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Impact of a 12-week olfactory training programme in women with migraine with aura: protocol for a double-blind, randomised, placebo-controlled trial

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ABSTRACT

Introduction Migraine is a leading cause of disability and suffering worldwide. However, conventional pharmacological migraine preventive therapies are often challenging and accompanied by adverse effects. Recently, structured odour exposure has shown to successfully increase pain thresholds in patients with chronic back pain. Despite the importance of the olfactory system in migraine, there are no studies investigating the impact of structured odour exposure in patients with migraine.

Methods and analysis This double-blind randomised placebo-controlled trial will be conducted at the Headache Clinic of the University Pain Center at TU Dresden, Germany and aims at investigating the impact of a 12-week structured exposure to odours in women with migraine. Fifty-four women between 18 and 55 years with migraine with aura will be recruited and randomised to training with odours and odourless training. The primary outcomes are mechanical and electrical pain thresholds. Secondary outcomes comprise olfactory threshold and the number of headache days. Other exploratory measurements are headache associated pain intensity, acute analgesic intake, symptoms of anxiety and depression, and quality of life. Additionally, this protocol assesses neuroanatomical and neurofunctional changes associated with the 12-week olfactory training. Data analysis will be executed on the basis of the general linear model considering repeated measurements.

Ethics and dissemination Ethical approvals were obtained from the Ethics Board of the TU Dresden (Protocol No. BO-EK-353082020). Participation will only be possible after written informed consent is provided. Findings will be disseminated through peer-reviewed journals and scientific conferences.

Trial registration number DRKS00027399.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This double-blind randomised placebo-controlled trial will focus on the impact of a 12-week structured exposure to odours, that is, olfactory training (OT) versus odourless training in female patients with migraine.
⇒ This study protocol seeks to further our understanding regarding the underlying mechanisms behind OT by assessing an array of psychophysical tests and questionnaires in nociception, emotion and cognitive domains.
⇒ Additionally, this study protocol will also adopt a neural mechanistic approach by exploring the neurofunctional changes during olfactory, trigeminal and emotional processing before and after the 12-week OT programme as well as the impact of OT in the olfactory bulb volume.
⇒ As a limitation, this study will not include a healthy control group, OT will be contrasted to odourless training in female patients with migraine and thus migraine specific clinical and neural OT effects will not be explored.

INTRODUCTION

Migraine, a leading cause of suffering and disability worldwide, is a major public health concern predominantly affecting women during the most productive years of life.[1 2] Adult females patients report more frequent, longer lasting and more painful headaches compared with males.[3 4] Besides the heavy individual burden, migraine is also associated with an extensive socioeconomic burden.[5]

Characterised by recurrent intermittent headache episodes, migraine and its associated symptoms can last 4–72 hours. In up to one-third of affected patients, the headache is preceded or accompanied by an aura: visual, sensory, speech or motor disturbances, which can make it even more debilitating.[6] While severe and pulsating headaches are the hallmark of migraine, an important overlooked feature of the disorder is the presence of osmophobia.[7–9] Up to 95% of all migraineurs seem to be affected by osmophobia during and between migraine attacks.[10–13] Odours are known to trigger and aggravate migraine attacks and migraineurs often display altered odour threshold and hypersensitivity to odours.[13–15] Moreover, increased sensitivity

to smell seems to be closely related with migraine chronicity and increased migraine disability.[13 16] Accumulating imaging studies report changes in the olfactory bulb volume in disorders associated with olfactory function.[17–19] Recently, olfactory bulb atrophy has also been observed in migraine patients emphasising the importance of olfaction in migraine.[20]

Aiming at relieving pain and its associated disability, as well as decreasing the frequency and the severity of the attacks, conventional migraine management frequently includes acute and or preventive pharmacological treatments. However, traditional pharmacological migraine therapies are often associated with unsatisfactory efficacy and poor tolerance, which can lead to complications such as medication overuse and low therapeutic compliance.[21] On the other hand, specific novel pharmacological treatments such as calcitonin gene-related peptide (CGRP) and CGRP receptor antibody treatments are restricted due to therapy costs, economic efficiency requirements of the treatment plan and prescribing guidelines.[22] Nowadays, novel pain therapy treatments are increasingly relying on new non-pharmacological therapeutic strategies that might offer promising areas of development.[23–25] Besides its known efficacy in restoring olfactory function, structured exposure to odours has been gradually receiving more attention in pain management.[26] Recent findings suggest that a structured exposure to odours, that is, olfactory training (OT), positively affects the detection of applied painful stimuli by successfully increasing pain thresholds in patients with chronic back pain.[27] The efficacy of structured odour exposure has been also observed in attenuating symptoms of depression, and in improving emotional well-being,[28 29] as well as cognitive performance.[30 31] In healthy participants, OT has also been shown to increase olfactory bulb volumes.[32] However, little is still known about the mechanisms behind these beneficial effects. Indirect hedonic effects on mood and concentration have been discussed as likely candidates and this may be related with the inherent connection between olfactory, limbic and pain structures.[33] Previous functional imaging findings indicate that patients with migraine have a selective differential neural activity to negative pictures,[34] suggesting that migraine sensory hypersensitivity may feature a generalised altered cerebral processing of negative stimuli. When it comes to the success of OT, in pain and migraine related pain, it may be also related to olfactory desensitisation resulting from structured odour exposure. Similarly to depression, olfaction and pain share several intersections at higher central nervous processing levels, including, but not limited to, neuroanatomical communications via insular cortex, cingular gyrus, hippocampus and amygdala, emphasising a mutual interference between pain, emotion and odour perception.[26] Insights into these relations may bring valuable understanding into migraine beneficial treatment options.

Despite the importance that the olfactory system seems to have in migraine pathophysiology, olfaction in migraine patients has received little attention and there are no studies investigating the impact of OT in patients with migraine. This double-blind randomised placebo-controlled trial aims to investigate for the first time the psychophysical and neural impact of a 12-week structured exposure to odours in female patients with migraine with aura. To systematically evaluate the psychophysical impact of OT on experimental pain, this study focuses on mechanical and electrical pain thresholds (EPTs). The clinical relevance of OT on migraine pain, will be assessed by the number of headache days (secondary outcome). Secondary outcomes will also comprise changes in olfactory threshold. Headache-associated pain intensity, acute analgesic intake, symptoms of anxiety and depression, quality of life, and cognitive function are exploratory measurements. Additionally, this study will evaluate the neurofunctional changes during olfactory, trigeminal and emotional stimuli processing before and after the 12-week OT programme as well as the impact of the OT programme on OB volume.

METHODS AND ANALYSIS

Study design, patients and randomisation

This double-blind randomised placebo-controlled trial investigating the clinical and neural effects of a structured exposure to odours in female patients with migraine with aura will be conducted at the Headache Clinic of the University Pain Center at TU Dresden. Using a between-subject design, 54 female patients (age between 18 and 55 years) with diagnosed migraine with aura (according to the international classification of headache disorders, third edition)[35] will be recruited and randomly and blindly allocated to one of the two study arms (ie, 12-week odourless training—sham OT or 12-week training with odours—verum OT) according to an apriori randomisation list generated by an independent member of the clinic using block randomisation in Excel generating the allocation sequence. Patients will be enrolled by GG. Assigning the patients to interventions will follow the randomisation. In the randomisation list, numerical codes are assigned to patients. These number codes are noted on envelopes in which the verum or placebo smelling sticks are presorted, ensuring that the investigator is also blinded.

The first patient was included on 24 January 2022. Data acquisition is planned to be completed by the end of September 2023. Study design is illustrated in figure 1.

Patient or public involvement

Participants' previous experiences with OT[27]were used to improve the OT experience during this study and to improve the design of the study with for example the creation of a credible OT placebo arm. Moreover, in this study, patients will be asked how satisfied they were with the OT; and whether they would recommend the OT to a friend or relative who also suffers from migraine.

Patients eligibility

Patients' selection is based on the following inclusion and exclusion criteria. Female participants meeting the

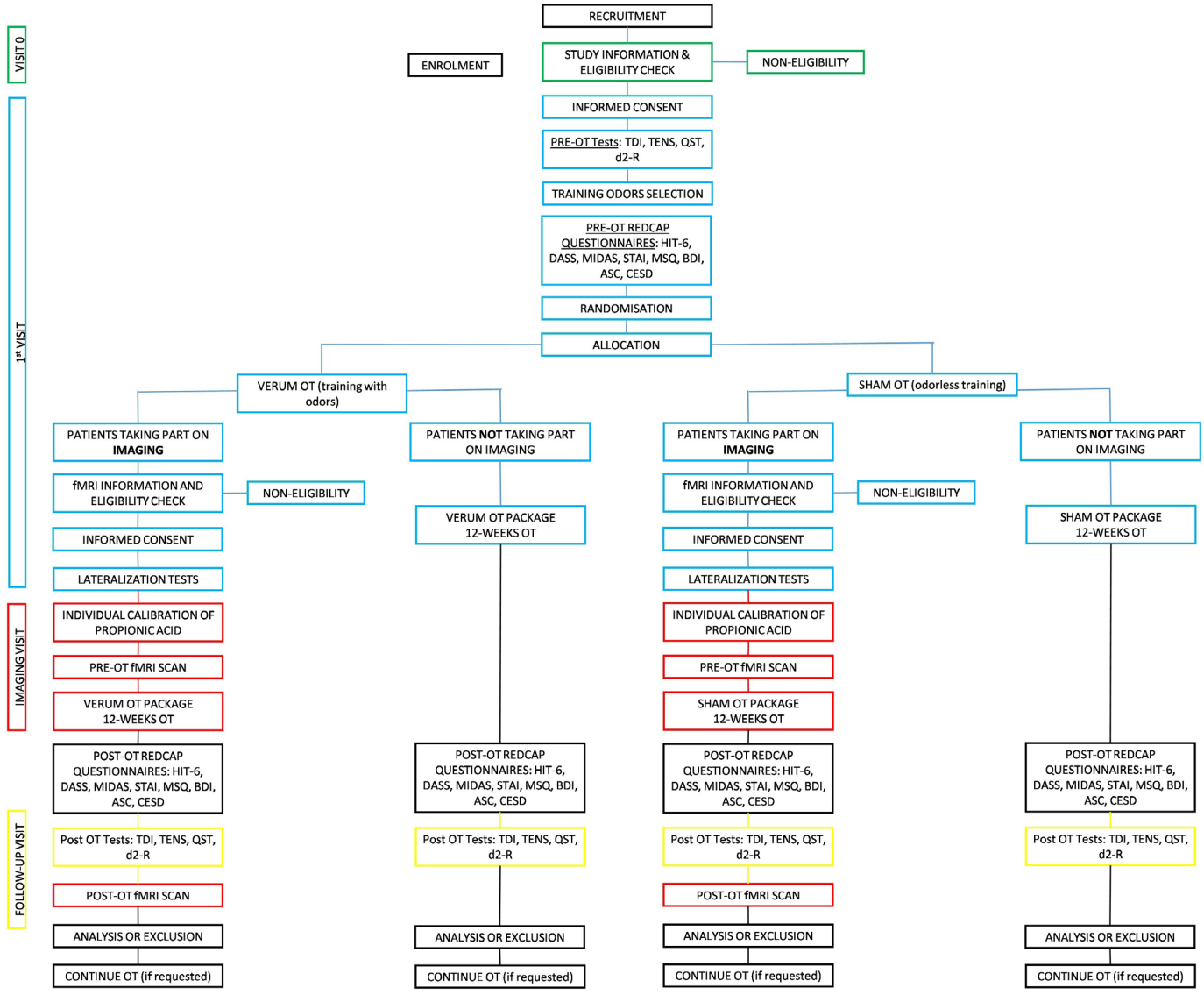

Figure 1 Patient flow diagram and visit schedule. OT, olfactory training; TDI, threshold, discrimination, and identification test; TENS, transcutaneous electrical nerve stimulation; QST, quantitative sensory testing; d2-R, Test of attention; HIT-6, headache impact test; DASS, depression and anxiety stress scale; MIDAS, Migraine disability assessment questionnaire; STAI, state-trait anxiety inventory; MQS, migraine-specific quality of life questionnaire; BDI, Beck's depression inventory; ASC, allodynia symptom checklist; CESD, center for epidemiological studies depression scale; fMRI, functional magnetic resonance imaging; Sham/Verum OT package, will contain four felt-tip pens (verum- training with odors, or sham- Odorless training) an instruction sheet, the headache calendar and the olfactory diary; Lateralization test, used to assess the trigeminal sensitivity.

international classification of Headache disorders (third edition)[35] criteria for episodic migraine with aura as the primary diagnosis will be included (ie, ≥1 migraine episode a month, but <15 headache days a month). Inclusion criteria also entail participants' age, which will range between 18 and 55 years. Additionally, all participants must be normosmic, that is, no olfactory loss (olfactory assessment by means of Sniffin' Sticks battery (Burghart, Germany)[36] the sum score of Threshold, Discrimination, Identification cut-off of 30.75),[37] and free of any acute or chronic sinunasal ailments. When it comes to the use of prophylactic drugs, patients taking stable doses (for at least 3 months) of prophylactic drugs will be included. Regarding acute migraine medication, ≤9 days per month with acute analgesic medication will also be allowed.

Participants will be excluded if they report taking opioids, cannabis, serotonin and norepinephrine reuptake inhibitors, due to the known interference with emotional and sensory perception. Patients will also be excluded if they report taking more than >9 days per month of acute analgesic medication. Pregnancy, significant medical problems such as uncontrolled asthma or seizure disorder, acute cardiac disease, severe and instable psychiatric problems, other chronic pain syndromes, other (non-migraine) neurological diseases or any uncontrolled disease are also part of the exclusion criteria. Patients will also be excluded if there are any

cognitive signs of dementia (evaluated through Montreal Cognitive Assessment).[38] Patients taking part on the MRI session will be scanned during the interictal state. MRI compatibility and eligibility will be assessed by the local MRI technicians.

Recruitment

Participants will be recruited through local advertisements at the University Hospital of Dresden and through public billboards and online platforms such as websites and social networks. Potential participants will be informed that participation is voluntary and withdrawal is possible at any time without further explanations or any associated consequences. Study approvals were obtained from the Ethics Board of the TU Dresden (Protocol No. BO-EK-353082020) which complies with the standards established by the Declaration of Helsinki. Eventual protocol amendments will have to be approved by the ethics board of the TU Dresden. A written informed consent will be obtained from all participants after the nature of the study is explained and the possibility of clarifications is offered by a neurologist (GG). Participation will only be possible after written informed consent is provided (consent form and patient information are provided as online supplemental materials 1 and 2, respectively). Post-trial care will be conducted at the headache outpatient clinic at the University Hospital of Dresden if needed.

Verum and sham OT procedure

During the OT programme, all patients (N=54) will be offered to choose four out of eleven, commercially available, pleasant odours (citronellal: lemon odour (#ABX321602), orange odour (#FJJ232836D) and eugenol: cloves odour (#S0100148), coffee odour (#P0604646), vanilla odour (#DGI178677B), dark chocolate odour (#JVA332845B), strawberry odour (#ABX321354A), apple odour (#P0602153), lavender odour (#DGFLO794), bergamont odour (#A1285) and sage odour (#A1700), presented in felt-tip pens ('sniffin' sticks'), based on their individual preferences. Lemon, orange, vanilla, dark chocolate, strawberry and lavender will be provided by Takasago International Corporation, Japan. Cloves, coffee and apple will be provided by Frey+Lau, Henstedt-Ulzburg, Germany and bergamont and sage by Primavera Life GmbH Oy-Mittelberg, Germany. The chosen odours will be used to perform the daily olfactory exposure. All pens will be labelled with the odour name and patients will be instructed to sniff each pen for 20 s twice a day (during the morning and in the evening). The treatment groups (sham and verum OT) will differ solely with regard to the ingredient contained in the training felt-tip pens given to the participants. Whereas in the verum group, the training pens will contain the active solution previously selected, in the placebo group, the training pens will be filled with a placebo odourless solvent (propylene glycole). To increase the overall compliance and to ascertain that the placebo (odourless) group remains blinded to the treatment allocation, all patients are provided with a cover story. Patients are informed that the training concentrations of the therapy odours are different from the ones that participants have previously smelled in the lab, when choosing the odours. Patients are told that whereas the odours used during the therapy tend to be less strong, and may be insufficiently intense to produce an odour sensation (ie, subliminal odours) they are intense enough to be perceived by the brain and may influence mental processes and behaviour. The training will last for 12 weeks. All participants will receive a phone call by an experimenter every 4 weeks to assess participant's olfactory function and to reinforce compliance with the training programme (reminder of the cover story). After study completion, all participants will be individually contacted and their group allocations will be revealed. All patients will be offered the possibility of performing or continuing a training with odours.

Spontaneously reported adverse events will be collected by VF and JD, assessed and managed by GG, and reported in the results section.

Primary, secondary and exploratory outcomes

All outcome measures will be assessed by a blinded researcher at the pain centre, TU Dresden or self-administered online using REDCap electronic data capture tools hosted at the University Hospital Dresden.[39 40]

Pain thresholds have been previously reported to significantly increase in patients with chronic low back pain after OT.[27] Hence, the primary outcomes that will be used to assess the effects of OT in pain in migraine patients will comprise the observed change (from pre-OT to post-OT) in mechanical pain threshold (MPT) and in EPT, assessed using quantitative sensory testing[41] and transcutaneous electrical nerve stimulation (TENS),[42] respectively. MPT will be carried out on the right forehead with the right volar arm used as reference and will be performed with seven pinpricks, with standardised stimulus intensities (8, 16, 32, 64, 128, 256 and 512 mN) and a flat contact surface (0.25 mm diameter). The threshold will be determined in five series of ascending and descending stimulus intensities. EPT will be carried out on the right volar arm using TENS (frequency Hz, pulse duration µs, 2 circular electrodes diameter 3,2 cm). TENS is a well-tolerated system to measure electric thresholds, commonly used in therapeutic settings.[43] Electrical detection threshold will be measured by single stimuli of increasing electric current until participants detect the stimulus. After that, a stepwise increase in mA will lead to the level of perception of pain.

Secondary outcomes

Secondary outcomes will comprise changes in olfactory threshold and the number of headache days from pre to post OT. With regard to olfactory threshold, participants will undergo a standardised, validated psychophysical olfactory test, the 'Sniffin' sticks' test battery[36] that includes the assessment of odour sensitivity or threshold. Odour threshold is evaluated using phenyl ethyl alcohol (PEA, rose like odour), using a three-alternative forced

choice presented by means of a single staircase, using stepwise dilutions in a row of 16 felt-tip pens. A change of 2.5 in the threshold after treatment is considered a significant change. An olfactory diary, where patients report their daily training, the perceived odour intensity during training (range 0–10), and the occurrence of events that can potentially affect patients' olfactory sensitivity during OT, such as allergies, or viral infections like COVID-19, will be collected and further considered during analysis. To assess OT-related changes on headache days, a standardised headache pain diary[44] and the migraine disability assessment questionnaire[45] commonly used to evaluate headache related disability as lost time due to migraine, will be used.

Other exploratory measurements such as headache associated pain intensity, acute analgesic intake (both assessed by a standardised headache diary),[44] the impact of headaches on life (assessed by the Migraine-Specific Quality of Life Questionnaire,[46] Headache Impact Test),[47] allodynia (evaluated by Allodynia Symptom Checklist),[48] anxiety & depression (evaluated by Depression and Anxiety Stress Scale,[49] State-Trait Anxiety Inventory,[50] Beck's Depression Inventory,[51] and the Centre for Epidemiological Studies Depression Scale)[52] and cognitive function[53] will also be assessed before and after OT.

Additionally, this protocol evaluates the neurofunctional changes and the OB volume changes associated with the OT programme. Structural and functional imaging data will be acquired with a 3 Tesla MRI scanner (Siemens Prisma, Erlangen, Germany) using a 32-channel head coil. Structural scans will consist of a T1-weighted 3D MPRAGE (voxel size: 1×1×1 mm, FOV: 256 mm, slices: 160, TR: 2300 ms, TE: 3.43 ms, TI: 900 ms, flip angle: 9°, TA: 5:11 min, acceleration mode: GRAPPA, acceleration factor PE: 2) with full-brain coverage and a T2-weighted turbo-spin echo (voxel size: 0.2×0.2×1 mm, FOV: 87 mm, slices: 28, TR: 6200 ms, TE: 117 ms, flip angle: 160°, TA: 8:30 min, averages: 3) with coverage of the olfactory bulb in coronal direction. The functional scans will use slightly different protocols for olfactory and visual stimuli: Olfactory EPI (voxel size: 3×3×3 mm, FOV: 192 mm, slices: 45, TR: 1000 ms, TE: 40 ms, flip angle: 60°, TA: 3:33 min, acceleration mode: slice acceleration, acceleration factor PE: 2, acceleration factor slice: 3, volumes: 203, multislice mode: interleaved); visual EPI (voxel size: 3×3×3 mm, FOV: 192 mm, slices: 45, TR: 2500 ms, TE: 30 ms, flip angle: 80°, TA: 8:53 min, acceleration mode: slice acceleration, acceleration factor PE: 2, acceleration factor slice: 1, volumes: 210, multislice mode: interleaved). In addition a fieldmap will be acquired (voxel size: 3×3×3 mm, FOV: 192 mm, slices: 48, TR: 508 ms, TE1: 4.92 ms, TE2: 7.38 ms, flip angle: 60°, TA: 3:33 min, multislice mode: interleaved).

Neurofunctional tasks

Interictal (migraine free at least 48 hours before and 24 hours after the imaging session) female patients with migraine with aura will undergo two functional MRI sessions (before and after the structured OT programme). During each imaging session, participants will undergo four tasks: (A) one olfactory, (B) two trigeminal and one (C) emotional task:

A. The olfactory task consists of passive intranasal birhinal administration of peach (#LA1300245, Frey+Lau, Henstedt-Ulzburg, Germany), a pleasant odorant stimulus, commonly used in olfactory imaging studies.[54] Peach will be presented in undiluted concentrations and is expected to be clearly perceivable, without causing any trigeminal sensation.
B. Intranasal administration of peppermint (#ABX321352, Takasago, Japan) will be used as a pleasant trigeminal stimulant and will be administered in undiluted concentrations. For trigeminal nociceptive stimulation, we will use intranasal administration of propionic acid (#W292400, Sigma Aldrich, Germany) known to induce nasal irritation.[55] The intensity of the propionic acid will be calibrated/adjusted individually using airflow (L/min). For the individual calibration of propionic acid, before the MRI scan, patients will be instructed to lie on their backs, place the intranasal tubes in their noses and assess the discomfort associated with the Propionic administration (aimed to be a 7 on NRS range 0–10). The propionic acid stimulation starts with an airflow 2.5 L/min and the patients will be asked how they perceived the stimulation until an airflow is found at which the patients give a stable (three consecutive) rating of 7. For both olfactory and trigeminal stimulations, odourless/unscented air will serve as a control/baseline stimulus.

During the functional runs for the olfactory and trigeminal stimulations, a block design will be adopted. During each functional run, each block will last for 20 s. In each block, peach or peppermint will be delivered to the patients' (8 s) alternatively with the baseline stimulus, that is, unscented air (12 s) (figure 2). In the case of propionic acid, the ON stimulation will be divided into 8 blocks of 1 s each that consist of 500 ms of propionic acid and 500 ms of unscented air. In both, olfactory and trigeminal stimulations there will be a total of 10 blocks per run, and each run will last for 200 s. Both odour and trigeminal stimulations will be presented orthonasally using a portable and scanner compatible custom-design, computer controlled olfactometer. Pulses of stimulus embedded in clean air will be delivered birhinally via Teflon tubing (flow rate 2.5 L/min for both Peach and Peppermint). Immediately after each olfactory and trigeminal stimulation, participants will be requested to assess, the intensity of the olfactory and trigeminal stimulation on a scale from 0 to 10 (0 corresponding to 'not perceivable' and 10 'extremely intense'), and the valence on a scale from −5 (extremely unpleasant) to +5 (extremely pleasant). An additional question related to the level of pain/discomfort felt during the propionic acid stimulation, and regarding the cooling effect felt during the peppermint stimulation will be assessed on a similar scale from 0 to 10.

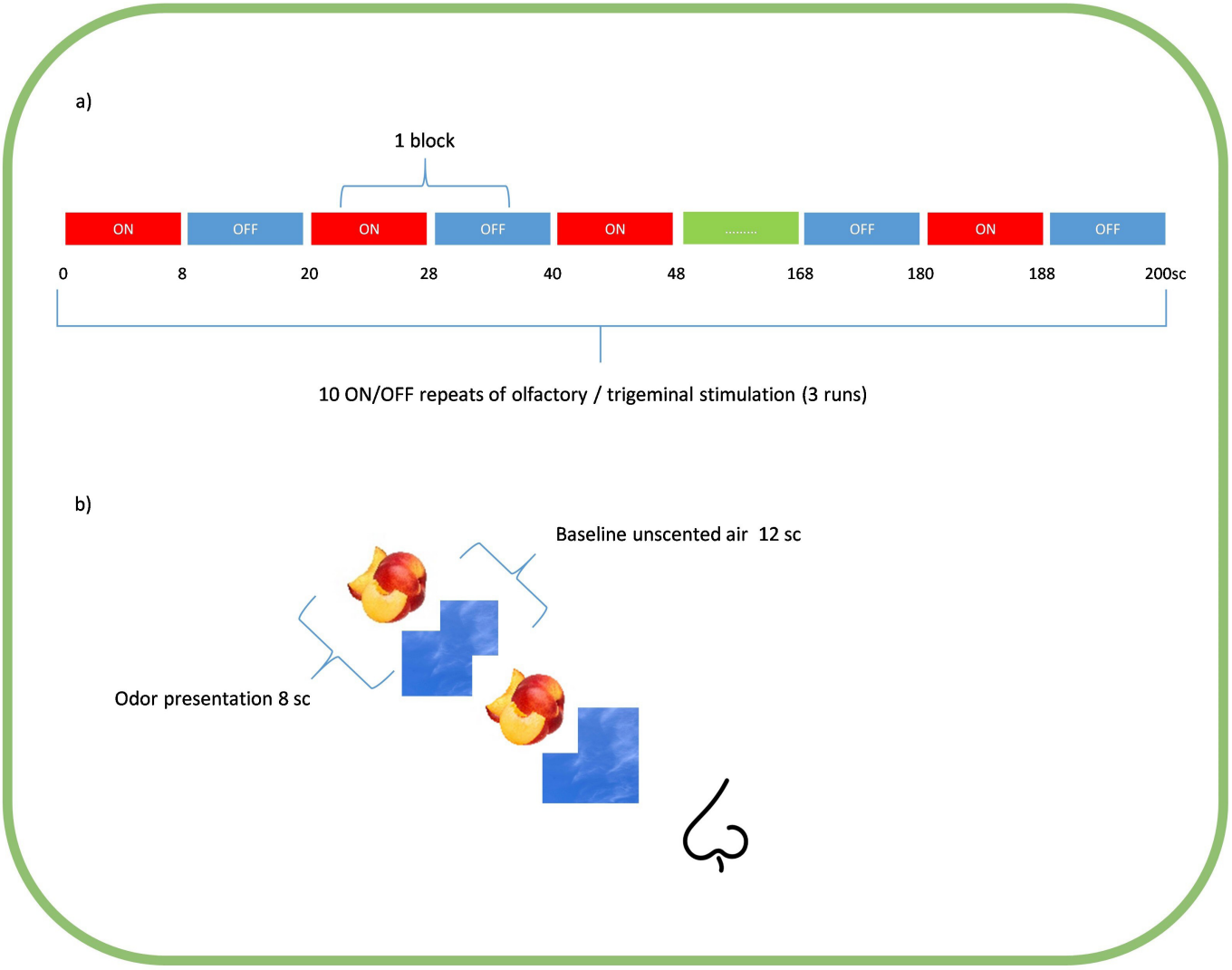

Figure 2 Schematic diagram of the experimental paradigm regarding olfactory and trigeminal stimulations during the fMRI scan. a) Representation of the functional runs. In total, there will be three functional runs – one for each stimulus ie. peach, peppermint, and propionic acid. Each run will be composed of 10 blocks, lasting 200 seconds each. b) Representation of each block. Each block will comprise an ON (olfactory or trigeminal stimulation lasting for 8 seconds) and OFF (unscented air that lasts for 10 seconds) stimulation. Note that for propionic acid the ON stimulation will be divided into 8 blocks of 1 second each that consist of 500ms of propionic acid and 500ms of unscented air. Image source Free Stock photos by Vecteezy.com.

C. The emotional visual task will consist in the presentation and evaluation of emotional loaded pleasant, unpleasant and neutral photographs selected from the International Affective Picture System (IAPS).[56] The IAPS is a standardised, emotionally evocative visual stimulus that has been widely used in imaging studies of emotion and pain. A total of 90 pictures, that is, 30 pleasant, 30 unpleasant and 30 neutral, were selected and will be used. The picture selection will be based on the standardised reported mean valence and arousal.[56]

The experimental paradigm will consist of 10 blocks of emotionally evocative visual stimuli that will be alternated with a crosshair presented in the middle of the screen. During each block, 10 emotionally evocative pictures will be presented for 2.5 s each followed by a baseline cross displayed for 30 s. Each block (ON and OFF) will last for 55 s and there will be a total of nine blocks lasting in total 495 s (figure 3). The order of the ON blocks as well as the order of the images in each block will be randomised for every participant and session. The presentation of the visual stimuli will be programmed using stimulus presentation software Presentation V.20.1 (Neurobehavioral Systems). While laying in the scanner, patients will view the images displayed on a large screen (1920×1080 pixel) reflected through a mirror.

When it comes to the assessments of the affective picture system, in line with previous procedures,[34] once outside the scanner, patients will be presented with the same blocks of images and will be requested to rate each block of pictures for emotional valence and arousal, using the nine point Self-Assessment Manikin Scale (SAM). SAM scale is an affective rating system that uses graphical figures to depict emotional reactions for valence and arousal.[57] The procedure in the scanner takes about 45 min.

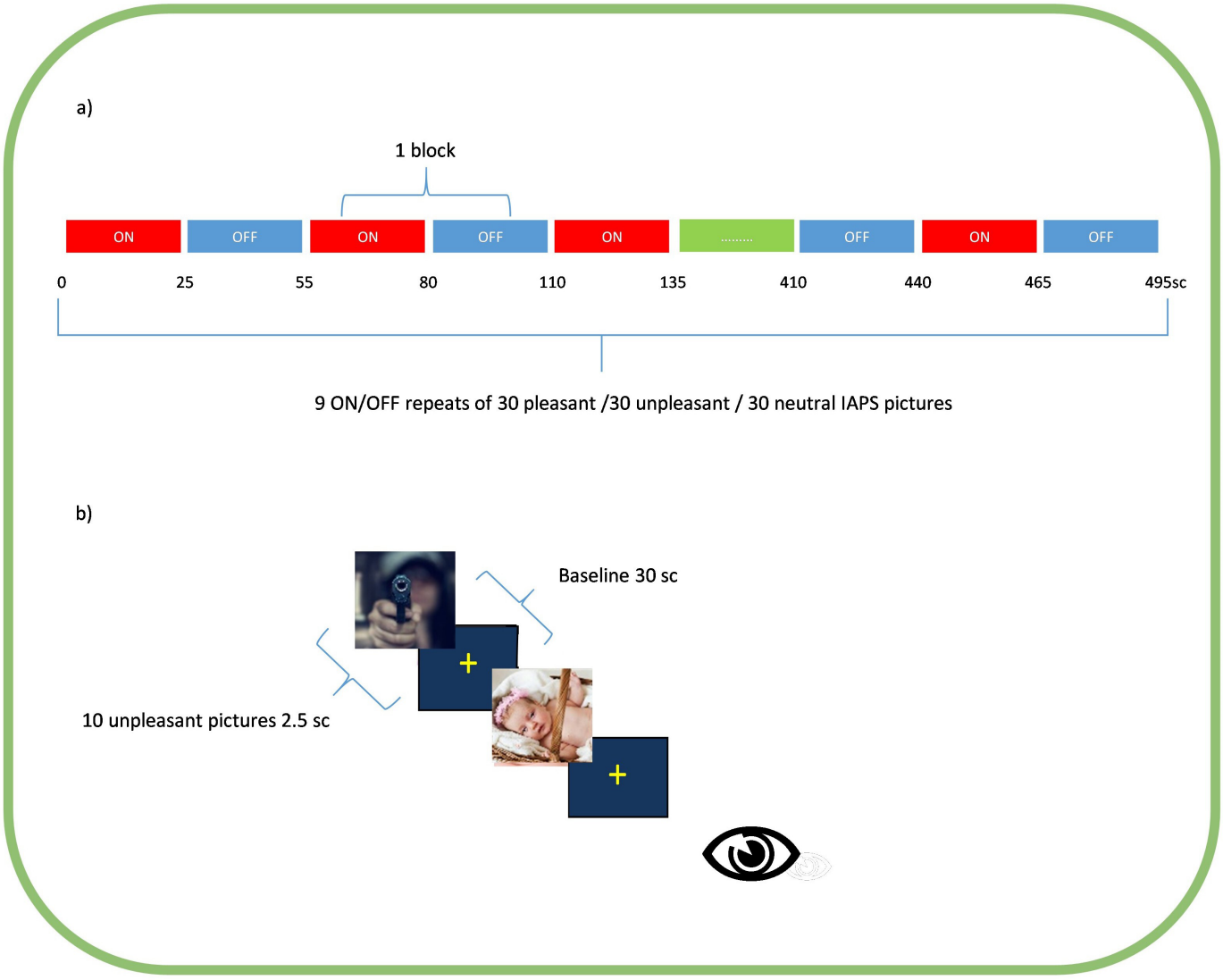

Figure 3 Schematic diagram of the visual emotional experimental paradigm during the fMRI scan. a) Representation of the functional run which will be composed of nine blocks (3 pleasant, 3 neutral, and 3 unpleasant) presented in a randomized order during 495 seconds. b) Representation of the blocks. Each block will consist of an ON phase (comprising 10 pleasant, 10 unpleasant, or 10 neutral pictures - each picture presented for 2.5 seconds (25 seconds)) and an OFF phase (comprising the baseline cross with a duration of 30 seconds). Image source Free Stock photos by Vecteezy.

Credibility ratings

To assess the credibility of the cover story, three questions are added to the last day of training on the patient's diary. Patients will be asked how much they think their migraine-related pain has improved since they started training; how satisfied they were with the OT; and whether they would recommend the OT to a friend or relative who also suffers from migraine. Responses to these questions will be given on a scale from 0 to 10, 0 indicating 'not at all' and 10 indicating 'very much'. Additionally and right before unblinding of the study, participants will be asked to which group they think they were allocated (placebo or OT group) and how sure they were that the treatment they had been assigned to was effective for migraines on a scale from 0 (not at all) to 10 (very much).

Sample size calculations

Based on the available literature and previous clinical results,[27] we expect an increase in either mechanical or EPT in 55% of patients in the verum group and in 25% of patients in placebo group. The null hypothesis of no difference between increase rates of the two groups will be tested using a binomial test for two independent proportions. If a significance level of 5% (two sided) is assumed, at least 42 patients (21 per group) have to be analysed in order to achieve an 80% test power. To account for large reported drop-out rates of 30%,[58] we plan to enrol N=54 participants (27 per group).

Statistical analysis

The primary endpoint of the study is the improvement in either mechanical or EPT after the treatment and will

be quantified using the percentage of patients whose pain thresholds increased by at least 30% in comparison to their baseline value. A binomial test for two independent proportions will be performed in order to test the difference in improvement rates between the verum and placebo groups (with a significance level of 5%, two sided). Additionally, independent samples t-test will be carried out in order to compare the average change in pain thresholds between the study groups.

Data collected will be first presented using relevant descriptive statistics, namely, mean and SD or median and IQR (continuous variables), absolute or relative frequencies (count data). The association between study outcomes will be summarised using either a correlation coefficient or OR, as appropriate, with a 95% CI. Questionnaire data measured over time will be presented graphically, highlighting possible differences in average between two arms. Additionally, two-sample tests, for example, Mann-Whitney-Wilcoxon U test, t-test, χ^2 or Fisher's exact test, will be performed to compare the study outcomes between arms and within each arm (over time). Finally, a model-based analysis will be carried out, aiming to explore a potential influence of patient characteristics on the endpoints of interest. Mixed-effects regression models will be employed to investigate the time trends in pain level and quality of life. For secondary outcomes and relevant effects, standardised mean differences and CIs will be provided, in addition to p values. Statistical analysis will be implemented using R (R Foundation for Statistical Computing), the latest version available by the time of analysis. Missing data will be handled by methods recommended in ICH E9 (R1).[59] If data imputation is performed, sensitivity analyses will be carried out, in order to assess the effect of imputation on the study results.

Neuroimaging data will be preprocessed using the latest fmriprep pipeline.[60] Individual difference images, representing changes in blood oxygenation level dependence reactivity (ie, olfactory/trigeminal stimulation vs unscented air; emotional vs neutral visual stimuli) will be calculated by subtracting pre from post-OT contrast maps and further used in second level group analysis. During the second level analysis, between group t-tests will be used to assess the neural reactivity changes associated with OT. Based on previous migraine imaging findings, a region of interest approach will be used. Additionally, a more liberal and general whole brain approach will be also performed.

Based on previous studies evaluating the effect of OT, we expect to see an increase in pain thresholds[27] (mechanical and EPT—study primary outcomes), in patients with migraine that will undergo verum as compared sham OT. Additionally, we expect to see an increase in olfactory threshold and a reduction in the number of headache days in patients that were enrolled in verum OT as compared with sham OT. With regard to the functional brain imaging data, we hypothesise that a 3-month OT results in increased olfactory related activity, whereas decreased activations are expected in pain-related areas.

Data management

Behavioural data will be partially collected via EDC-System REDCap (Vanderbilt University, Tennessee). Data evaluation will be pseudonymised after patients have given their consent. The data will be stored pseudonymously for 10 years on a secure database server of the REDCap infrastructure. Pseudo anonymisation is carried out according to a fixed one way algorithm. Lists will be stored separately on secure media. When it comes to neuroimaging data acquisition, personal data of the participants will also be pseudonymised. During conversion, imaging data will be anonymised to omit personal identifiable data from the field headers. Imaging data will be stored (anonymised) on a cloud storage provided by the University Hospital of Dresden https://caruscloud.uniklinikum-dresden.de/. Only authorised study personal will have access to the media and servers and only the principal investigator will be able to export data. All data will be made available on request.

Ethics and dissemination

This study was approved by the Ethics Board of the TU Dresden (protocol no. BO-EK-353082020) and will be carried out according to the principles of Declaration of Helsinki. Patients will be informed that they will have a chance to receive either verum or sham OT. All steps will be taken to minimise any discomfort associated with the study. Immediately on study termination, or voluntary ending of the study, a debriefing session will occur and to minimise any potential disappointment related to randomisation, patients will be offered the possibility of enrolling a verum OT programme. Findings of the study will be disseminated through peer-reviewed journals and scientific conferences.

DISCUSSION

Despite being ranked a worldwide leading cause of disability, traditional migraine prophylactic pharmacotherapies are often associated with lack of efficacy and burdensome side effects, emphasising the need for alternative approaches.[1] In this protocol, we aim to investigate both clinical and neural effects of a 3-month structured odour training in female patients with migraine. Recent studies have shown that OT is effective not only in restoring OT but also in attenuating symptoms of depression, improving emotional well-being and cognitive function and in increasing pain thresholds in patients with chronic pain.[27 30] This study protocol is the first to further explore the therapeutic potential of an otherwise well-known relation between migraine and olfaction. While using an emerging olfactory therapy approach based on a systematic exposure to odours during a period of 12 weeks, we seek to further our understanding regarding the underlying mechanisms behind OT by assessing an array of different tests and questionnaires in nociception, emotional and cognitive domains. Moreover, in the presented study protocol, we will be able to acquire

further mechanistic information regarding the underlying neural processes involved in OT.

There are a couple of limitations that should be considered in light of this study protocol. First, we will not include a healthy control group which will dampen our conclusions in terms of migraine specific clinical and neural OT effects. However, studies evaluating the effects of OT have been performed with healthy populations[30] and these findings will allow us to make some extrapolations. Nevertheless, in this protocol study, we have included a placebo/sham OT group that will allow us to assess, for the first time, the effects of OT beyond the placebo effect in a clinical population. A further limitation is related to the OT compliance. In this study protocol, compliance will be assessed via diary self-reports that are meant to maintain and stimulate compliance. However, self-reports can be subject to social desirability biases.[61] In order to account for these biases, we will also contact the patients every 4 weeks, to maintain and stimulate compliance throughout the training. Finally, OT and data acquisition will be spread across distinct annual seasons which might affect olfactory sensitivity, performance and odour perception, especially in migraine patients that suffer from allergies. However, in the patients' olfactory diaries, data concerning patients' olfactory sensitivity will be collected and this will be considered during analysis. Furthermore, in this study, the use of migraine prophylactic antiepileptic drugs, previously suggested to potentially affect olfaction,[62] will be allowed. Notably, however, in this study, participants sense of smell will be assessed with the 'sniffin sticks' battery and only normosmic patients (cut-off of 30.75) will be included in the study. In summary, the presented study protocol aims to, for the first time, provide clinical and neural mechanistic insights regarding the potential beneficial effects of a structured odour exposure in migraine patients.

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REFERENCES

1 Steiner TJ, Stovner LJ, Jensen R, *et al*. Migraine remains second among the world's causes of disability, and first among young women: findings from Gbd2019. *J Headache Pain* 2020;21:137.
2 Vos T, Lim SS, Abbafati C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet* 2020;396:1204–22.
3 Safiri S, Pourfathi H, Eagan A, *et al*. Global, regional, and national burden of migraine in 204 countries and territories, 1990 to 2019. *Pain* 2022;163:e293–309.
4 Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol* 2017;16:76–87.
5 Seddik AH, Branner JC, Ostwald DA, *et al*. The socioeconomic burden of migraine: an evaluation of productivity losses due to migraine headaches based on a population study in Germany. *Cephalalgia* 2020;40:1551–60.
6 Lucas C. Migraine with aura. *Rev Neurol (Paris)* 2021;177:779–84.
7 Lovati C, Lombardo D, Peruzzo S, *et al*. Osmophobia in migraine: multifactorial investigation and population-based survey. *Neurol Sci* 2020;41(Suppl 2):453–4.
8 Sjöstrand C, Savic I, Laudon-Meyer E, *et al*. Migraine and olfactory stimuli. *Curr Pain Headache Rep* 2010;14:244–51.
9 Kayabaşoglu G, Altundag A, Kotan D, *et al*. Osmophobia and olfactory functions in patients with migraine. *Eur Arch Otorhinolaryngol* 2017;274:817–21.
10 Snyder RD, Drummond PD. Olfaction in migraine. *Cephalalgia* 1997;17:729–32.
11 Saisu A, Tatsumoto M, Hoshiyama E, *et al*. Evaluation of olfaction in patients with migraine using an odour stick identification test. *Cephalalgia* 2011;31:1023–8.
12 Fornazieri MA, Neto AR, de Rezende Pinna F, *et al*. Olfactory symptoms reported by migraineurs with and without auras. *Headache* 2016;56:1608–16.
13 Gossrau G, Frost M, Klimova A, *et al*. Interictal Osmophobia is associated with longer migraine disease duration. *J Headache Pain* 2022;23:81.
14 Silva-Néto RP, Peres MFP, Valença MM. Odorant substances that trigger headaches in migraine patients. *Cephalalgia* 2014;34:14–21.
15 Lima A de, Sapienza GB, Giraud V de O, *et al*. Odors as triggering and worsening factors for migraine in men. *Arq Neuropsiquiatr* 2011;69:324–7.
16 Demarquay G, Royet JP, Mick G, *et al*. Olfactory hypersensitivity in migraineurs: a H(2)(15)O-PET study. *Cephalalgia* 2008;28:1069–80.
17 Li J, Gu C-Z, Su J-B, *et al*. Changes in olfactory bulb volume in parkinson's disease: a systematic review and meta-analysis. *PLoS ONE* 2016;11:e0149286.

18 Rottstädt F, Han P, Weidner K, *et al*. Reduced olfactory bulb volume in depression-A structural moderator analysis. *Hum Brain Mapp* 2018;39:2573–82.
19 Negoias S, Croy I, Gerber J, *et al*. Reduced olfactory bulb volume and olfactory sensitivity in patients with acute major depression. *Neuroscience* 2010;169:415–21.
20 Aktürk T, Tanık N, Serin Hİ, *et al*. Olfactory bulb atrophy in migraine patients. *Neurol Sci* 2019;40:127–32.
21 Gallagher RM, Kunkel R. Migraine medication attributes important for patient compliance: concerns about side effects may delay treatment. *Headache* 2003;43:36–43.
22 Negro A, Martelletti P. Patient selection for migraine preventive treatment with anti-CGRP(R) monoclonal antibodies. *Expert Rev Neurother* 2019;19:769–76.
23 Danilov A, Danilov A, Barulin A, *et al*. Interdisciplinary approach to chronic pain management. *Postgrad Med* 2020;132:5–9.
24 Lopresti AL, Smith SJ, Drummond PD. Herbal treatments for migraine: a systematic review of randomised-controlled studies. *Phytother Res* 2020;34:2493–517.
25 Chaibi A, Tuchin PJ, Russell MB. Manual therapies for migraine: a systematic review. *J Headache Pain* 2011;12:127–33.
26 Lötsch J, Hähner A, Gossrau G, *et al*. Smell of pain: intersection of nociception and olfaction. *Pain* 2016;157:2152–7.
27 Gossrau G, Baum D, Koch T, *et al*. Exposure to odors increases pain threshold in chronic low back pain patients. *Pain Med* 2020;21:2546–51.
28 Komori T, Fujiwara R, Tanida M, *et al*. Effects of citrus fragrance on immune function and depressive states. *Neuroimmunomodulation* 1995;2:174–80.
29 Machado DG, Cunha MP, Neis VB, *et al*. Rosmarinus Officinalis L. hydroalcoholic extract, similar to fluoxetine, reverses depressive-like behavior without altering learning deficit in olfactory bulbectomized mice. *J Ethnopharmacol* 2012;143:158–69.
30 Pieniak M, Oleszkiewicz A, Avaro V, *et al*. Olfactory training - thirteen years of research reviewed. *Neurosci Biobehav Rev* 2022;141:104853.
31 Birte-Antina W, Ilona C, Antje H, *et al*. Olfactory training with older people. *Int J Geriatr Psychiatry* 2018;33:212–20.
32 Negoias S, Pietsch K, Hummel T. Changes in olfactory bulb volume following lateralized olfactory training. *Brain Imaging Behav* 2017;11:998–1005.
33 Gottfried JA. Smell: central nervous processing. *Adv Otorhinolaryngol* 2006;63:44–69.
34 Wilcox SL, Veggeberg R, Lemme J, *et al*. Increased functional activation of limbic brain regions during negative emotional processing in migraine. *Front Hum Neurosci* 2016;10:366.
35 Headache classification committee of the international headache society (IHS) the international classification of headache disorders. *Cephalalgia* 2018;38:1–211.
36 Hummel T, Kobal G, Gudziol H, *et al*. Normative data for the "sniffin' sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. *Eur Arch Otorhinolaryngol* 2007;264:237–43.
37 Oleszkiewicz A, Schriever VA, Croy I, *et al*. Updated sniffin' sticks normative data based on an extended sample of 9139 subjects. *Eur Arch Otorhinolaryngol* 2019;276:719–28.
38 Nasreddine ZS, Phillips NA, Bédirian V, *et al*. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–9.
39 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
40 Harris PA, Taylor R, Minor BL, *et al*. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
41 Mücke M, Cuhls H, Radbruch L, *et al*. Quantitative sensory testing. *Schmerz* 2014;28:635–46.
42 Teoli D, An J. Transcutaneous electrical nerve stimulation. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2022.
43 Patil SB, Popali DD, Bondarde PA, *et al*. Comparative evaluation of the effectiveness of different pain-alleviating methods before local anesthetic administration in children of 6 to 12 years of age: a clinical study. *Int J Clin Pediatr Dent* 2021;14:447–53.
44 Tassorelli C, Diener H-C, Dodick DW, *et al*. Guidelines of the international headache society for controlled trials of preventive treatment of chronic migraine in adults. *Cephalalgia* 2018;38:815–32.
45 Stewart WF, Lipton RB, Dowson AJ, *et al*. Development and testing of the migraine disability assessment (MIDAS) questionnaire to assess headache-related disability. *Neurology* 2001;56(6 Suppl 1):S20–8.
46 Jhingran P, Davis SM, LaVange LM, *et al*. MSQ: migraine-specific quality-of-life questionnaire. Further investigation of the factor structure. *Pharmacoeconomics* 1998;13:707–17.
47 Kosinski M, Bayliss MS, Bjorner JB, *et al*. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res* 2003;12:963–74.
48 Lipton RB, Bigal ME, Ashina S, *et al*. Cutaneous allodynia in the migraine population. *Ann Neurol* 2008;63:148–58.
49 Osman A, Wong JL, Bagge CL, *et al*. The depression anxiety stress scales-21 (DASS-21): further examination of dimensions, scale reliability, and correlates. *J Clin Psychol* 2012;68:1322–38.
50 Speilberger CD, Gorsuch R, Lushene R, *et al*. *Manual for the state-trait anxiety inventory*. Palo Alto, CA: Consulting Psychologists, 1983.
51 Jackson-Koku G. Beck depression inventory. *Occup Med (Lond)* 2016;66:174–5.
52 Kliem S, Beller J, Tibubos AN, *et al*. A reanalysis of the center for epidemiological studies depression scale (CES-D) using non-parametric item response theory. *Psychiatry Res* 2020;290:113132.
53 Bates ME, Lemay EP. The D2 test of attention: construct validity and extensions in scoring techniques. *J Int Neuropsychol Soc* 2004;10:392–400.
54 Zang Y, Chen B, Hummel T. Assessment of odor perception related to stimulation modes in a mock MRI scanner. *J Neurosci Methods* 2020;341:108754.
55 Hey K, Juran S, Schäper M, *et al*. Neurobehavioral effects during exposures to propionic acid--an indicator of chemosensory distraction? *Neurotoxicology* 2009;30:1223–32.
56 Lang PJ, Bradley MM, Cuthbert BN. *International affective picture system (IAPS): Affective ratings of pictures and instruction manual: NIMH, Center for the Study of Emotion & Attention Gainesville*. FL, 2005.
57 Bradley MM, Lang PJ. Measuring emotion: the self-assessment manikin and the semantic differential. *J Behav Ther Exp Psychiatry* 1994;25:49–59.
58 Gracia-Naya M, Santos-Lasaosa S, Ríos-Gómez C, *et al*. Predisposing factors affecting drop-out rates in preventive treatment in a series of patients with migraine. *Rev Neurol* 2011;53:201–8.
59 E9 (R1) Addendum on Estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Proceedings of the international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use; 2019.
60 Esteban O, Markiewicz CJ, Blair RW, *et al*. fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nat Methods* 2019;16:111–6.
61 Deshields TL, Tait RC, Gfeller JD, *et al*. Relationship between social desirability and self-report in chronic pain patients. *Clin J Pain* 1995;11:189–93.
62 Doty RL, Bromley SM. Effects of drugs on olfaction and taste. *Otolaryngol Clin North Am* 2004;37:1229–54.