treatment period. The device and techniques were the same as the previous study[2].

Adverse events and safety

The participants were asked to report adverse events as well as other signs and symptoms immediately after each of the stimulation sessions. Participants were also closely observed by a physician (Auvichayapat P) during and just after the study sessions.

Data analysis

Data were processed by Stata software, version 10.0 (StataCorp, College Station, Texas, USA) and results were presented in means and standard deviations (mean±SD). Changes in pain intensity over

the course of treatment and throughout the follow-up period were evaluated using repeated measure analysis of variances (ANOVAs). The non-parametric Wilcoxon signed-rank test was used to evaluate differences of the metabolite changes between baseline and after completion of five daily tDCS sessions (metabolite changes on day 5). Finally, the authors examined the associations between metabolite levels and pain intensity by computing Pearson's correlation coefficients between pre- to post-treatment changes in the measures of these domains.

Sample size calculation

The number of subjects needed in the pilot study was determined based on the findings from the previous study, which evaluated five healthy subjects and found that a single tDCS induced a significant increase in the concentration of mI at 30 minutes after stimulation offset (141.5±16.7%, $p<0.001$)[12]. If tDCS had a similar effect on the outcomes as in the current study, 10 participants would provide a power of 0.90 to detect this as significant with an alpha of 0.05.

Results

Sample description

Ten male patients with SCI and NP were enrolled in the present study. No participants were screened out of the study due to psychological factors or cognitive dysfunction. They had a mean age of 32.7±6.88 years, baseline average pain intensity was 4.61±0.66, baseline duration of pain was 73.60±41.98 months, and baseline duration of SCI was 80.50±35.18 months. No participants had serious adverse effect or withdrew from the study.

Change in pain intensity

The repeated-measures ANOVA with pain intensity as the dependent variable and time (baseline, day 1 to 5, and 1-week, 2-week, and 3-week follow-up) as a within-subjects independent variable revealed a significant main effect for time with a large effect size ($F(8, 9)=7.03$; $p<0.001$, $\eta^2=0.339$). In order to interpret the significant effect of time, the authors performed post-hoc analyses of the time factor. These revealed a significant decrease in pain intensity from baseline to post-session at day 2 (–0.613, 95% CI –0.002 to –1.224; p=0.049), day 3 (–1.413, 95% CI –0.113 to –2.713; p=0.036), day 4 (–1.613, 95% CI –0.155 to –3.071; p=0.034), day 5 (–2.213, 95% CI –0.836 to –3.570; p=0.005), 1-week follow-up (–2.213, 95% CI –0.735 to –3.691; p=0.008), and 2-week follow-up (–1.613, 95% CI –0.043 to –3.183; p=0.045) respectively. An increase in average pain intensity towards baseline levels began at the 2-week follow-up point, and the 3-week rating was not significantly different from the baseline rating (–0.213, 95% CI –0.541 to 0.115, p=0.175).

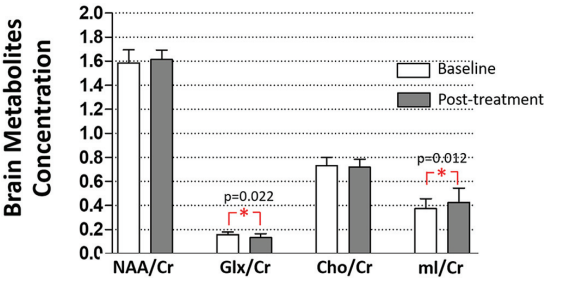

Figure 1. Metabolite changes in the thalami.

Data are presented as mean of brain metabolites compared between baseline and post-transcranial direct current stimulation treatment. Vertical lines represent SD.

* Significant difference p<0.01.

Change in metabolite concentrations

For all individuals, MR spectroscopic data were acquired from the left and right thalamus. Statistical analysis revealed no significant difference between the two sides for each of the metabolite concentrations. Thus, for each participant, the concentrations of each metabolite were averaged across the two sides of thalamus. Paired differences between baseline and post-treatment of average brain metabolites between right and left thalamus showed statistical decrease in Glx/Cr and significant increase in ml/Cr after tDCS treatment. No statistically significant pre- to post-treatment difference in NAA/Cr and Cho/Cr was found in the present study (see Figure 1, Table 1). With respect to effect sizes (Cohen's d), the pre- to post-treatment changes in Glx/Cr, ml/Cr, NAA/Cr, and Cho/Cr were 0.99 (large), 0.50 (medium), 0.31 (weak), and –0.20 (less than weak), respectively.

The associations between pain intensity and metabolite change

The results presented moderate and significant associations between improvements in pain and a decrease in Glx/Cr (r=–0.72, p=0.018) and an increase in mI/Cr (r=0.68, p=0.030). The associations between improvement in pain and change in the concentration of NAA/Cr (r=0.12, p=0.745), and that between improvement in pain and an increase in Cho/Cr (r=0.48, p=0.160).

Table 1. Differences of brain metabolites concentration between baseline and post-treatment in the thalami (n = 10)

Brain metabolites	Time	Right thalamus Mean±SD	Left thalamus Mean±SD	Average brain metabolites between right and left thalamus Mean±SD	Paired differences between baseline and post-treatment				
					Mean	SD	95% CI of the difference		p-value
							Lower	Upper	
NAA/Cr	Baseline	1.538±0.13	1.634±0.11	1.616±0.11					
	Post-treatment	1.596±0.09	1.636±0.10	1.586±0.09	–0.030	0.094	–0.098	0.037	0.341
Glx/Cr	Baseline	0.158±0.02	0.160±0.02	0.159±0.02					
	Post-treatment	0.133±0.03	0.135±0.04	0.135±0.03	–0.025	0.028	–0.004	–0.045	0.022*
Cho/Cr	Baseline	0.741±0.07	0.723±0.07	0.720±0.07					
	Post-treatment	0.719±0.07	0.717±0.06	0.733±0.07	0.013	0.035	–0.012	0.038	0.267
ml/Cr	Baseline	0.369±0.08	0.385±0.08	0.377±0.08					
	Post-treatment	0.402±0.10	0.450±0.13	0.425±0.12	0.049	0.049	0.014	0.083	0.012*

SD=standard deviation; CI=confidence interval; NAA=N-acetyl aspartate; CR=creatine; Glx=glutamine combined glutamate; Cho=choline; mI=myo-inositol

Discussion

The present findings showed statistically significant and large effect pre- to post-treatment improvements in pain intensity as well as a significant and moderate effect pre- to post-treatment increase in mI/Cr and a large effect decrease Glx/Cr in the thalami. Significant and moderate associations between pain reduction and increase in mI/Cr and decreases Glx/Cr were also found. However, the size of the association between improvements in pain and change in NAA/Cr were only moderate, and that between improvements in pain and change in Cho/Cr were weak.

The pain perception is mediated through the spinothalamic pathway and then modulated and processed by higher cortical brain regions, such as the thalamus. The damage of a spinothalamic tract is associated with the development and maintenance of NP after SCI. It interferes with natural pain inhibitory processes, and results in highly refractory and very severe in NP[15].

These processes are likely influenced by the release and uptake of brain metabolites. For example, mI is a sugar-like molecule found in brain glial cells that can be viewed as a marker of glial proliferation, given that the osmotic balance in the tissue is preserved by regulation of mI transport across the plasma membrane[16]. The authors' findings showed an increase of mI/Cr in the thalamus after tDCS treatment, and a moderately strong statistically significant association between this increase in mI/Cr concentration and pain reduction. These findings suggest that the increase in mI after tDCS found here could be a potential explanation for at least some of the benefit of tDCS on pain reduction.

Several mechanisms could potentially facilitate an increase in mI. The primary source of brain mI comes from the brain recycling of inositol-containing phospholipids that are tightly linked to membrane phospholipids and their metabolism[17]. The after effects of tDCS are thought to be partly mediated by changes in the biophysical properties of membranes[18]. It is thought to influence membrane phospholipids metabolism in thalamus and, in turn, increase mI concentration[12]. However, it is important to remember that the findings reported here are from a small number of participants, and therefore, should be viewed as preliminary. Further studies are needed to better understand the role that changes in mI, may or may not, play a role in explaining pain reduction after tDCS in patients with SCI- related pain, as well as, in patients with other chronic pain conditions.

The role of Glx in human pain perception is increasing[19]. The present study showed a positive association between general thalamic activity and chronic NP[20] supports the role of thalamus as a key component of the pain matrix. Consistent with the notion of Glu as an activating neurotransmitter, researches have shown higher thalamic Glu in individuals with chronic pain, relative to healthy subjects[13,21,22]. Such increase could be associated with the brain's attempts activating inhibition processes. The author found evidence of decrease in Glx/Cr in thalamus after tDCS treatment, and this reduction was associated with pain reduction. This finding is consistent with the previous research which found

thalamic Glu levels decreased after five tDCS sessions in individual with chronic pain from fibromyalgia[23]. Moreover, another previous research has also found a decrease in Glu in the insular area that correlated with pain reduction in chronic pain after using pregabalin. Thus, the decrease in Glu might facilitate pain relief by affecting functional connectivity of neural cells involved in pain processing[24].

NAA is found only in central nervous system (CNS) neurons and considered as a marker of global neuronal health and attenuation[25]. Lower levels of NAA are found in a variety of CNS disorders that caused neuronal cell destruction[26,27] and in some chronic conditions that have chronic pain components[8,28,29]. Therefore, it is reasonable to hypothesize that patients with chronic pain might have lower NAA levels in the thalamus, relative to healthy individual[7]. Consistent with a role for this metabolite in chronic pain, a research has found a negative correlation between pain and NAA in thalamus in patients with SCI[30]. However, the author found a very weak effect of tDCS on NAA concentrations in the present pilot study. There are possible reasons for this null finding, including the low sample size of the current study and very low levels of NAA in the present sample at baseline. Given the potential role that NAA plays in pain, however, it is probably too early to rule out NAA as a potential mechanism for the benefits of tDCS and other pain treatments.

Cho is thought to responsible for cell membranes synthesis[25]. A previous study has shown Cho increasing in glia cell tumors, suggesting that Cho concentration correlates with increase cellularity[31]. There has been few pain research in Cho measurement, however, the first study found an elevation in Cho concentrations in the anterior cingulate cortex in a sample of individuals with SCI and chronic pain[32]. A second study found no significant difference in Cho concentrations in the thalamus in patients with chronic pain, relative to healthy individuals[33]. The present study's results are more consistent with the second study, as we found a weak effect of tDCS on thalamic Cho concentrations in the study sample. Thus, it appears that thalamic Cho plays a very limited role in the experience of pain or benefits of tDCS on pain, although it remains possible that Cho concentrations in the anterior cingulate cortex might be important for pain modulation. Further study is needed to better understand Cho's role in pain processing.

Limitation

The present study had some limitations. First, the pilot study had limited power that may have been unable to detect significant effects. Therefore, the findings presented here should be viewed as tentative and in need of replication in studies using larger samples. Second, the tDCS intervention considered only five consecutive days of 20-minute tDCS. This standard tDCS protocol might not be enough to remodel thalamic neurons or glia cell. Further study using a higher dose or more sessions of tDCS may have a larger impact on changes in pain and metabolite concentrations.

Conclusion

The present study provided important new information regarding the beneficial effects of tDCS on NP, and these effects might be explained by tDCS-related changes in metabolite concentrations. Specifically, tDCS increased thalamic mI/Cr and decreased thalamic Glx/Cr in individuals with SCI-related NP. The decrease observed in Glx/Cr is consistent with the possibility that tDCS improves the efficacy of the descending pain modulation system in the thalamus. The increase observed in mI/Cr might reflect higher glia cell activity. The larger sample size and even larger dose of tDCS treatment are warranted.

What is already known on this topic?

NP from SCI is both common and highly refractory to treatment. Several studies have shown that the beneficial effects of tDCS in patients with NP may be related to the up-regulation of motor cortex excitability in pain-modulating areas, such as thalamic nuclei.

1HMRS study has revealed that pain intensity was associated with lower levels of neuronal metabolites e.g., NAA/Cr in the thalamus. Greater concentrations of the glial marker mI have also been shown to be commonly associated with SCI-related NP. Elevated levels of Glx/Cr have also been found in a number of brain regions in individuals with chronic pain, relative to those who do not have chronic pain. Consistent with these findings, it has been hypothesized that alterations in brain metabolites, specifically a reduction in the concentrations of NAA and an increase in concentration of mI, in the thalamus may result in an increase in pain.

What this study adds?

The results showed treatment-related reductions in pain, as well as a decrease in Glx/Cr and an increase in mI/Cr in the thalamus. The observed decrease in Glx/Cr is consistent with the possibility

that tDCS increases activity in the descending pain modulation system. The observed increase in mI/Cr may represent an increase in glia cell activity in the thalamus. The findings suggest the possibility that tDCS's beneficial effects on NP may be due to the changes in Glx/Cr and mI/Cr levels in the thalamus.

Acknowledgement

The authors thank Niran Ngernyam and Anuwat Amatachaya for subjects recruitment, Au Auvichayapat and Vichaya Auvichayapat for statistical analysis and graphs presentation.

Funding disclosure

The present study was supported by an invitation research grant, Faculty of Medicine, Khon Kaen University, Thailand (Grant number: IN61106), a grant of National Research Council of Thailand (NRCT).

Conflicts of interest

The authors declare no conflict of interest.

References

1. Nicholson BD. Evaluation and treatment of central pain syndromes. Neurology 2004;62(5 Suppl 2):S30-6.
2. Ngernyam N, Jensen MP, Arayawichanon P, Auvichayapat N, Tiamkao S, Janjarasjitt S, et al. The effects of transcranial direct current stimulation in patients with neuropathic pain from spinal cord injury. Clin Neurophysiol 2015;126:382-90.
3. Peyron R, Faillenot I, Mertens P, Laurent B, Garcia-Larrea L. Motor cortex stimulation in neuropathic pain. Correlations between analgesic effect and hemodynamic changes in the brain. A PET study. Neuroimage 2007;34:310-21.
4. Gustin SM, Wrigley PJ, Youssef AM, McIndoe L, Wilcox SL, Rae CD, et al. Thalamic activity and biochemical changes in individuals with neuropathic pain after spinal cord injury. Pain 2014;155:1027-36.
5. Sankarasubramanian V, Cunningham DA, Potter-Baker KA, Beall EB, Roelle SM, Varnerin NM, et al. Transcranial direct current stimulation targeting primary motor versus dorsolateral prefrontal cortices: Proof-of-Concept Study Investigating Functional Connectivity of Thalamocortical Networks Specific to Sensory-Affective Information Processing.. Brain Connect 2017;7:182-96.
6. Pattany PM, Yezierski RP, Widerstrom-Noga EG, Bowen BC, Martinez-Arizala A, Garcia BR, et al. Proton magnetic resonance spectroscopy of the thalamus in patients with chronic neuropathic pain after spinal cord injury. AJNR Am J Neuroradiol 2002;23:901-5.
7. Fukui S, Matsuno M, Inubushi T, Nosaka S. N-Acetylaspartate concentrations in the thalami of neuropathic pain patients and healthy comparison subjects measured with (1)H-MRS. Magn Reson Imaging 2006;24:75-9.
8. Sorensen L, Siddall PJ, Trenell MI, Yue DK. Differences in metabolites in pain-processing brain regions in patients with diabetes and painful neuropathy. Diabetes Care 2008;31:980-1.
9. Chang L, Munsaka SM, Kraft-Terry S, Ernst T. Magnetic resonance spectroscopy to assess neuroinflammation and neuropathic pain. J Neuroimmune Pharmacol 2013;8:576-93.
10. Harris RE, Clauw DJ. Imaging central neurochemical alterations in chronic pain with proton magnetic resonance spectroscopy. Neurosci Lett 2012;520:192-6.
11. Petrou M, Harris RE, Foerster BR, McLean SA, Sen A, Clauw DJ, et al. Proton MR spectroscopy in the evaluation of cerebral metabolism in patients with fibromyalgia: comparison with healthy controls and correlation with symptom severity. AJNR Am J Neuroradiol 2008;29:913-8.
12. Rango M, Cogiamanian F, Marceglia S, Barberis B, Arighi A, Biondetti P, et al. Myoinositol content in the human brain is modified by transcranial direct current stimulation in a matter of minutes: a 1H-MRS study. Magn Reson Med 2008;60:782-9.
13. Simis M, Reidler JS, Duarte MD, Moreno D, I, Wang X, Lenkinski R, et al. Investigation of central nervous system dysfunction in chronic pelvic pain using magnetic resonance spectroscopy and noninvasive brain stimulation. Pain Pract 2015;15:423-32.
14. Auvichayapat P, Aree-uea B, Auvichayapat N, Phuttharak W, Janyacharoen T, Tunkamnerdthai O, et al. Transient Changes in Brain Metabolites after transcranial direct current stimulation in spastic cerebral palsy: A pilot study. Front Neurol 2017;8:366.
15. Widerström-Noga E, Cruz-Almeida Y, Felix ER, Pattany PM. Somatosensory phenotype is associated with thalamic metabolites and pain intensity after spinal cord injury. Pain 2015;156:166-74.
16. Brand A, Richter-Landsberg C, Leibfritz D. Multinuclear NMR studies on the energy metabolism of glial and neuronal cells. Dev Neurosci 1993;15:289-98.
17. Fisher SK, Novak JE, Agranoff BW. Inositol and higher inositol phosphates in neural tissues: homeostasis, metabolism and functional significance. J Neurochem 2002;82:736-54.
18. Ardolino G, Bossi B, Barbieri S, Priori A. Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. J Physiol 2005;568:653-63.
19. Ramadan S, Lin A, Stanwell P. Glutamate and glutamine: a review of in vivo MRS in the human brain. NMR Biomed 2013;26:1630-46.
20. Ab Aziz CB, Ahmad AH. The role of the thalamus in modulating pain. Malays J Med Sci 2006;13:11-8.
21. Feraco P, Bacci A, Pedrabissi F, Passamonti

L, Zampogna G, Pedrabissi F, et al. Metabolic abnormalities in pain-processing regions of patients with fibromyalgia: a 3T MR spectroscopy study. AJNR Am J Neuroradiol 2011;32:1585-90.
22. Valdés M, Collado A, Bargalló N, Vázquez M, Rami L, Gómez E, et al. Increased glutamate/glutamine compounds in the brains of patients with fibromyalgia: a magnetic resonance spectroscopy study. Arthritis Rheum 2010;62:1829-36.
23. Foerster BR, Nascimento TD, DeBoer M, Bender MA, Rice IC, Truong DQ, et al. Excitatory and inhibitory brain metabolites as targets of motor cortex transcranial direct current stimulation therapy and predictors of its efficacy in fibromyalgia. Arthritis Rheumatol 2015;67:576-81.
24. Harris RE, Napadow V, Huggins JP, Pauer L, Kim J, Hampson J, et al. Pregabalin rectifies aberrant brain chemistry, connectivity, and functional response in chronic pain patients. Anesthesiology 2013;119:1453-64.
25. Verma A, Kumar I, Verma N, Aggarwal P, Ojha R. Magnetic resonance spectroscopy - Revisiting the biochemical and molecular milieu of brain tumors. BBA Clin 2016;5:170-8.
26. Rigotti DJ, Inglese M, Gonen O. Whole-brain N-acetylaspartate as a surrogate marker of neuronal damage in diffuse neurologic disorders. AJNR Am J Neuroradiol 2007;28:1843-9.
27. Gonen O, Catalaa I, Babb JS, Ge Y, Mannon LJ, Kolson DL, et al. Total brain N-acetylaspartate: a new measure of disease load in MS. Neurology 2000;54:15-9.
28. Shigemura T, Kishida S, Eguchi Y, Ohtori S, Nakamura J, Kojima M, et al. Proton magnetic resonance spectroscopy of the thalamus in patients with osteoarthritis of the hip. Bone Joint Res 2012;1:8-12.
29. Yabuki S, Konno S, Kikuchi S. Assessment of pain due to lumbar spine diseases using MR spectroscopy: a preliminary report. J Orthop Sci 2013;18:363-8.
30. Castillo M, Kwock L, Mukherji SK. Clinical applications of proton MR spectroscopy. AJNR Am J Neuroradiol 1996;17:1-15.
31. Chang L, McBride D, Miller BL, Cornford M, Booth RA, Buchthal SD, et al. Localized in vivo 1H magnetic resonance spectroscopy and in vitro analyses of heterogeneous brain tumors. J Neuroimaging 1995;5:157-63.
32. Widerström-Noga E, Pattany PM, Cruz-Almeida Y, Felix ER, Perez S, Cardenas DD, et al. Metabolite concentrations in the anterior cingulate cortex predict high neuropathic pain impact after spinal cord injury. Pain 2013;154:204-12.
33. Grachev ID, Fredrickson BE, Apkarian AV. Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study. Pain 2000;89:7-18.