Vol. 22, e220001 (2025)
doi: 10.2142/biophysico.bppb-v22.0001

Biophysics and Physicobiology
https://www.jstage.jst.go.jp/browse/biophysico/

Regular Article

Near-infrared spectroscopic study of blood flow changes in the dorsolateral prefrontal cortex during pain relief by odor stimulation

Yuki Okamura[1], Shogo Takayama[1], Kengo Namiki[1], Fusako Koshikawa[2], Etsuro Ito[1]

[1] *Department of Biology, Waseda University, Tokyo 162-8480, Japan*
[2] *Department of Psychology, Waseda University, Tokyo 162-8644, Japan*

Received July 26, 2024; Accepted December 24, 2024;
Released online in J-STAGE as advance publication December 26, 2024
Edited by Suguru Kawato

Chronic pain is an unpleasant experience caused by sensory and emotional instability, sometimes independent of actual tissue damage. Pain relief can greatly impact psychologic, social, and economic well-being. Aromatherapy has long been used to alleviate pain and previous studies demonstrated that odors alter cerebral blood flow. In the present study, we used near-infrared spectroscopy to test our hypothesis that olfactory stimulation contributes to pain relief by altering cerebral blood flow in brain regions associated with pain. Pain was induced by transcutaneous electrical stimulation and assessed using a visual analog scale. Peppermint and lavender olfactory stimuli were used. Based on previous results, we focused on the prefrontal cortex. A placebo experiment in which only air stimulation was presented revealed minimal changes in blood flow in the ventromedial prefrontal cortex when comparing pain stimulation alone and a combination of placebo and pain stimulation. We then examined changes in blood flow following the presentation of peppermint or lavender scents. Significant differences in blood flow were observed in the dorsolateral prefrontal cortex (DLPFC) between pain stimulation alone and pain stimulation combined with odor stimulation. These findings supported our previous finding that the DLPFC is involved in pain relief by patch-adhered stimulation, but odor stimulation activated the right DLPFC whereas patch-adhered stimulation suppressed the left DLPFC. One interpretation of the discrepancy is that the contrast of activation between the right and left DLPFC is important in pain relief. Our research will help to elucidate the neurologic mechanisms underlying pain relief.

Key words: lavender, peppermint, placebo, transcutaneous electrical stimulation, visual analog scale

Significance

Pain relief improves the quality of life for patients suffering from pain. Odor stimulation has the potential to alleviate pain. We used near-infrared spectroscopy to explore the areas of the brain that change when pain is relieved. Pain relief was observed when a peppermint or lavender scent was presented, and cerebral blood flow changes in areas of the prefrontal cortex were observed during pain relief. Our research will help to elucidate the neural mechanisms underlying pain relief.

Introduction

Pain is a major stressor for the body and mind, and a social and ecologic problem because it significantly reduces the quality of life. Therefore, pain relief is of great importance. Current mainstream methods for pain relief include the

Corresponding author: Etsuro Ito, Department of Biology, Waseda University, Tokyo 162-8480, Japan. ORCID iD: https://orcid.org/0000-0002-1877-6566, e-mail: eito@waseda.jp

administration of analgesics and transcranial magnetic stimulation (TMS). Administration of analgesics, referred to as painkillers, is currently the most common treatment for relieving pain, but side effects such as stomach pain and headaches can occur with continued use [1,2]. TMS, used to treat chronic pain [3], instantly changes the magnetic field to create a weak current in the brain that stimulates nerve cell axons. Targeted TMS changes blood flow in the dorsolateral prefrontal cortex (DLPFC), a region of the brain involved in pain relief [4–6]. TMS may also cause side effects, however, such as headaches, facial spasms, discomfort, and nausea [7]. In addition, as TMS requires very expensive equipment, the cost of treatment is high [8]. Due to these disadvantages of the current mainstream pain relief methods, other treatments are strongly desired.

Recent studies searching for alternative pain relief methods demonstrated that the application of pyramidal thorn patches alleviates somatic pain [9–11]. Applying these patches to pain regions decreases the pain induced by transcutaneous electrical stimulation (TCES) as assessed with a visual analog scale (VAS). Near-infrared spectroscopy (NIRS) measurements during patch treatment revealed that oxygenated hemoglobin (oxyHb) levels were likely to be decreased in the left DLPFC (lDLPFC), suggesting that the lDLPFC is a potential target brain region for pain relief therapy.

Odor stimulation, or aromatherapy, has long been used to provide pain relief [12,13]. Aromatherapy is considered safe because it primarily stimulates the human sense of smell and there are no adverse side effects. In addition, odor stimulation is inexpensive, making it potentially superior to the current mainstream methods of pain relief therapy. Clarifying whether odor stimulation effectively targets areas of the brain affected by other established pain relief treatments is expected to help elucidate the mechanisms underlying pain relief.

NIRS studies have provided insight into olfactory perception in humans [14]. Odor stimulation, such as by peppermint and lavender scents, alters cerebral blood flow and affects the physiologic state [15,16]. Whether odor stimulation targeting pain relief alters blood flow in regions of the brain associated with pain relief, including the DLPFC, however, is unclear. Therefore, we evaluated changes in cerebral blood flow and pain when peppermint and lavender scents were presented as pain relief treatments. In addition, we examined whether the pain relief was directly related to the participant's perception of the odor (placebo effect). By comparing the results following the presentation of peppermint and lavender scents with those following the presentation of odorless air, we expected to more clearly define the relationship between olfactory stimulation and pain relief.

The present study investigated whether odor stimulation induces pain relief and, if so, whether it also alters blood flow in areas known to be involved in pain relief, such as the DLPFC.

Materials and methods

Ethics statement

The present study was carried out in accordance with the recommendations of the principles and guidelines of the Declaration of Helsinki. All participants provided written informed consent to participate after they were informed of the safety of NIRS and the purpose of the experiments. The protocol was approved by the Office of Research Ethics at Waseda University (2021-018 and 2023-057).

Participants

Data from 20 volunteer participants (right-hand dominant, ages 21–24 years) were available for analysis, including 13 men and 10 women. The participants were from the Tokyo area in Japan and self-reported experiencing no pain.

Pain stimulation

TCES (Pain Vision, PS 2100, NIPRO, Osaka, Japan) was used for pain stimulation because the 'pain degree' can be calculated from the current perception threshold, which was defined as the lowest electrical current detected by each participant [11]. TCES stimulation was performed near the cubital fossa on the right forearm. The minimum sensory threshold was measured for each participant, and a current with a pain level of 500 was applied as the pain stimulus.

Pain measurement

A VAS was used as the pain rating scale to measure the intensity of pain. The amount of pain experienced by a participant falls along a continuum from none to an extreme amount of pain. From the participant's perspective, this spectrum appears continuous, as a categorization of none, mild, moderate, and severe would suggest. The VAS used in the present study was a straight horizontal line of fixed length, 100 mm. The ends are defined as the extreme limits of the parameter to be measured, oriented from left (worst) to right (best).

Odor stimulation

Peppermint and lavender scents were used as odor stimuli. These are essential oils (TREE OF LIFE Co., Ltd., Tokyo, Japan). A 0.1-mL aliquot was dispensed into a 1.5-mL tube and the top of the open tube was placed 5 cm from the

participants' nostrils for 60 s. For placebo stimulation, we used an empty 1.5-mL tube.

NIRS oxyhemoglobin measurements

NIRS (ETG-4000/OT-R40, Fujifilm Healthcare Systems Corporation, Tokyo, Japan) was used to measure the relative concentration of oxyHb flow over the prefrontal cortex, including the DLPFC and orbitofrontal cortex (OFC) (Figure 1) [17]. NIRS experiments were conducted in a quiet room at a room temperature of 22–23˚C. Participants wore earphones and were exposed to environmental sounds (the sound of a babbling river and chirping birds) to promote relaxation and psychologic equilibrium. Participants were given instructions to rest, close their eyes, and remain awake.

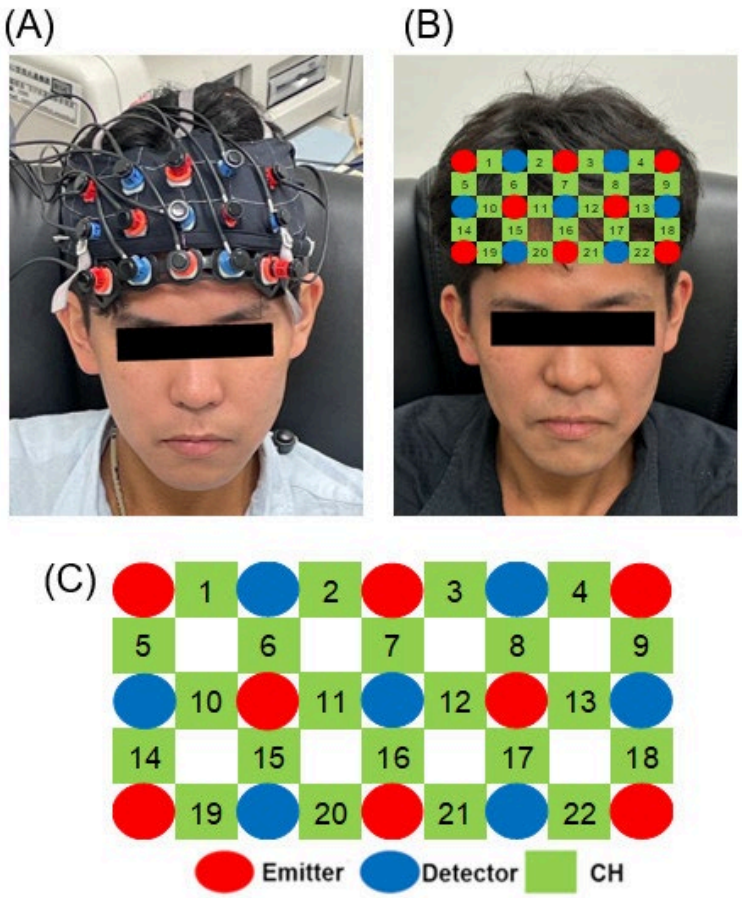

Figure 1 Near-infrared spectroscopy (NIRS) optodes. (A) Picture of a typical participant equipped with NIRS optodes. (B) and (C) The NIRS comprised 8 elements for the NIR light emitter (red) and 7 elements for the detector (blue). The numbers indicate the channels (green) recorded. The NIRS channels were placed above the dorsolateral prefrontal cortex and the orbitofrontal cortex. The channels between the optodes measured on the skull were assigned to the brain regions using the virtual registration method.

Details of NIRS measurements were described previously [17]. Briefly, the NIRS optodes were placed in the proper position for each participant according to the international 10–20 system [18]. According to the atlas by Talairach and Tournoux [19], the dorsomedial prefrontal cortex (DMPFC) was covered by Ch. 2, 3, 7, 11, and 12; the ventromedial prefrontal cortex (VMPFC) was covered by Ch. 16; the left DLPFC (lDLPFC) was covered by Ch. 4, 8, 9, 13, 17, and 18; the right DLPFC (rDLPFC) was covered by Ch. 1, 5, 6, 10, 14, and15; the left OFC (lOFC) was covered by Ch. 21 and 22; and the right OFC (rOFC) was covered by Ch. 19 and 20. The ventrolateral prefrontal cortex (VLPFC) was not measured. Absorption of NIR light is caused by oxyHb and deoxygenated hemoglobin (deoxyHb). Although they have different absorption spectra, the isosbestic point is around 805 nm. Therefore, it is possible to calculate the concentration change of oxyHb and deoxyHb by measuring the absorbance change at 2 wavelengths (780 nm and 830 nm), taking into account the molar molecular extinction coefficients of oxyHb and deoxyHb. We analyzed oxyHb in our experiments to calculate the area under the curve (AUC).

Experimental procedure

The pain and odor experiments were conducted over 3 days using 3 different odor stimulations (placebo, peppermint, and lavender) That is, one odor stimulus was used per day. First, the NIRS optodes were attached to the scalp. Next, the minimum sensory threshold was measured using 3 TCES, and the mean value was calculated. NIRS and VAS measurements were conducted 3 times for each odor (Figure 2A). NIRS and VAS measurements were then conducted 3 times for each odor as shown in Figure 2B. When the "pain only" stimulus is presented first in an experiment, as shown in Figure 2A, participants may become accustomed to the pain. Therefore, we also collected data from an experiment in which the odor was presented first (Figure 2B). The interval between the two procedures was 30 s. The average values of the AUC of pain only and the average values of the AUC of odor + pain shown in Figure 2A and B were used in the subsequent analyses.

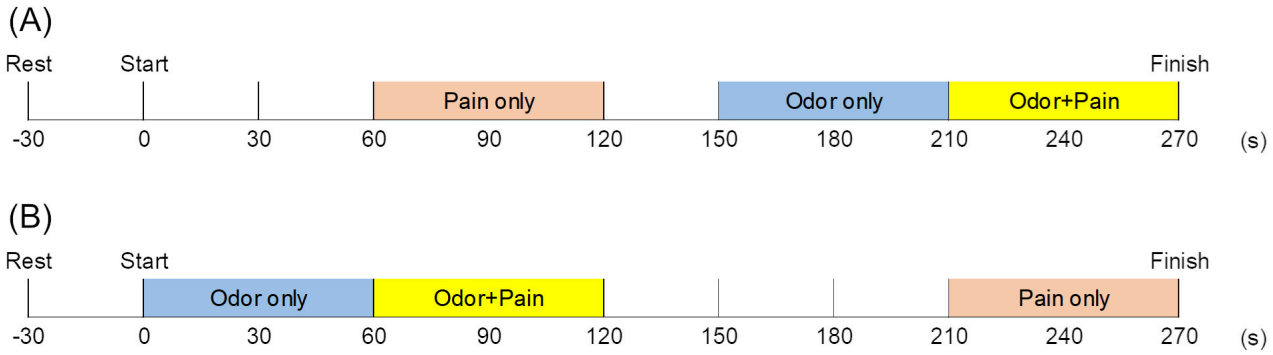

Figure 2 Time flow of pain and odor experiments. (A) Experimental procedure in which the pain stimulus is presented first. Participants were seated in a chair and resting, and 60 s after starting NIRS measurements, a TCES current was applied as a pain stimulus for 60 s. After 30 s, the participants were exposed to an odor for 60 s, and then an electrical current as a pain stimulus was applied again along with the odor. This sequence comprised 1 experiment, and the experiment was conducted 3 times. The mean value of the AUC of the NIRS oxyHb data was determined. (B) Experimental procedure in which the odor exposure was administered first. In both (A) and (B), there was a 90-s interval between pain stimuli to allow for sufficient recovery of the participants. To avoid habituation to the pain stimuli, both experiments (A) and (B) were performed and the mean values were used.

NIRS data analysis

The NIRS data were analyzed with R (version 4.2.1; https://www.r-project.org/). The sampling rate of the NIRS was 10 Hz. All NIRS data were processed using high band-pass (0.01 Hz) and low band-pass (1 Hz) filters to remove artifacts, such as heartbeat and body movements. An AUC of oxyHb was obtained for the NIRS data. The NIRS data were averaged using a moving average, and the values of the 3 trials were averaged.

Statistics

A P value of 0.05 was considered significant. For the VAS values and NIRS data, a Wilcoxon signed rank sum test was used. For examination of correlation, a ϕ coefficient was obtained and a P value was calculated by Fisher's exact probability test in R (version 4.3.2).

Results

Odor-induced pain relief (VAS measurements)

First, pain relief was measured using a VAS when pain relief treatment was presented using odorless air, ie, placebo (Figure 3A). A Wilcoxon signed rank test showed no significant difference (P = 0.193, N = 20), although 11 of 20 participants reported reduced pain levels. After presentation of the peppermint scent, 15 of 20 participants reported a decrease in the pain intensity (P = 0.041, Figure 3B). After presentation of the lavender scent, 15 of 20 participants showed a decrease in pain intensity, but the Wilcoxon signed rank test revealed no significant difference (P = 0.084, Figure 3C). One participant disliked the lavender odor [16]; therefore, we removed the data of this participant from Figure 3C and the Wilcoxon signed rank test revealed a significant difference (P = 0.029, N = 19; Figure 3D).

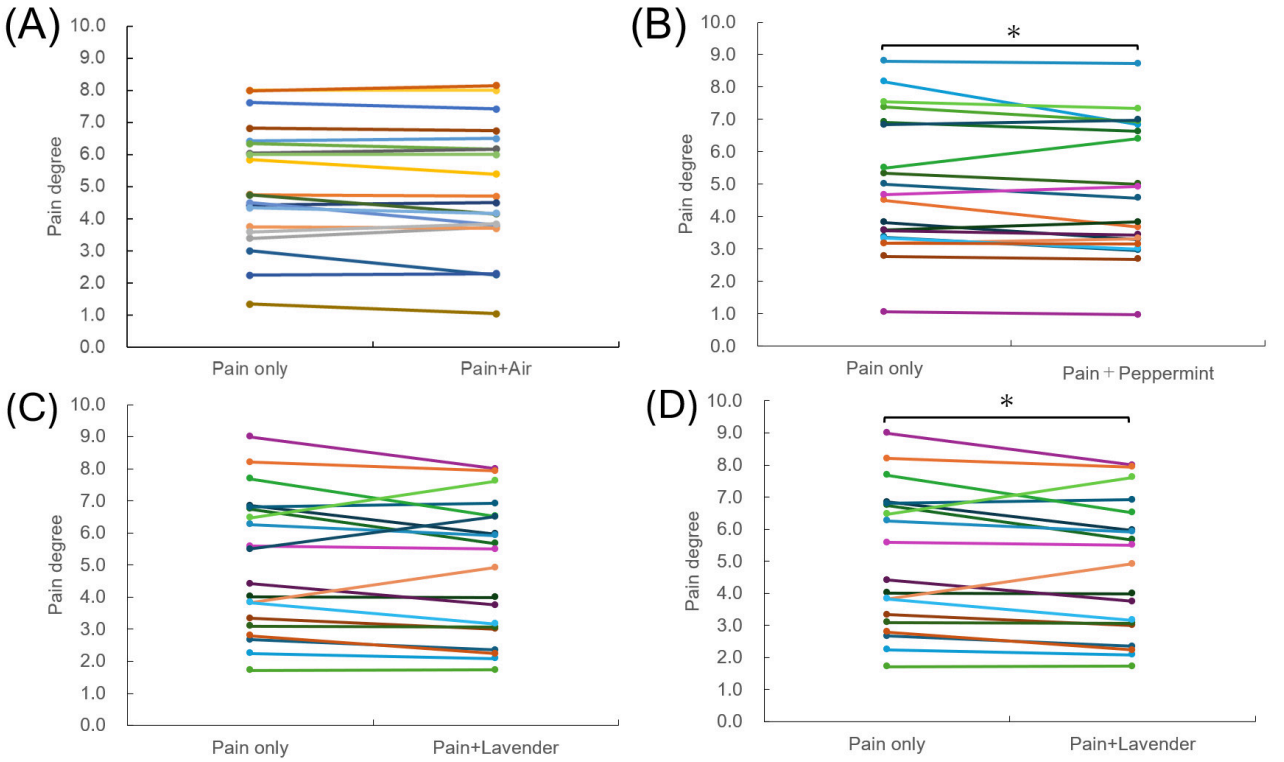

Figure 3 Changes in VAS values (pain degree) by odor stimulation. (A) Placebo (air puff). $P = 0.193$. N = 20. (B) Peppermint. $P = 0.041$. N = 20. (C) Lavender. $P = 0.084$. N = 20. (D) Lavender. Data from (C) excluding one participant who disliked lavender. $P = 0.029$. N = 19.

Odor-induced NIRS oxyhemoglobin changes

When pain relief treatment was presented using odorless air (placebo), a change in the oxyHb concentration was measured using NIRS, and a Wilcoxon signed rank test was performed to compare "pain only" and "pain + air". Cerebral blood flow was significantly increased in Ch. 16 (ie, VMPFC) (Figure 4A). For this channel, the AUC change was obtained as $P = 0.036$ for Ch. 16 (Figure 4B).

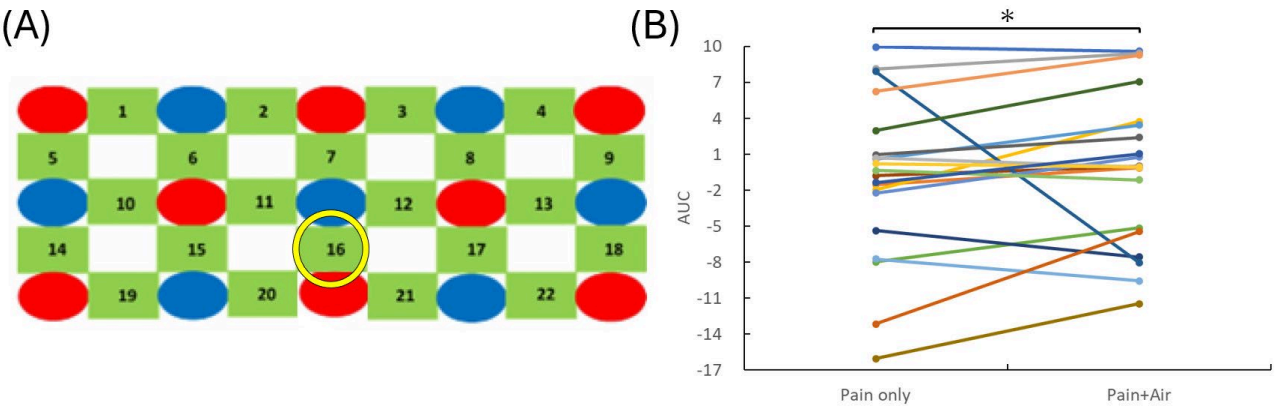

Figure 4 Changes in cerebral blood flow by placebo stimulation. (A) NIRS channels. Yellow circle indicates the channel showing the changes in cerebral blood flow. (B) Ch16. Placebo stimulation increased blood flow ($P = 0.036$).

When pain relief treatment was performed with peppermint, changes in the oxyHb concentration were measured using NIRS, and a Wilcoxon signed rank test was performed to compare “pain only” and “pain + peppermint”. Cerebral blood flow significantly increased in Ch. 15 (ie, rDLPFC) and Ch. 16 (ie, VMPFC) (Figure 5A). The changes in cerebral blood flow were significant in Ch. 15 ($P = 0.033$, Figure 5B) and Ch. 16 ($P = 0.003$, Figure 5C).

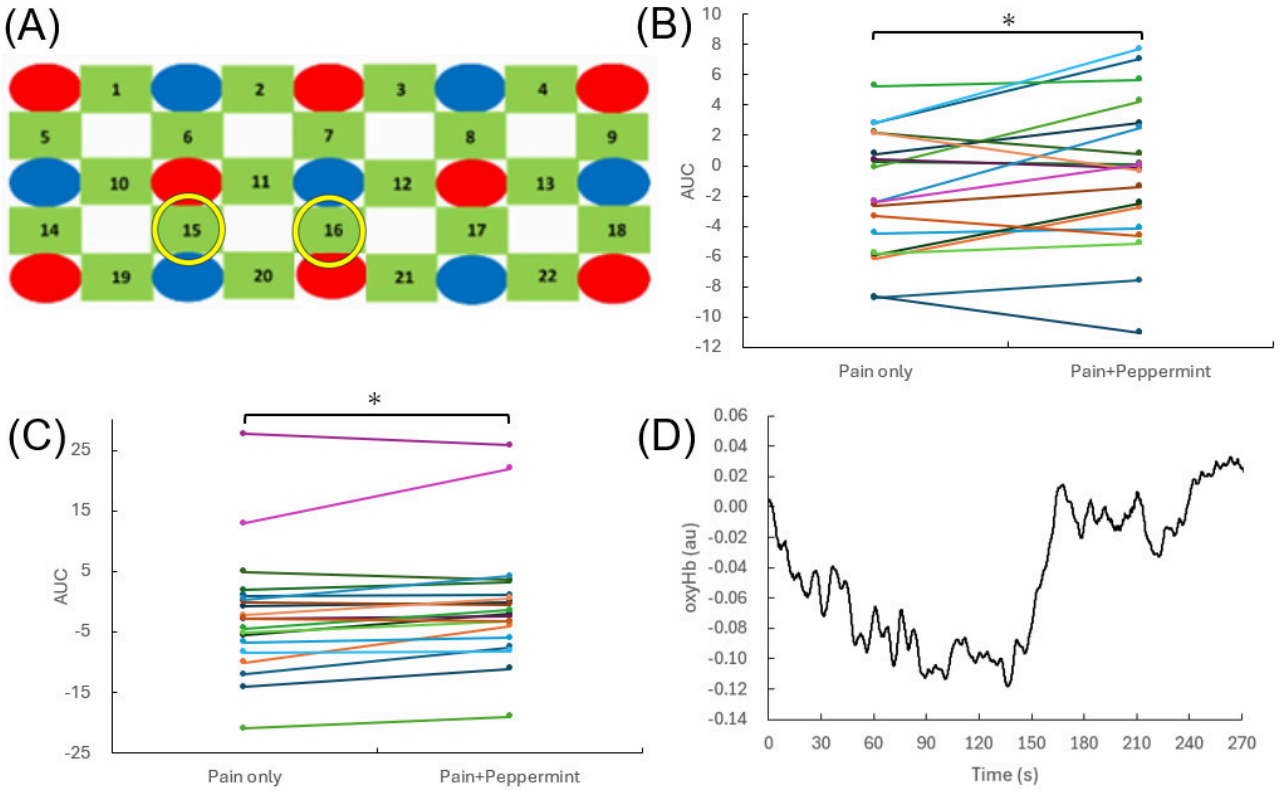

Figure 5 Changes in cerebral blood flow by peppermint stimulation. (A) NIRS channels. Yellow circles indicate the channels showing the changes in cerebral blood flow. (B) Ch. 15. Peppermint stimulation increased blood flow ($P = 0.033$). (C) Ch. 16. $P = 0.003$. (D) Typical change in oxyHb level (ie, raw NIRS data) in Ch 15 of a participant. The vertical axis is the oxyHb level expressed in an arbitrary unit, and the horizontal axis is time (s). Only electrical stimulation was applied for 60–120 s, only peppermint stimulation was applied for 150–210 s, and both electrical and peppermint stimulation were applied for 210–270 s.

When pain relief treatment was performed with lavender, changes in the oxyHb concentration were measured using NIRS, and a Wilcoxon signed rank test was performed to compare “pain only” and “pain + lavender” (Figure 6A). Cerebral blood flow significantly increased in Ch. 1 (ie, rDLPFC; $P = 0.049$, Figure 6B), Ch. 7 (ie, DMPFC; $P = 0.020$, Figure 6C), Ch. 15 (ie, rDLPFC; $P = 0.049$, Figure 6D), Ch. 19 (ie, rOFC; $P = 0.045$, Figure 6E), and Ch. 22 (ie, lOFC; $P = 0.049$, Figure 6F)

Ch. 15 is a rDLPFC channel where blood flow increased when stimulated with peppermint and lavender, when looking at the average value across all participants. However, an increase in blood flow with peppermint does not necessarily mean an increase with lavender ($r = 0.190$, $P = 0.613$) for an individual participant. In other words, there was no correlation between peppermint and lavender stimulation in Ch. 15 for individual participants.

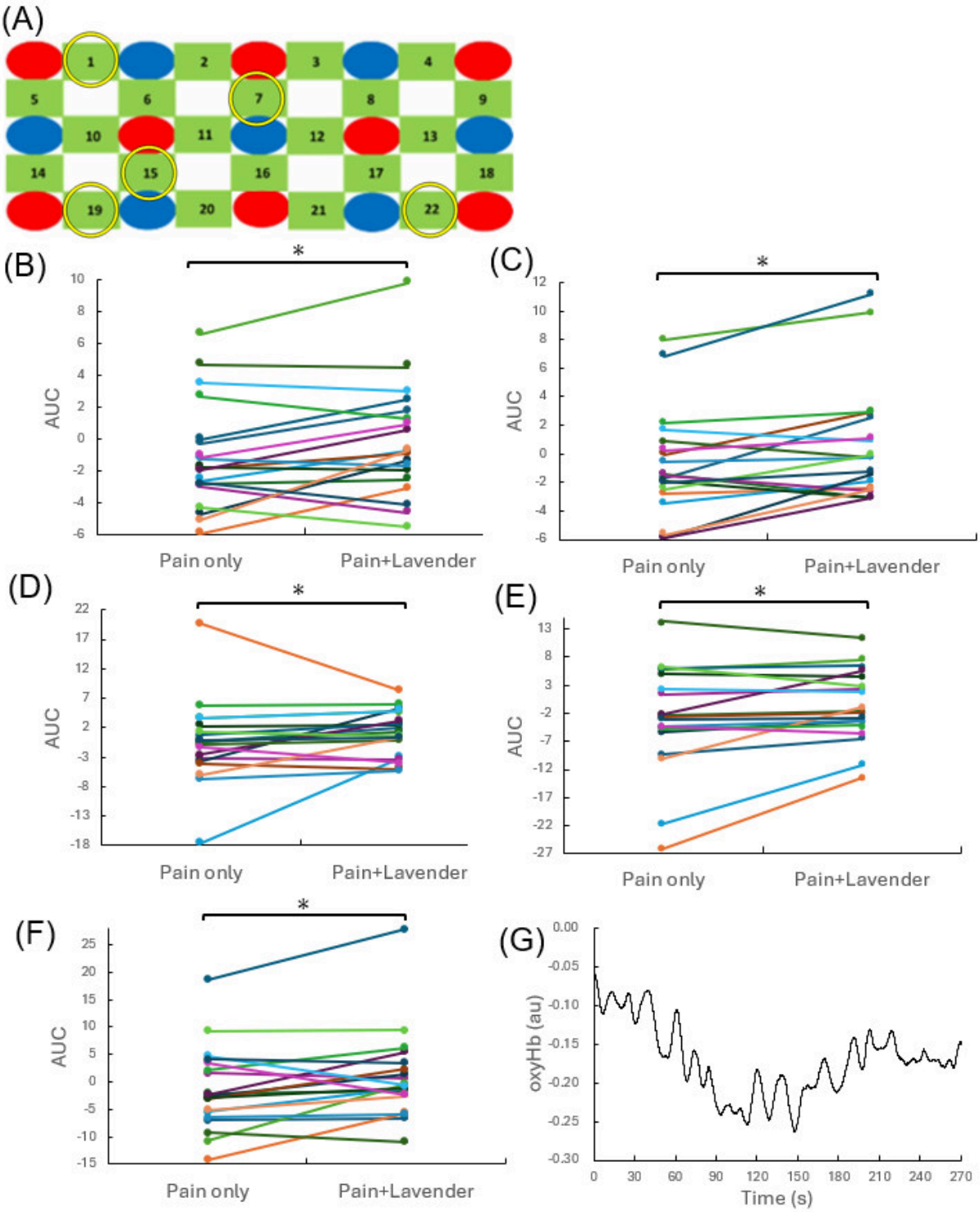

Figure 6 Changes in cerebral blood flow by lavender stimulation. Data for one participant who disliked the lavender scent were excluded. (A) NIRS channels. Yellow circles indicate the channels showing the changes in cerebral blood flow. (B) Ch1. Lavender stimulation increased blood flow (P = 0.049). (C) Ch7. P = 0.020. (D) Ch15. P = 0.049. (E) Ch19. P = 0.045. (F) Ch22. P = 0.049. (G) Typical change in oxyHb level (ie, raw NIRS data) in Ch 15 of a participant. The vertical axis is the oxyHb level expressed in an arbitrary unit, and the horizontal axis is time (s). Only electrical stimulation was applied for 60–120 s, only lavender stimulation was applied for 150–210 s, and both electrical and peppermint stimulation were applied for 210–270 s.

Discussion

Placebo-induced changes in blood flow were observed in Ch16 (VMPFC). Therefore, this channel was excluded from the odor-induced results. Peppermint-induced changes in blood flow were observed in Ch15 (rDLPFC) and Ch16 (VMPFC). Lavender-induced changes in blood flow were observed in Ch1 (rDLPFC), Ch7 (DMPFC), Ch15 (rDLPFC), Ch19 (rOFC), and Ch22 (lOFC). Thus, we concluded that channel 15 (rDLPFC) represents the region where odor-induced pain relief and increases in blood flow occur.

When pain was relieved by the patch-adhered stimulation in our previous study (11), cerebral blood flow in the lDLPFC was decreased. In contrast, the present experiments revealed that cerebral blood flow increased in the rDFPFC. This discrepancy suggests that the contrast between the lDLPFC and rDLPFC is important for pain relief. Differences in the brain regions involved in pain relief may be due to differences in the stimulation methods, but both studies revealed the involvement of the DLPFC. Repeatedly, the relationship between DLPFC and pain processing has been much discussed in the past, and there is no doubt that DLPFC is involved [20]. The issue is the difference in DLPFC function between the left and right sides, but not much research has been done on this topic. Previously, the results using TMS showed that repetitive TMS application to rDLPFC has a selective effect by increasing pain tolerance and also sustains a right hemisphere preference in pain processing [6]. Thus, the selective laterality effect observed during right-side stimulation (in the present case, the right forearm was stimulated) may be explained according to the suggestion that the right hemisphere is dominant for pain processing.

The brain regions activated/inactivated in association with pain relief are an important area of study in neuroscience [21]. Recent publications reported a relationship between pain/pain relief and an activation change in the DLPFC [22], especially by analgesic treatments with repeated transcranial magnetic stimulation and transcranial direct or alternating current stimulation [23–26]. One study evaluating electronic wrist-ankle acupuncture showed an analgesic effect accompanied by inactivation of the DLPFC [27]. Mindfulness meditation is another well-known complementary and integrative approach for achieving pain relief. The relationship between pain relief due to mindfulness meditation and changes in brain regions, including the DLPFC, is well examined [28]. A recent study, however, suggested that DLPFC neuromodulation may attenuate or enhance the expression of placebo-induced analgesia, including an individual's prior experience and expectations of improvement [29]. Thus, the function of DLPFC in pain relief requires further examination.

The effects of peppermint and lavender scents on pain relief have gained attraction in the field of aromatherapy. Khalaf et al. showed that peppermint oil tablets improved symptoms such as difficulty swallowing and non-cardiac chest pain [30]. Sassanejad et al. found that stimulation using a lavender scent effectively decreased the severity of migraine headache symptoms [31]. Stimulation using lavender may help treat pain in children; children who inhaled the scent of lavender were able to reduce their daily dose of acetaminophen post-tonsillectomy [32]. Silva and colleagues found that lavender essential oil can be an effective pain reliever and anti-inflammatory [33]; the topical application of diluted lavender essential oil to rats in a formalin-induced pain test provided pain relief comparable to that of the prescription medication tramadol. Together these findings suggest that lavender could be used to help treat pain and any associated inflammation. While many studies have investigated the effects of odor stimuli on pain relief, few studies have investigated the brain mechanisms underlying these effects.

So what is the effect of an external stimulus (in this case, an odor stimulus) on the brain? It has been shown that TMS stimulation releases endogenous opioids in the prefrontal cortex that have the effect of causing pain relief [34]. Interestingly, placebo analgesia is also thought to produce an actual antinociceptive effect through the release of endogenous opioids [34]. Therefore, the difference between pain-relieving stimuli and placebo stimuli may simply be the difference in the amount of endogenous opioids secreted. Thus, it may be that odor stimuli also release endogenous opioids in the same way, but the details are currently unknown.

Oxytocin has many interesting physical and psychologic effects regarding pain relief [35], and may at least partially underlie the effects of odor on pain relief. We hypothesized that oxytocin secretion is increased during pain relief [9], but the molecular and cellular mechanisms of pain relief by oxytocin are not yet established because of its complicated effects [36,37]. In the central nervous system, oxytocinergic antinociception is thought to be mediated by GABAergic interneurons that inhibit the primary nociceptive inputs conveyed by Aδ and C fibers to the spinal cord [38,39]. Oxytocin broadly affects DLPFC function. For example, in trauma-exposed war veterans, oxytocin significantly attenuated aberrant alpha activity in the lDLPFC, which is thought to be involved in working memory and cognitive control [40]. In addition, individuals with post-traumatic stress disorder who were treated with nasal oxytocin spray performed well on a 2-back task, and the connectivity between the DLPFC and anterior cingulate was increased during the 2-back task [41]. The anterior cingulate is involved in various functions, such as attention allocation, reward anticipation, decision-making, ethics and morality, impulse control, and emotion. Oxytocin modulates the effective connectivity between the precuneus and the lDLPFC, which controls social cognition [42]. The precuneus is involved in egocentric mental imagery strategies and in the successful retrieval of episodic memories. On the other hand, significantly increased oxytocin receptor mRNA levels were observed in the DLPFC in human postmortem brain tissue from patients with depressive or bipolar disorders

[41,43]. Although the relationship between the function of oxytocin in the DLPFC and pain relief has not yet been clarified, the actions of oxytocin in the DLPFC appear to be a key factor in pain relief.

According to conventional textbooks, oxytocin is synthesized in neurosecretory cells in the paraventricular and supraoptic nuclei of the hypothalamus, and secreted from the posterior pituitary [44,45]. Denda and colleagues, however, reported that oxytocin is expressed in keratinocytes [46]. Furthermore, Fujimoto et al. supported this result by showing that oxytocin and neurophysin I are generated in peripheral keratinocytes [47]. Oxytocin and neurophysin I are generated together as cleavage products after splitting the precursor molecule preprooxyphysin. When keratinocytes are stimulated, signals are transmitted to the dorsal root ganglion (DRG) and then to the central nervous system [48]. Some DRG neurons express oxytocin. Therefore, the influence of oxytocin is involved in signal transmission all the way from the input to the central nervous system, especially the DLPFC.

Noguri and colleagues investigated oxytocin and its related receptors in DRG neurons because oxytocin plays a local role in the actions of DRG neurons [49]. They measured the mRNA levels of oxytocin, oxytocin receptor, vasopressin-1a receptor, transient receptor potential cation channel subfamily V member 1 (TRPV1), and piezo-type mechanosensitive ion channel component 2 (Piezo2) in individual DRG neurons and performed a cluster analysis. According to the gene expression patterns, the DRG neurons were classified into 4 clusters: Cluster 1 was mainly characterized by Piezo2, Cluster 2 by TRPV1, and Cluster 4 by oxytocin receptors; neurons in Cluster 3 did not express any of the target genes. The cell body diameter of oxytocin-expressing neurons was significantly larger in Cluster 1 than in Cluster 2. These findings suggest that oxytocin-expressing DRG neurons with small cell bodies (Cluster 2) and large cell bodies (Cluster 1) correspond to C-fiber neurons and Aβ-fiber neurons, respectively. Furthermore, the oxytocin-expressing neurons contained not only TRPV1 but also Piezo2, suggesting that oxytocin may be released by mechanical stimulation independent of nociception. Thus, mechanoreception and nociception themselves may induce the autocrine/paracrine function of oxytocin in the DRG, contributing to pain relief.

Conclusion

The DLPFC is a brain region involved in pain relief, and the relationship between the right and left sides of the DLPFC is a key point. In the present study, activation of the rDLPFC – that is, an increase in blood flow – was observed during pain relief by odor stimulation. A decrease in blood flow to the lDLPFC was previously observed during pain relief induced by applying a patch. The mechanism underlying the difference in activation between the right and left sides of the DLPFC in pain relief requires further investigation.

Conflict of interest

The authors declare no competing interests. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Author contributions

Conceptualization, E.I.; methodology, E.I.; investigation, Y.O., S.T. and K.N.; writing—original draft preparation, Y.O. and E.I.; writing—review and editing, S.T., K.N., and F.K.; project administration, E.I.; funding acquisition, F.K. All authors have read and agreed to the published version of the manuscript.

Data availability

The evidence data generated and/or analyzed during the current study are available from the corresponding author on reasonable request. The R program used for the present data processing is stored in the RforNIRS repository on GitHub (https://github.com/ShogoTKYM/RforNIRS).

Acknowledgements

This work was supported by a Grant-in-Aid [KAKENHI, grant number 19H00633] for Scientific Research (A) from the Japan Society for the Promotion of Science to F.K. The editors of SciTechEdit International LLC (Highlands Ranch, CO, USA) provided editorial support for the production of this manuscript.

References

[1] Coxib and traditional NSAID Trialists' (CNT) Collaboration; Bhala, N., Emberson, J., Merhi, A., Abramson, S.,

Arber, N., Baron, J. A., et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 382, 769–779 (2013). https://doi.org/10.1016/S0140-6736(13)60900-9

[2] Martín Arias, L. H., Martín González, A., Sanz Fadrique, R., Salgueiro Vázquez, E. Gastrointestinal safety of coxibs: systematic review and meta-analysis of observational studies on selective inhibitors of cyclo-oxygenase 2. Fundam. Clin. Pharmacol. 33, 134–147 (2019). https://doi.org/10.1111/fcp.12430

[3] Lefaucheur, J. P., Antal, A., Ahdab, R., Ciampi de Andrade, D., Fregni, F., Khedr, E. M., et al. The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. Brain Stimul. 1, 337–344 (2008). https://doi.org/10.1016/j.brs.2008.07.003

[4] Cao, T. T., Thomson, R. H., Bailey, N. W., Rogasch, N. C., Segrave, R. A., Maller, J. J., et al. A near infra-red study of blood oxygenation changes resulting from high and low frequency repetitive transcranial magnetic stimulation. Brain Stimul. 6, 922–924 (2013). https://doi.org/10.1016/j.brs.2013.04.006

[5] Lefaucheur, J. P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin. Neurophysiol. 125, 2150–2206 (2014). https://doi.org/10.1016/j.clinph.2014.05.021

[6] Graff-Guerrero, A., González-Olvera, J., Fresán, A., Gómez-Martín, D., Méndez-Núñez, J. C., Pellicer, F. Repetitive transcranial magnetic stimulation of dorsolateral prefrontal cortex increases tolerance to human experimental pain. Brain Res. Cogn. Brain Res. 25, 153–160 (2005). https://doi.org/10.1016/j.cogbrainres.2005.05.002

[7] Taylor, R., Galvez, V., Loo, C. Transcranial magnetic stimulation (TMS) safety: A practical guide for psychiatrists. Australas. Psychiatry 26, 189–192 (2018). https://doi.org/10.1177/1039856217748249

[8] Zemplényi, A., Józwiak-Hagymásy, J., Kovács, S., Erdősi, D., Boncz, I., Tényi, T., et al. Repetitive transcranial magnetic stimulation may be a cost-effective alternative to antidepressant therapy after two treatment failures in patients with major depressive disorder. BMC Psychiatry 22, 437 (2022). https://doi.org/10.1186/s12888-022-04078-9

[9] Saito, N., Shima, R., Yamada, Y., Nagaoka, M., Ito, E., Yoshioka, T. A proposed molecular mechanism for physical analgesia in chronic pain. Neural Plast. 2018, 1260285 (2018). https://doi.org/10.1155/2018/1260285

[10] Saito, N., Shima, R., Yen, C. T., Yang, R. C., Ito, E., Yoshioka, T. Adhesive pyramidal thorn patches provide pain relief to athletes. Kaohsiung J. Med. Sci. 35, 230–237 (2019). https://doi.org/10.1002/kjm2.12044

[11] Miyashiro, S., Yamada, Y., Nagaoka, M., Shima, R., Muta, T., Ishikawa, H., et al. Pain relief associated with decreased oxyhemoglobin level in left dorsolateral prefrontal cortex. PLoS One 16, e0256626 (2021). https://doi.org/10.1371/journal.pone.0256626

[12] Lee, H. W., Ang, L., Kim, J. T., Lee, M. S. Aromatherapy for symptom relief in patients with burn: A systematic review and meta-analysis. Medicina 58, 1 (2021). https://doi.org/10.3390/medicina58010001

[13] Izadi, F., Mazhari, S. A., Najafi, M., Ashoobi, M. T., Sarafi, M., Karkhah, S., et al. The effect of aromatherapy with lavender on pain of needle insertion and severity of restless legs syndrome in hemodialysis patients; A systematic review and meta-analysis. Arch. Acad. Emerg. Med. 12, e4 (2023). https://doi.org/10.22037/aaem.v12i1.2071

[14] Gunasekara, N., Gaeta, G., Levy, A., Boot, E., Tachtsidis, I. fNIRS neuroimaging in olfactory research: A systematic literature review. Front. Behav. Neurosci. 16, 1040719 (2022). https://doi.org/10.3389/fnbeh.2022.1040719

[15] Shinno, A., Isawa, M., Itoh, H., Kose, N., Ishino, H., Nishimura, T., et al. Effectiveness of aromatherapy evaluated with subjective and objective cognitive indicators: A clinical trial on young adults using near-infrared spectroscopy. Jpn. J. Pharm. Health Care Sci. 38, 265–271 (2012). https://doi.org/10.5649/jjphcs.38.265

[16] Kouzuma, N., Yamakawa, T. Associations between autonomic nervous system activity, cerebral blood flow, and essential oil preferences across the menstrual cycle. Integr. Med. Rep. 3, 9–18 (2024). http://online.liebertpub.com/doi/10.1089/imr.2023.0032

[17] Miyashiro, S., Yamada, Y., Muta, T., Ishikawa, H., Abe, T., Hori, M., et al. Activation of the orbitofrontal cortex by both meditation and exercise: A near-infrared spectroscopy study. PLoS One 16, e0247685 (2021). https://doi.org/10.1371/journal.pone.0247685

[18] Herwig, U., Satrapi, P., Schönfeldt-Lecuona, C. Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr. 16, 95–99 (2003). https://doi.org/10.1023/B:BRAT.0000006333.93597.9d

[19] Talairach, J., Tournoux, P. Co-planar stereotaxic atlas of the human brain: 3-d proportional system: An approach to cerebral imaging (Thieme Medical Publisher, India, 1988).

[20] Seminowicz, D. A., Moayedi, M. The dorsolateral prefrontal cortex in acute and chronic pain. J. Pain. 18, 1027–1035 (2017). https://doi.org/10.1016/j.jpain.2017.03.008

[21] Ito, E., Oka, K., Koshikawa, F. Dorsolateral prefrontal cortex sensing analgesia. Biophys. Physicobiol. 19, e190014 (2022). https://doi.org/10.2142/biophysico.bppb-v19.0014

[22] Du, J., Shi, P., Fang, F., Yu, H. Cerebral cortical hemodynamic metrics to aid in assessing pain levels? A pilot study of functional near-infrared spectroscopy. Front. Neurosci. 17, 1136820 (2023). https://doi.org/10.3389/fnins.2023.1136820

[23] Che, X., Cash, R. F. H., Luo, X., Luo, H., Lu, X., Xu, F., et al. High-frequency rTMS over the dorsolateral prefrontal cortex on chronic and provoked pain: A systematic review and meta-analysis. Brain Stimul. 14, 1135–1146 (2021). https://doi.org/10.1016/j.brs.2021.07.004

[24] Li, H., Song, Q., Zhang, R., Zhou, Y., Kong, Y. Enhanced temporal coupling between thalamus and dorsolateral prefrontal cortex mediates chronic low back pain and depression. Neural Plast. 2021, 7498714 (2021). https://doi.org/10.1155/2021/7498714

[25] Mohamad Safiai, N. I., Mohamad, N. A., Basri, H., Inche Mat L. N., Hoo, F. K., Abdul Rashid, A. M., et al. High-frequency repetitive transcranial magnetic stimulation at dorsolateral prefrontal cortex for migraine prevention: A protocol for a systematic review of controlled trials. PLoS One 16, e0251528 (2021). https://doi.org/10.1371/journal.pone.0251528

[26] Garcia-Larrea, L., Quesada, C. Cortical stimulation for chronic pain: From anecdote to evidence. Eur. J. Phys. Rehabil. Med. 58, 290–305 (2022). https://doi.org/10.23736/S1973-9087.22.07411-1

[27] Shi, P., Liu, J., Du, J., Yu, H., Fang, F. Pain modulation induced by electronic wrist-ankle acupuncture: A functional near-infrared spectroscopy study. Pain Pract. 22, 182–190 (2022). https://doi.org/10.1111/papr.13076

[28] Seminowicz, D. A., Burrowes, S. A. B., Kearson, A., Zhang, J., Krimmel, S. R., Samawi, L., et al. Enhanced mindfulness-based stress reduction in episodic migraine: A randomized clinical trial with magnetic resonance imaging outcomes. Pain 161, 1837–1846 (2020). https://doi.org/10.1097/j.pain.0000000000001860

[29] Crawford, L. S., Mills, E. P., Peek, A., Macefield, V. G., Keay, K. A., Henderson, L. A. Function and biochemistry of the dorsolateral prefrontal cortex during placebo analgesia: How the certainty of prior experiences shapes endogenous pain relief. Cereb. Cortex. 33, 9822–9834 (2023). https://doi.org/10.1093/cercor/bhad247

[30] Khalaf, M. H. G., Chowdhary, S., Elmunzer, B. J., Elias, P. S., Castell, D. Impact of peppermint therapy on dysphagia and non-cardiac chest pain: A pilot study. Dig. Dis. Sci. 64, 2214–2218 (2019). https://doi.org/10.1007/s10620-019-05523-8

[31] Sasannejad, P., Saeedi, M., Shoeibi, A., Gorji, A., Abbasi, M., Foroughipour, M. Lavender essential oil in the treatment of migraine headache: A placebo-controlled clinical trial. Eur. Neurol. 67, 288–291 (2012). https://doi.org/10.1159/000335249

[32] Soltani, R., Soheilipour, S., Hajhashemi, V., Asghari, G., Bagheri, M., Molavi, M. Evaluation of the effect of aromatherapy with lavender essential oil on post-tonsillectomy pain in pediatric patients: A randomized controlled trial. Int. J. Pediatr. Otorhinolaryngol. 77, 1579–1581 (2013). https://doi.org/10.1016/j.ijporl.2013.07.014

[33] Silva, G. L., Luft, C., Lunardelli, A., Amaral, R. H., Melo, D. A., Donadio, M. V., et al. Antioxidant, analgesic and anti-inflammatory effects of lavender essential oil. An. Acad. Bras. Cienc. 87 (2 Suppl), 1397–1408 (2015). https://doi.org/10.1590/0001-3765201520150056

[34] Martin, L., Borckardt, J. J., Reeves, S. T., Frohman, H., Beam, W., Nahas, Z., et al. A pilot functional MRI study of the effects of prefrontal rTMS on pain perception. Pain Med. 14, 999–1009 (2013). https://doi.org/10.1111/pme.12129

[35] Ito, E., Shima, R., Yoshioka, T. A novel role of oxytocin: Oxytocin-induced well-being in humans. Biophys. Physicobiol. 16, 132–139 (2019). https://doi.org/10.2142/biophysico.16.0_132

[36] Tracy, L. M., Georgiou-Karistianis, N., Gibson, S. J., Giummarra, M. J. Oxytocin and the modulation of pain experience: Implications for chronic pain management. Neurosci. Biobehav. Rev. 55, 53–67 (2015). https://doi.org/10.1016/j.neubiorev.2015.04.013

[37] Grinevich, V., Charlet A. Oxytocin: Pain relief in skin. Pain 158, 2061–2063 (2017). https://doi.org/10.1097/j.pain.0000000000001006

[38] Breton, J. D., Veinante, P., Uhl-Bronner, S., Vergnano, A. M., Freund-Mercier, M. J., Schlichter, R., et al. Oxytocin-induced antinociception in the spinal cord is mediated by a subpopulation of glutamatergic neurons in

lamina I-II which amplify GABAergic inhibition. Mol Pain 4, 19 (2008). https://doi.org/10.1186/1744-8069-4-19

[39] Condés-Lara, M., Rojas-Piloni, G., Martínez-Lorenzana, G., López-Hidalgo, M., Rodríguez-Jiménez, J. Hypothalamospinal oxytocinergic antinociception is mediated by GABAergic and opiate neurons that reduce A-delta and C fiber primary afferent excitation of spinal cord cells. Brain Res. 1247, 38–49 (2009). https://doi.org/10.1016/j.brainres.2008.10.030

[40] Eidelman-Rothman, M., Goldstein, A., Levy, J., Weisman, O., Schneiderman, I., Mankuta, D., et al. Oxytocin affects spontaneous neural oscillations in trauma-exposed war veterans. Front. Behav. Neurosci. 9, 165 (2015). https://doi.org/10.3389/fnbeh.2015.00165

[41] Flanagan, J. C., Hand, A., Jarnecke, A. M., Moran-Santa Maria, M. M., Brady, K. T., Joseph, J. E. Effects of oxytocin on working memory and executive control system connectivity in posttraumatic stress disorder. Exp. Clin. Psychopharmacol. 26, 391–402 (2018). https://doi.org/10.1037/pha0000197

[42] Kumar, J., Iwabuchi, S. J., Völlm, B. A., Palaniyappan, L. Oxytocin modulates the effective connectivity between the precuneus and the dorsolateral prefrontal cortex. Eur. Arch. Psychiatry Clin. Neurosci. 270, 567–576 (2020). https://doi.org/10.1007/s00406-019-00989-z

[43] Lee, M. R., Sheskier, M. B., Farokhnia, M., Feng, N., Marenco, S., Lipska, B. K., et al. Oxytocin receptor mRNA expression in dorsolateral prefrontal cortex in major psychiatric disorders: A human post-mortem study. Psychoneuroendocrinology 96, 143–147 (2018). https://doi.org/10.1016/j.psyneuen.2018.05.039

[44] Dale, H. H. On some physiological actions of ergot. J. Physiol. 34, 163–206 (1906). https://doi.org/10.1113/jphysiol.1906.sp001148

[45] Landgraf, R., Neumann, I. D. Vasopressin and oxytocin release within the brain: A dynamic concept of multiple and variable modes of neuropeptide communication. Front. Neuroendocrinol. 25, 150–176 (2004). https://doi.org/10.1016/j.yfrne.2004.05.001

[46] Denda, S., Takei, K., Kumamoto, J., Goto, M., Tsutsumi, M., Denda, M. Oxytocin is expressed in epidermal keratinocytes and released upon stimulation with adenosine 5'-[γ-thio]triphosphate in vitro. Exp. Dermatol. 21, 535–537 (2012). https://doi.org/10.1111/j.1600-0625.2012.01507.x

[47] Fujimoto, K., Inada, K., Oka, K., Ito, E. Revisiting oxytocin generation in keratinocytes. Biophys. Physicobiol. 20, e200003 (2023). https://doi.org/10.2142/biophysico.bppb-v20.0003

[48] Seto, C., Toyoda, K., Inada, K., Oka, K., Ito, E. Influence of gap junctions upon Ca^{2+} propagation from stimulated keratinocytes to DRG neurons. Biophys. Physicobiol. 19, e190041 (2022). https://doi.org/10.2142/biophysico.bppb-v19.0041

[49] Noguri, T., Hatakeyama, D., Kitahashi, T., Oka, K., Ito, E. Profile of dorsal root ganglion neurons: Study of oxytocin expression. Molec. Brain 15, 44 (2022). https://doi.org/10.1186/s13041-022-00927-6