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Brain morphology, functional performance, and clinical features of migraine patients - a cross-sectional study

PROGRAMA DE PÓS-GRADUAÇÃO EM REABILITAÇÃO E DESEMPENHO FUNCIONAL
FMRP-USP

Nicoly Machado Maciel

Tese

NICOLY MACHADO MACIEL

Brain morphology, functional performance, and clinical features of migraine patients - a cross-sectional study

Thesis presented to Ribeirão Preto Medical School of University of São Paulo to obtain a doctoral degree (PhD) in sciences

Area: Physical Therapy

Advisor: Débora Bevilaqua Grossi, PhD

Ribeirão Preto

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NICOLY MACHADO MACIEL

Morfologia cerebral, desempenho funcional e características clínicas de pacientes com migrânea – um estudo transversal

Tese apresentada à Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Área de concentração: Fisioterapia

Orientadora: Profa. Dra. Débora Bevilaqua Grossi

Ribeirão Preto

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Nicoly Machado Maciel

Brain morphology, functional performance, and clinical features of migraine patients - a cross-sectional study

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Area: Physical Therapy

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FOLHA DE APROVAÇÃO

Nicoly Machado Maciel

Morfologia cerebral, desempenho funcional e características clínicas de pacientes com migrânea – um estudo transversal

Tese apresentada à Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo junto ao Departamentode Ciências da Saúde para obtenção do título de Doutor em Ciências pelo Programa de Pós-Graduação em Reabilitaçãoe Desempenho Funcional.

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“O sucesso de uma pessoa não se mede apenas por onde ela chegou, mas também de onde ela partiu”

Theunis Marinho

Abstract

Maciel NM. Brain morphology, functional performance, and clinical features of migraine patients - a cross-sectional study. [thesis]. São Paulo. University of São Paulo. Ribeirão Preto Medical School, 2022. 74p.

Objective: To investigate locomotion in patients with migraine and healthy controls during tasks that involve anticipatory control (obstacle crossing, stepping up and down a curb) with increasing levels of sensory disturbance (visual and auditory). And to verify if the clinical signs related to functional performance can be related to morphological brain changes **Methods:** Initially, for the first study 51 women with migraine and 22 healthy women performed three walking tasks: crossing an obstacle, stepping-up and stepping-down a curb, in a control situation with ambient lighting (≅350 lux), bright light (≅1200 lux), and loud sound (≅90 dBa). For the kinematic evaluation, the VICON motion capture system was used. The second study we considered of 45 women with migraine, and we only consider stepping-up and stepping-down tasks in a control situation with ambient lighting. Afterwards, these 45 volunteers underwent to analysis of the brain volumes and withe matter lesions which were calculated from 3 Tesla magnetic resonance imaging. For statistical analysis, in the first study a t-test, a Spearman correlation test, and a repeated measures mixed ANOVA were applied. And in the second study a multiple backward linear regression was used. **Results:** The first study showed that migraineurs presented higher discomfort induced by light ($p \leq 0.0001$) and sound ($p = 0.001$). In the obstacle task, migraineurs had greater step width than controls in the ambient light condition ($p = 0.038$) and participants of both groups placed their leading foot farther away from the obstacle in the light ($p = 0.033$) than in the ambient light condition. For the step-up task, this distance increased for both groups and limbs in the light (leading limb: $p = 0.015$; trailing limb: $p = 0.002$) and sound (leading limb: $p = 0.010$; trailing limb: $p \leq 0.0001$) conditions compared to the ambient light condition. Step speed increased for light and sound conditions compared to ambient light condition, except for the sound condition in the step-down task. In the second study in the step-up task, 31.4% of the step width variation was explained by subcortical gray volume, cingulate gyrus, and average withe matter lesions volume ($p=0.001$). And 31.2% of the step speed variation was explained by cerebellum, parietal lobe, and temporal lobe ($p=0.001$). In the step-down task, 37.3% of the step width variation was explained by the basal ganglia, brainstem, nucleus accumbens, cingulate gyrus and average withe matter lesions volume ($p=0.002$). And 25.1% of the step speed variation was explained by the volume of the cerebellum, parietal lobe, and temporal lobe ($p=0.007$).

Conclusions: Although the discomfort induced by light and sound was higher in the migraine

group, bright light and loud sound had an impact on functional activities, regardless of migraine status, except for step width in one task. Furthermore, the variability of functional performance during dynamic tasks possibly can be explained in parts by changes in the volume of brain regions, some specifically related to functional performance in migraine patients. Future studies are still needed to identify longitudinal changes in neuroimaging markers as possible predictors of poor functional performance in patients with migraine.

KEY-WORDS: Migraine Disorders. Postural Balance. Magnetic Resonance. Hyperacusis. Photophobia.

Resumo

Maciel NM. Morfologia cerebral, desempenho funcional e características clínicas de pacientes com migrânea – um estudo transversal. [tese]. São Paulo: Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, 2022. 74p.

Objetivo: Investigar a locomoção de pacientes com migrânea e controles saudáveis durante tarefas que envolvem controle antecipatório (ultrapassar obstáculos, subir e descer um degrau) com níveis crescentes de distúrbios sensoriais (visuais e auditivos). E verificar se os sinais clínicos relacionados ao desempenho funcional podem estar relacionados às alterações morfológicas do cérebro. **Métodos:** Inicialmente, para o primeiro estudo 51 mulheres com migrânea e 22 saudáveis realizaram três tarefas de caminhada: ultrapassar um obstáculo, subir e descer um degrau, em uma situação controle com iluminação ambiente (≅350 lux), luz forte (≅1200 lux) e som alto (≅90 dBa). Para a avaliação cinemática, foi utilizado o sistema de captura de movimento VICON. O segundo estudo considerou 45 mulheres com migrânea, e consideramos apenas as tarefas de subida e descida de degrau com iluminação ambiente. Posteriormente, essas 45 voluntárias foram submetidas à análise dos volumes cerebrais e lesões de substância branca que foram calculados a partir de imagens de ressonância magnética de 3 Tesla. Para análise estatística, no primeiro estudo foram aplicados um teste t, um teste de correlação de Spearman e uma ANOVA mista de medidas repetidas. No segundo estudo foi usada uma regressão linear múltipla, com método retroceder. **Resultados:** O primeiro estudo mostrou que os migranosos apresentam maior desconforto induzido pela luz ($p \leq 0,0001$) e pelo som ($p = 0,001$). Na tarefa de obstáculo, os pacientes com migrânea tiveram uma largura de passo maior do que os controles na condição de luz ambiente ($p = 0,038$) e os participantes de ambos os grupos colocaram seu pé dianteiro mais longe do obstáculo na condição luz forte ($p = 0,033$) do que na condição de luz ambiente. Para a tarefa de subida de degrau, esta distância aumentou para ambos os grupos e pernas na condição luz (perna de abordagem: $p = 0,015$; perna de suporte: $p = 0,002$) e som (perna de abordagem: $p = 0,010$; perna de suporte: $p \leq 0,0001$) em comparação com a condição de luz ambiente. A velocidade do passo aumentou para as condições de luz e som em comparação com a condição de luz ambiente, exceto para a condição som na tarefa de descida de degrau. No segundo estudo na tarefa de subida de degrau, 31,4% da variação da largura do passo foi explicada pelo volume cinza subcortical, giro cingulado e volume médio das lesões de substância branca ($p = 0,001$). E 31,2% da variação da velocidade do passo foi explicada pelo cerebelo, lobo parietal e lobo temporal ($p = 0,001$). Na tarefa de descida de degrau, 37,3% da variação da largura do passo foi explicada pelos gânglios da base, tronco encefálico, núcleo accumbens, giro cingulado e volume médio das lesões de

substância branca (p = 0,002). E 25,1% da variação da velocidade do passo foi explicada pelo volume do cerebelo, lobo parietal e lobo temporal (p = 0,007).

Conclusões: Embora o desconforto induzido pela luz e pelo som tenha sido maior no grupo migrânea, a luz forte e o som alto tiveram impacto nas atividades funcionais, independente da presença de migrânea. Além disso, a variabilidade do desempenho funcional durante tarefas dinâmicas pode ser explicada em partes por mudanças no volume das regiões do cérebro, algumas especificamente relacionadas ao desempenho funcional. Estudos futuros ainda são necessários para identificar mudanças longitudinais nos marcadores de neuroimagem como possíveis preditores do baixo desempenho funcional em pacientes com migrânea.

PALAVRAS–CHAVE: Transtornos Migranosos. Equilíbrio Postural. Ressonância Magnética. Fotofobia. Hiperacusia.

Abbreviation List

ANOVA – Analysis of variance

BMI – Body mass index

CNS – Central nervous system

FMRI – Functional Magnetic Resonance Image

ICHD - International Classification of Headache Disorders

LL – Leading limb

MRI – Magnetic Resonance Image

TL – Trailing limb

TUG – Time up and go

WM – White matter

WML – White matter lesions

Summary

1 THEORETICAL CONTEXTUALIZATION

Migraine is a disabling disorder that affects the central nervous system (CNS), recognized mainly as pulsatile and unilateral headache related to neurological symptoms, which include hypersensitivity to sound, light and smell, nausea, and vast emotional, autonomic, cognitive, and motor complications[1].

This primary headache affects approximately 15% of the world population, and prevalence estimates may vary according to geography, socioeconomic conditions, age, race, and sex[2,3,4]. In Brazil, the estimated prevalence is 15.2% of the population, predominantly affecting women, individuals with higher education, with lower income and sedentary[5].

Based on the frequency of the attacks, we can didactically classify migraine as: episodic, characterized by headache in less than 15 days a month; or chronic, in which the headache occurs on 15 days or more per month in the last 3 months[6]. The worldwide prevalence of chronic migraine varies from 0.1 to 5.1%[7] and each year approximately 2.5% of people with episodic migraine evolve to the chronic form[8].

Migraine can be further subdivided into two main subtypes: migraine without aura and migraine with aura[2]. Aura consists of reversible neurological signs and symptoms such as visual changes, dizziness, paresthesia, among others, and headache may be preceded by aura in 10% to 12% of migraineurs[2].

Regarding the pathophysiology of migraine, its definition has undergone an important development in recent years. It is currently understood that migraine attacks are the result of a dysfunction in cortical excitability and activation of the trigeminovascular system[9,10], that occur in susceptible individuals due to genetic and environmental factors[11,12].

From triggering factors such as stress, some types of food, hormonal variations in the menstrual cycle, among others, they can start a phenomenon called cortical spreading depression, which is a wave of depolarization that starts in the occipital lobe to the frontal lobe[13,14]. This event triggers the abnormal activity of the trigeminal nerve nucleus with subsequent release of neurotransmitters in the blood vessels of the meninges, defined as neurogenic inflammation. Meningeal cranial vessel nociceptors respond to neurogenic inflammation by transmitting stimuli to the trigeminal nerve and nucleus, which travel to the brainstem and thalamus and then to the somatosensory cortex, where the stimulus is interpreted as pain.[13,14]. During spreading cortical depression, hemodynamic changes occur in cerebral blood vessels, characterized by vasoconstriction followed by vasodilation[13,14].

As a result of these vascular changes, regions of microvascular ischemia in the territory of the vertebrobasilar arteries were verified in migraineurs, with a considerable involvement of the cerebellum, especially in those patients with aura[15,16,17]. In addition to the cerebellum, the brainstem and the vestibular system can also be affected by these vascular changes that would lead to damage to the central nervous tissue[18].

Over time, an association between migraine and morphological changes in the brain have been reported in the literature due to studies carried out through MRI[19,20]. And despite the clinical significance, as well as the underlying mechanisms related to these morphological changes are still not well understood, some findings have been consistently observed[21]. For example, the decrease in the volume of white matter (WM) and gray matter (GM) in the frontal lobe[22-25], decreased volume of GM from the anterior cingulate cortex[22,25-27], and the decrease in the volume of the trunk and cerebellum[28,29]. In addition to volume-related changes, white matter lesions (WML) were also investigated, in a systematic review carried out by Bashir et al., (2013) [28] the reported prevalence rates of WML in patients with migraine ranged from 4% to 59% in the selected studies. Thus, through imaging studies it is suggested that migraine may be a risk factor for morphological changes in the brain, especially in those patients with aura and with a high frequency of attacks[16,28-30]. However, the clinical or functional impact of these brain alterations in migraine patients is still uncertain.

Morphological alterations, identified from neuroimaging studies, can manifest as clinical and functional alterations, although the relationship between them is still a gap in the literature. There is also evidence that patients with migraine in relation to healthy individuals presented balance deficits in functional activities identified through motor assessments[31]. In activities such as up/downstairs, sit-to-stand transitions, and even gait, the individual with migraine needs more time to perform than controls without a headache. As well as in the Timed Up and Go test (TUG) where migraine sufferers show a decrease in task execution speed compared to healthy[31,32]. In the standing posture, an increase in the sway area and lower stability limits than controls were identified[33,24]. These anomalies related to postural sway, mobility, and motor agility in patients with migraine could be attributed to alterations of central origin[34] or also change in the contribution of sensory systems involved with balance control[35].

Regarding the involvement of sensory systems in motor repercussions, we can consider the presence of photophobia and phonophobia, which are symptoms often presented by migraine patients[1,36], and are part of the migraine diagnostic criteria. Although light and sound are irritating factors for the patient with migraine [1], the mechanisms involved in its contribution from the sensory systems involved with balance control are not clearly defined yet. Previous

investigations suggest that the vasoconstriction and ischemia of the vertebrobasilar artery, which occur during a migraine crisis, cause vestibulocochlear dysfunction[37], and that hyperexcited trigeminovascular thalamic neurons, which get information from the retina, by projecting into many cortical areas[38] such as motor and somatosensory, may play a role in the lack of motor skills and difficulty concentrating, for example[1]. However, the literature is scarce, and the available studies do not elucidate the motor strategies, nor the actual contribution that sensory systems and/or the morphological changes of central origin have with the motor strategies of these patients.

The current thesis will present two articles developed during the doctoral period about the investigation of clinical and functional repercussions related to migraine and its possible relationships with brain structures. First (Study 1), we assessed 73 individuals divided into two groups of patients with migraine and a control group to investigate if the exposure to bright light and loud sound has an impact on the functional performance in this population. And secondly (Study 2) evaluated the possible relationships between brain morphology and functional aspects of migraine of 45 patients with migraine through brain magnetic resonance, and functional performance evaluations through locomotor dynamic tests.

Our first objective was to investigate locomotion in patients with migraine and healthy controls during tasks that involve anticipatory control (obstacle crossing, stepping up and down a curb) with increasing levels of sensory disturbance (visual and auditory).Subsequently, the second aim of our study was to verify if the clinical signs related to functional performance can be related to morphological brain changes.

Many clinical and functional aspects and their relationship with neuroimaging findings still need to be investigated. Identify the clinical and functional changes and their damage that are susceptible to intervention, and whether they are linked to morphological alterations of the central nervous system is very important. Since imaging findings without clinical significance do not contribute to the management of the disease. Once identified that such clinical changes are present, and these are likely to be modified, it is possible to adopt new treatment ways to contain the functional repercussion of migraine in the productive life of these individuals.

2 MATERIAL AND METHODS

Study 1 (Article 1)

Ethical Aspects

The Research Ethics Committee of the Ribeirão Preto Clinics Hospital (process HCRP nº 16210/2015) approved this study. All volunteers signed a consent form before enrolling in the study.

Sample

Seventy-three individuals participated in this study (51 with migraine and 22 headache-free controls). Participants in the migraine group were screened from a tertiary clinic and the local community. This group was composed of 18 patients with migraine without aura, 16 with aura, and 17 with chronic migraine. They were diagnosed by specialized neurologists according to the International Classification of Headache Disorders[2]. Migraineurs were considered eligible if they reported at least three migraine episodes per month within the last three months. The control group was composed of non-headache participants identified in the community.

We included women aged between 18 and 55 years-old. We excluded individuals with diabetes mellitus, high blood pressure and dyslipidemia, history of acute myocardial infarction, stroke, other obstructive vasculopathies, degenerative brain diseases, neurosurgery and head trauma, diagnosis of another headache, BMI greater than 30, musculoskeletal dysfunction, and pregnancy. In addition to these exclusion criteria, the control group could not have been diagnosed with any primary headache and had no headache episodes in the past 10 years.

Experimental procedures

The evaluation of all patients with migraine was carried out during the interval between the attacks (interictal period). For the kinematic assessment, we used the VICON motion capture system (Centennial, CO, USA) with ten cameras (8 MX-T-40S e 2 Vintages) sampled at 100 Hz. We collected three-dimensional coordinates of 39 anatomical markers (14 mm diameter), placed according to the Plug-In Gait Full Body (VICON) model, and two markers to identify the obstacle and curb location in space. In the present study, we used only the heel and toe markers for data analysis. We instructed the volunteers to perform three different tasks: walking and stepping over an obstacle, walking and stepping up a curb, and walking and

stepping down a curb. They performed all those tasks in three conditions: (1) control situation with ambient lighting ≅350 lux, (2) bright light ≅1200 lux, and (3) loud sound ≅90 dBA.

For the obstacle crossing task, the participant walked in a straight line for 4 m following a mark on the floor, crossed a rectangular obstacle (width: 55.5 cm × height: 9 cm × length: 9.5 cm) positioned on the floor, and continued walking for 4 m. For stepping up the curb, the volunteer walked in a straight line for 4 m and then stepped up a platform elevated 16 cm and continued walking for 4 m. For stepping down the curb, participants walked the same distance and stepped down the curb. Participants performed three trials for each condition, totaling 27 trials. They walked barefoot and initiated gait always with the dominant leg.

In the light condition, the participants walked between a set of 8 reflectors equally distributed around the obstacle and the curb. We arranged these reflectors in parallel, 4 on each side, spaced 0.8 m apart, with a lateral distance of 1.6 m from the opposite side. These reflectors were positioned 2.10 m from the floor, with the face tilted 45° upwards. The reflectors emitted a total illuminance of ≅1200 lux (the lower luminance level needed to induce a minimum light discomfort in migraine patients, identified through a previous study[39]). A digital luxmeter (Plux 1000, Instrutherm®) was positioned next to the volunteer at eye level to control the intensity of light emitted, while the volunteer stood at the exact location where the obstacle/curb would be negotiated during the walking trials.

In the sound condition, we used a sound simulating the noise of a party with an intensity of ≅90 dBA, transmitted through a headset (Sony®MDR-ZX220 Bluetooth). This intensity was the minimum sound needed to induce discomfort in migraineurs, as identified in a previous study[40]. In the ambient condition, the participants walked through the room with ambient light, with the reflectors turned off, with total lighting of ≅350 lux. In addition, the laboratory was a quiet environment and no equipment emitted sound in the room.

We blocked the trials according to three sensory conditions. The first block was always the ambient one. The order of the other two sensory conditions was random and defined by a draw. Within each block, the order of the three walking tasks was random and determined by a draw. Participants rated the level of discomfort induced by light and sound through a Likert scale, ranging from 0 (without discomfort) to 10 (maximum discomfort).

Study 2 (Article 2)

Ethical Aspects

The Research Ethics Committee of the Ribeirão Preto Clinics Hospital (process HCRP

nº 13068/2015) approved this study. All volunteers signed a consent form before participating in the present study

Sample

Forty-seven individuals with migraine were screened from a tertiary clinic and the local community and were included in this study. They were diagnosed by specialized neurologists according to the International Classification of Headache Disorders – ICHD-III[2] Migraineurs were considered eligible if they reported at least three migraine episodes per month within the last three months.

Demographic variables such as age, gender, diagnosis, headache onset, migraine frequency, intensity, medication was collected by a blind examiner. We included women aged between 18 and 55 years old. And we excluded individuals with systemic diseases such as fibromyalgia, diabetes mellitus, rheumatoid disease, uncontrolled hypertension and dyslipidemia, history of acute myocardial infarction, stroke, other obstructive vasculopathies, degenerative brain diseases, neurosurgery and head trauma, diagnosis of another headache, BMI > 30, musculoskeletal dysfunction, history of claustrophobia, metallic prostheses, and implants (only those capable of generating imaging artifacts), pacemaker and pregnancy.

Experimental procedures

Functional Performance Analysis

The evaluation of volunteers was carried out during the interval between the attacks (interictal period). For the functional performance assessment, we used the VICON motion capture system (Centennial, CO, USA) with ten cameras (8 MX-T-40S e 2 Vintages) sampled at 100 Hz. We collected three-dimensional coordinates of 39 anatomical markers (14 mm diameter), placed according to the Plug-In Gait Full Body (VICON) model, and two markers to identify the obstacle and curb location in space. In the present study, we used only the heel and toe markers for data analysis.

We instructed the volunteers to perform two different tasks: walking and stepping up a curb and walking and stepping down a curb. For stepping up the curb, the volunteer walked in a straight line for 4 m and then stepped up a platform elevated 16 cm and continued walking for 4 m. For stepping down the curb, participants walked the same distance and stepped down the curb. Participants performed three trials for each task, totaling 6 trials, and the task order

was randomized. They were instructed to walk barefoot and initiate the gait always with the dominant leg.

Magnetic Resonance Imaging

All volunteers underwent a brain magnetic resonance examination to assess the areas of interest in the supratentorial and infratentorial regions. The areas selected according to their relevance in the literature were[2-29, 41-44]: lobes frontal, temporal, parietal, and occipital lobes (all bilaterally), cingulate gyrus, basal ganglia, thalamus, hippocampus, amygdala, nucleus accumbens, insula, cerebellum, and brainstem.

Upon being positioned, the volunteers were instructed not to move during the image acquisition protocol, which lasted an average of 20 min. Images were acquired on an Achieve Duo 3-T scanner (Philips Medical Systems, Best, Netherlands) with a Quasar Dual Gradient system, on a 32-channel phased-array coil for skull study. The image acquisition protocol covered the entire brain consisting of the following sequences: 1- 2D axial T2-weighted images (Turbo spin-echo); 2- T2-weighted images with fluid suspension (Fluid Attenuated Inversion Recovery – FLAIR), volumetric, acquired in the sagittal plane and reconstructed in the 3 orthogonal planes, with isotropic voxel; 3- T1-weighted images, gradient – 3D echo (MPRAGE), high contrast, with isotropic voxel, acquired in the sagittal plane and reconstructed in the 3 orthogonal planes. Morphometry was performed using a 3DT1-weighted turbo-field-echo gradient sequence with the following parameters: 2500 ms repetition time, 3.2 ms echo time, 7.0 ms spaced echo time, 900 ms inversion time, 1 x 1 x 1 mm3 isotropic voxel, 8° flip turning angle, 240 x 240 x 160 mm^3 field of view, 176 sagittal slices 1mm thick each.

White matter lesions (WML) were considered when visible as hyperintense areas on T2-weighted and FLAIR sequences, without corresponding hypointensity on T1-weighted sequences, with a diameter greater than 3 mm and visible in at least two consecutive slices. All detected WML were counted and had their diameters measured. Each image was analyzed by three independent investigators (one trained Neurologist and two Neuroradiologists). After analyzing the images independently, if there was any disagreement, they reanalyzed the MRIs to reach a consensus.

Volume measurements (mm^3) were processed and analyzed using the Fresurfer software, version 6 (http://surfer.nmr.mgh.harvard.edu/). The Destrieux atlas was used for cortical parcellation since it has a good anatomical specificity by dividing the cortex into gyrus and sulcus with 74 regions per hemisphere[45]. A visual check of the cortical estimates was

performed. Further details of the procedures mentioned above are described in previous publications[45,46].

3 RESULTS

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Gait control of migraine patients with increasing light and sound levels

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Abstract

Background: Under a typical light and sound environment context, individuals with migraine showed balance control deficits on a series of functional activities, which helps to explain why migraineurs report more falls. it isn't established, the effects of intensity light and sound in migraineurs during functional tasks.

Research question: Based on the hypersensitivity to light and sound in migraineurs, not only during the attack but also in the interictal period, does the exposure to bright light and loud sound impact motor control in this population?

Methods: This cross-sectional study consisted of 51 women with migraine and 22 healthy women. They performed three walking tasks: crossing an obstacle, stepping-up and stepping-down a curb, in a control situation with ambient lighting (≅350 lux), bright light (≅1200 lux), and loud sound (≅90 dBa). For statistical analysis, a t-test, a Spearman correlation test, and a repeated measures mixed ANOVA were applied.

Results: Migraineurs presented higher discomfort induced by light ($p \leq 0.0001$) and sound ($p = 0.001$). In the obstacle task, migraineurs had greater step width than controls in the ambient light condition ($p = 0.038$) and participants of both groups placed their leading foot farther away from the obstacle in the light ($p = 0.033$) than in the ambient light condition. For the step-up task, this distance increased for both groups and limbs in the light (leading limb: $p = 0.015$; trailing limb: $p = 0.002$) and sound (leading limb: $p = 0.010$; trailing limb: $p \leq 0.0001$) conditions compared to the ambient light condition. Step speed increased for light and sound conditions compared to ambient light condition, except for the sound condition in the step-down task.

Significance: Despite the higher discomfort induced by light and sound in the migraineurs, the effects of these sensory manipulations were similar for both migraineurs and controls, except for step width. Light and sound manipulation induced a less conservative strategy to deal with uneven terrain in both groups.

Keywords: Headache, Walking, Photophobia, Hyperacusis, Migraine disorders.

Introduction

Migraine is a primary brain disorder characterized by headache that are often throbbing, unilateral and severe [1]. Data from the Global Burden of Disease Study [2] shows that migraine is three times more prevalent in women, with peaks in prevalence at 30–39 years. Furthermore, abnormal sensitivity to light (photophobia) and sound (phonophobia), which is part of the migraine diagnostic criteria, are usually present in migraineurs [3]. Since this hypersensitivity occurs not only during the attack but also in the attack-free period [4,5], the exposure to excessive light and sound may have an impact on motor control and maintenance of dynamic postural control in this population.

Our nervous system continuously monitors the afferent inputs from the vestibular, proprioceptive, auditory, and visual systems to maintain posture and to execute functional tasks [6]. The reweighting process increases the weight of a sensory modality while decreasing the importance of other modalities through a dynamic process, influenced by stimulation characteristics and context [7]. Due the photo and phonophobia, an impairment of the visual and auditory systems may occur in migraineurs, which should be compensated (i.e., reweighted) by the somatosensory and vestibular systems [8]. However, such sensory systems may also be impaired in migraineurs [9], and the absence of compensation in the presence of excessive light and sound would impact the motor control of migraineurs in contrast to healthy individuals.

Changes in postural control have been identified in migraineurs. Under typical light and sound environmental conditions, migraineurs exhibit balance deficits on functional activities compared to controls [10]. They require more time to perform functional activities such as gait, sit-to-stand transitions, and up/downstairs. Also, migraineurs present decrease speed on Timed Up and Go test and increased sway area when standing upright [11,12]. Furthermore, they presented longer reaction time, slower speed, and lower limits of stability than controls [13,14]. Altogether, these findings may justify the greater prevalence of falls among migraineurs [15]. Under visual discomfort provoked by light [16], migraineurs presented greater sway area in a bipedal stance task than controls, suggesting that photophobia can be a disturbing factor that worsens postural control of migraineurs.

Intense light levels did not influence controls during balancing tasks [8], although visual deprivation increased postural sway [6]. This last finding strengthens the relevance of the visual system in providing continuous information to the Central Nervous System about body position relative to the environment [16], which is critical for postural control. Although healthy were not affected by light intensity, some studies have shown that sound manipulation could

influence their postural control. In young controls, exposure to an auditory stimulus can either increase postural sway, when this stimulus is a high-frequency noise [17] or has no effect on postural sway when using a disturbing auditory signal [6].

The effects of intense light and sound on migraineurs during functional tasks encountered in daily living are currently unknown. When dealing with uneven terrains (e.g., obstacles, stairs, ramps, among others), our postural control system uses reactive, predictive and anticipatory motor strategies to ensure stability [18]. Following a visual identification of an obstacle or curb in the way of locomotion, one can plan the necessary adjustments to avoid the obstacle to ensure stability. Foot placement before the obstacle/curb (trailing limb, TL) and foot elevation over the obstacle/curb (leading limb, LL) are related to movement stability [19]. In addition to these factors, excessive anterior displacement of the center of mass also interferes with the control of postural stability [20].

As these tasks are more challenging and demand adaptations to avoid threats to stability, the effect of photophobia and phonophobia could negatively affect the migraineurs. Since photophobia influences postural control [8], a natural follow-up would be to investigate the effect of phonophobia and its potential to compromise gait control.

Therefore, this study aimed to investigate locomotion in migraineurs and healthy controls during tasks involving anticipatory control (obstacle crossing, stepping up/down a curb) with increasing levels of visual and auditory disturbance. We hypothesized that (1) migraineurs would feature higher discomfort induced by light and sound than controls; (2) migraineurs, compared to controls, would present changes in the performance of daily locomotor tasks in ambient condition; (3) performance would be further altered with increasing light and sound levels due to photophobia and phonophobia in migraineurs.

Methods

Sample

Seventy-three individuals participated in this study (51 with migraine and 22 headache-free controls). Participants in the migraine group were screened from a tertiary clinic and the local community. This group was composed of 18 patients with migraine without aura, 16 with aura, and 17 with chronic migraine. They were diagnosed by specialized neurologists according to the International Classification of Headache Disorders [1]. Migraineurs were considered eligible if they reported at least three migraine episodes per month within the last three months. The control group was composed of non-headache participants identified in the community.

We included women aged between 18 and 55 years-old. We excluded individuals with diabetes mellitus, high blood pressure and dyslipidemia, history of acute myocardial infarction, stroke, other obstructive vasculopathies, degenerative brain diseases, neurosurgery and head trauma, diagnosis of another headache, BMI greater than 30, musculoskeletal dysfunction, and pregnancy. In addition to these exclusion criteria, the control group could not have been diagnosed with any primary headache and had no headache episodes in the past 10 years.

The Research Ethics Committee of the Ribeirão Preto Clinics Hospital (process HCRP nº 16210/2015) approved this study. All volunteers signed a consent form before enrolling in the study.

Experimental procedures

The evaluation of all patients with migraine was carried out during the interval between the attacks (interictal period). For the kinematic assessment, we used the VICON motion capture system (Centennial, CO, USA) with ten cameras (8 MX-T-40S e 2 Vintages) sampled at 100 Hz. We collected three-dimensional coordinates of 39 anatomical markers (14 mm diameter), placed according to the Plug-In Gait Full Body (VICON) model, and two markers to identify the obstacle and curb location in space. In the present study, we used only the heel and toe markers for data analysis. We instructed the volunteers to perform three different tasks: walking and stepping over an obstacle, walking and stepping up a curb, and walking and stepping down a curb. They performed all those tasks in three conditions: (1) control situation with ambient lighting ≅350 lux, (2) bright light ≅1200 lux, and (3) loud sound ≅90 dBA.

For the obstacle crossing task, the participant walked in a straight line for 4 m following a mark on the floor, crossed a rectangular obstacle (width: 55.5 cm × height: 9 cm × length: 9.5 cm) positioned on the floor, and continued walking for 4 m. For stepping up the curb, the volunteer walked in a straight line for 4 m and then stepped up a platform elevated 16 cm and continued walking for 4 m. For stepping down the curb, participants walked the same distance and stepped down the curb. Participants performed three trials for each condition, totaling 27 trials. They walked barefoot and initiated gait always with the dominant leg.

In the light condition, the participants walked between a set of 8 reflectors equally distributed around the obstacle and the curb. We arranged these reflectors in parallel, 4 on each side, spaced 0.8 m apart, with a lateral distance of 1.6 m from the opposite side. These reflectors were positioned 2.10 m from the floor, with the face tilted 45° upwards. The reflectors emitted a total illuminance of ≅1200 lux (the lower luminance level needed to induce a minimum light

discomfort in migraine patients, identified through a previous study, according to [8]). A digital luxmeter (Plux 1000, Instrutherm®) was positioned next to the volunteer at eye level to control the intensity of light emitted, while the volunteer stood at the exact location where the obstacle/curb would be negotiated during the walking trials.

In the sound condition, we used a sound simulating the noise of a party with an intensity of ≅90 dBA, transmitted through a headset (Sony®MDR-ZX220 Bluetooth). This intensity was the minimum sound needed to induce discomfort in migraineurs, as identified in a previous study according to [4]. In the ambient condition, the participants walked through the room with ambient light, with the reflectors turned off, with total lighting of ≅350 lux. In addition, the laboratory was a quiet environment and no equipment emitted sound in the room.

We blocked the trials according to three sensory conditions. The first block was always the ambient one. The order of the other two sensory conditions was random and defined by a draw. Within each block, the order of the three walking tasks was random and determined by a draw. Participants rated the level of discomfort induced by light and sound through a Likert scale, ranging from 0 (without discomfort) to 10 (maximum discomfort).

Data analysis

For kinematic analysis, we filtered the marker coordinates with a 5^{th} order low-pass digital Butterworth filter with a cutoff frequency of 8 Hz. The Visual3D® software (C-Motion©, Inc, USA) was used for data processing. We computed the following primary dependent variables for all three walking tasks: step width and step speed at the moment of stepping over the obstacle or up/down the curb (Fig. 1); obtained from the ratio of the distance and time between the heel-contact of the TL and the heel-contact of the LL; the horizontal distance between foot-obstacle and foot-curb of both limbs (LL and TL; Fig. 2); and the vertical distance between foot-obstacle and foot-curb of both limbs (LL and TL; Fig. 2).

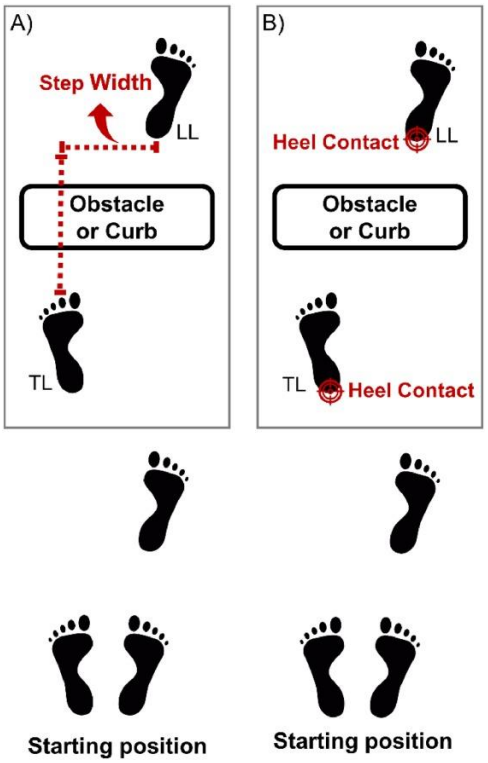

Figure. 1. Illustration of the step width (A) and the step used to compute the step speed (B). LL: Leading Limb; TL: Trailing Limb.

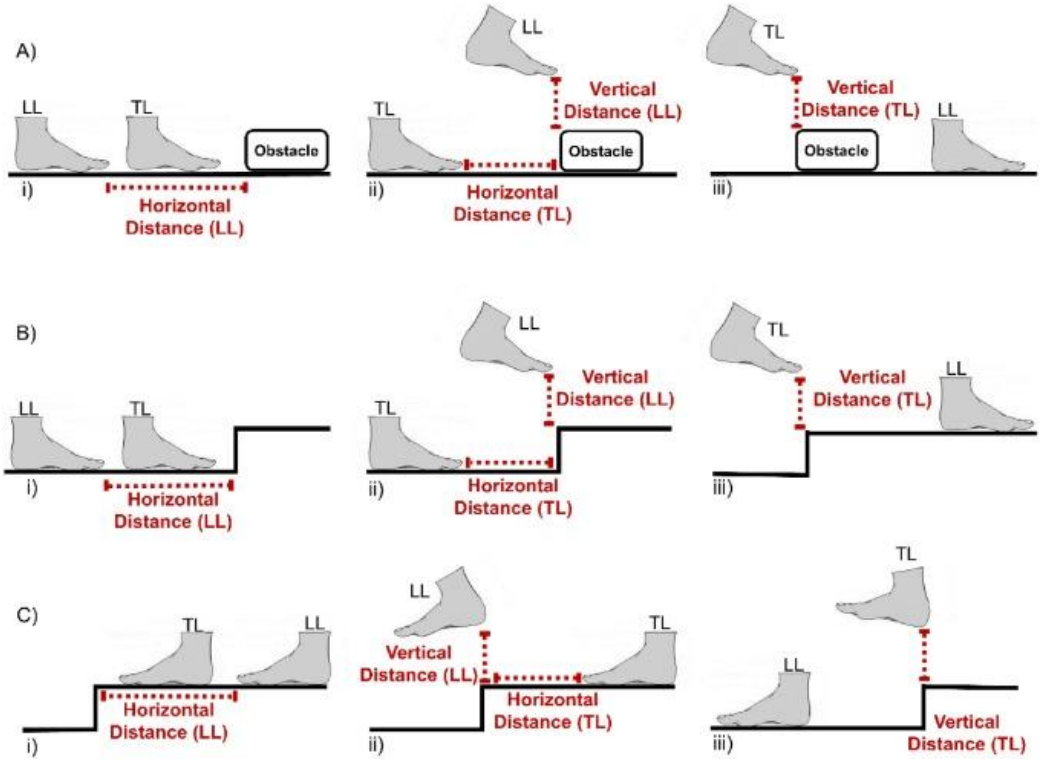

Figure 2. A) Obstacle task; B) Step up task; C) Step down task; i) Leading limb (LL) horizontal distance; ii) Trailing limb (TL) horizontal distance and LL vertical distance; iii) TL vertical distance.

Statistical analysis

The sample size was calculated with the aim to detect 18 cm/s of difference in the step speed between migraineurs and controls. It was based on a previous study [12] and calculated with power fixed at 90 % and α level of 5 %, which resulted in 22 participants for each group.

Demographic data and level of discomfort induced by light and sound of the two groups were normally distributed as indicated by the Shapiro-Wilk test and compared between groups using a two-tailed *t*-test for independent samples. A repeated-measures mixed-model ANOVA was used, including the independent variables of group and task condition, to assess the spatial-temporal gait parameters and the horizontal and vertical foot-obstacle/curb distances. We used post-hoc tests with Bonferroni adjustments. In addition, Spearman's correlation tests were performed within each group to correlate the spatial-temporal gait parameters and the horizontal and vertical foot-obstacle/foot-curb distances with the level of discomfort induced by light and sound. The significance level was set at $\alpha < 0.05$. The SPSS software version 20.0 (IBM, Armonk, NY) was used for statistical analysis. The between-group effect size was calculated for each variable. Effect sizes of $d = 0.2$ were classified as small, $d = 0.5$ were medium, and $d = 0.8$ were large [21].

Results

Table 1 shows that the migraineurs presented higher discomfort induced by light (t_{71} = -5.67, ≤0.0001) and by sound (t_{71} = -3.34, $p = 0.001$) than controls.

Table 1. Mean and standard deviation (±) of demographic of both groups, clinical characteristics of individuals in the migraine group, and level of discomfort induced by light and sound in both groups.

	Control (n=22)	**Migraine (n=51)**	**p-value**
Age (years)	30.3 ± 8.9	32.5 ± 8.8	0.33
Body mass index (kg/m^2)	25.5 ± 4.0	23.8 ± 3.5	0.18
Level of discomfort induced by light and sound (measured from 0-10)			
Light	0.4 ± 0.7	2.3 ± 2.1	≤0.0001*
Sound	3.9 ± 3.2	6.4 ± 2.7	0.001*
Ambient Light	0.0 ± 0.0	0.57±1.20	≤0.0001*
Migraine features			

Disease duration (years)	14.5 ± 8.4
Frequency (headache days/month)	12.4 ± 8.2
Intensity (0-10)	7.6 ± 1,4
Duration (hours)	28.7 ± 36.3

* Significant difference between migraine and control groups.

Obstacle task

There was a significant interaction effect between group and task conditions (Table 2) for step width ($F1,98 = 5.21$, $p = 0.007$). The post-hoc tests showed that the migraineurs had greater step width for the ambient condition than the control ($p = 0.038$), with a medium effect size ($d = 0.54$, $p = 0.04$). The control group increased step width in both the light ($p = 0.003$) and sound ($p = 0.005$) conditions compared to the ambient condition

Table 2. Mean and confidence interval of the spatial-temporal gait parameters for the obstacle task.

	Control (n = 22)	Migraine (n = 51)	p-value Group	p-value Condition	p-value Group* Condition
Step Width (cm)					
Ambient	6.64 (5.15 – 8.12)	8.82 (7.65 – 9.99)			
Light †	10.00 (8.60 – 11.40)	8.88 (7.76 – 9.99)	0.924	0.007*	0.007*
Sound †	9.61 (8.17 – 11.06)	8.77 (7.69 – 9.84)			
Step Speed (m/s)					
Ambient	2.89 (2.34 – 3.44)	2.60 (2.30 – 2.90)			
Light †	3.42 (2.89 – 3.95)	2.81 (2.48– 3.14)	0.091	0.005*	0.633
Sound †	3.39 (2.90 – 3.88)	2.96 (2.57 – 3.35)			
Horizontal Distance - LL (cm)					
Ambient	68.69 (61.73 – 75.65)	63.46 (58,57 – 68.34)			
Light †	76.32 (69.08 – 83.56)	67.07 (61.59 – 72.55)	0.092	0.022*	0.600
Sound	73.98 (66.80 – 81.17)	67.23 (61.64 –72.83)			
Horizontal Distance - TL (cm)					
Ambient	15.32 (12.75 – 17.89)	12.59 (10.95 – 14.23)			
Light	16.40 (13.67 – 19.13)	13.45 (11.61 – 15.30)	0.076	0.372	0.611
Sound	15.54 (13.17 – 17.91)	13.95 (12.27 – 15.63)			
Vertical Distance - LL (cm)					
Ambient	11.72 (10.24 – 13.21)	11.09 (10.28 – 11.90)			
Light	11.71 (10.34 – 13.09)	11.22 (10.50 – 11.94)	0.290	0.796	0.171
Sound	12.12 (10.56 – 13.67)	10.95 (10.31 – 11.60)			
Vertical Distance - TL (cm)					
Ambient	7.47 (6.51 – 8.44)	8.39 (7.63 – 9.15)	0.244	0.115	0.745
Light	7.31 (6.08 – 8.54)	8.08 (7.30 – 8.86)			

Sound	7.04 (5.92 – 8.15)	7.46 (6.66 – 8.25)

*Significant differences
† Post-hoc difference for the main effect of condition. The symbol represents the conditions that differed from the ambient condition. (LL: Leading limb | TL: Trailing limb).

For step speed, there was a main condition effect ($F_{1,75} = 5.90$, $p = 0.005$). The step speed increased for both light ($p = 0.039$) and sound ($p = 0.017$) compared to the ambient condition for both groups. In the light condition, a medium effect size was observed ($d = -0.50$, $p = 0.05$) between migraine and control groups. For the LL horizontal distance, there was a main condition effect ($F_{1,79} = 4.14$, $p = 0.022$), with the light ($p = 0.033$) showing higher values than the ambient condition.

Stepping-up task

For step speed, there was a main condition effect ($F1,79 = 6.45$, $p = 0.003$) (Table 3). Step speed was higher for both light ($p = 0.036$) and sound ($p = 0.001$) conditions than in the ambient condition. There were main condition effects for both LL ($F1,96 = 7.23$, $p = 0.001$) and TL ($F1,98 = 9.90$, $p \leq 0.0001$) horizontal distances. For both variables, these distances increased for the light ($p = 0.015$ and $p = 0.010$) and sound ($p = 0.00$ and $p \leq 0.0001$) conditions compared to the ambient condition.

Table 3. Mean and confidence interval of the spatial-temporal gait parameters for the step-up task.

	Control (n = 22)	Migraine (n = 51)	p-value Group	p-value Condition	p-value Group* Condition
Step Width (cm)					
Ambient	8.79 (7.30 – 10.29)	6.85 (5.62 – 8.08)			
Light	8.53 (7.23 – 9.82)	8.55 (7.57 – 9.52)	0.325	0.417	0.175
Sound	8.46 (6.72 – 10.19)	7.91 (6.66 – 9.17)			
Step Speed (m/s)					
Ambient	3.66 (3.27 – 4.06)	3.28 (2.97 – 3.58)			
Light †	3.85 (3.55 – 4.16)	3.58 (3.34 – 3.81)	0.163	0.003 *	0.781
Sound †	3.90 (3.52 – 4.28)	3.58 (3.28 – 3.88)			
Horizontal Distance - LL (cm)					
Ambient	83.05 (80.13 – 85.98)	79.08 (74.90 – 83.26)			
Light †	86.10 (83.67 – 88.53)	86.30 (82.25 – 90.36)	0.552	0.001*	0.449
Sound †	87.50 (84.47 – 90.53)	86.26 (81.94 – 90.58)			
Horizontal Distance - TL (cm)					
Ambient	21.92 (19.94 – 23.89)	22.14 (20.12 – 21.16)			
Light †	24.29 (21.94 – 26.64)	25.27 (23.02 – 27.51)	0.663	≤0.0001*	0.907
Sound †	25.44 (22.89 – 27.99)	25.37 (23.20 – 27.54)			
Vertical Distance - LL (cm)					

Ambient	9.24 (8.22 – 10.27)	9.22 (8.69 – 9.76)			
Light	8.86 (7.83 – 9.90)	9.03 (8.48 – 9.58)	0.963	0.102	0.662
Sound	9.11 (8.18 – 10.03)	9.04 (8.49 – 9.59)			
Vertical Distance - TL (cm)					
Ambient	7.06 (5.84 – 8.28)	8.28 (7.39 – 9.16)			
Light	8.44 (7.10 – 9.79)	7.95 (6.96 – 8.94)	0.751	0.319	0.050
Sound	8.06 (6.81 – 9.31)	8.02 (7.17 – 8.87)			

*Significant difference
† Post-hoc difference for the main effect of condition. The symbol represents the conditions that differed from the ambient condition. (LL: Leading limb | TL: Trailing limb).

A negative and weak correlation was found between step speed and the level of discomfort induced by light only in migraineurs (p=-0.279, p = 0.048).

Stepping-down task

For the step speed, there was an condition effect ($F_{1,91} = 4.75$, $p = 0.010$), where the light ($p = 0.004$) showed higher step speed compared to the ambient condition (Table 4). A negative and weak correlation was verified between step speed and the discomfort level induced by light only in migraineurs (ρ=-0.335; $p = 0.016$).

Table 4. Mean and confidence interval of the spatial-temporal gait parameters for the step-down task.

	Control (n = 22)	Migraine (n = 51)	p-value Group	p-value Condition	p-value Group* Condition
Step Width (cm)					
Ambient	11.58 (9.38 – 13.79)	11.32 (9.95 – 12.68)			
Light	11.80 (9.88 – 13.72)	11.33 (9.98 – 12.68)	0.578	0.922	0.868
Sound	11.77 (9.65 – 13.88)	10.85 (9.40 – 12.29)			
Step Speed (m/s)					
Ambient	2.86 (2.44 – 3.27)	2.77 (2.50 – 3.05)			
Light †	3.02 (2.61 – 3.42)	3.09 (2.81 – 3.38)	0.886	0.010 *	0.405
Sound	2.92 (2.42 – 3.42)	3.04 (2.72 – 3.37)			
Horizontal Distance - LL (cm)					
Ambient	74.38 (70.13 – 78.62)	71.78 (68.14 – 75.42)			
Light	73.87 (69.93 – 77.81)	74.04 (70.51 – 77.57)	0.584	0.464	0.468
Sound	73.55 (68.96 – 78.13)	71.39 (67.92 – 74.86)			
Horizontal Distance - TL (cm)					
Ambient	16.50 (14.07 – 18.93)	16.13 (13.92 – 18.33)			
Light	15.60 (12.92 – 18.28)	16.26 (14.29 – 18.24)	0.880	0.559	0.612
Sound	15.89 (12.92 – 18.86)	14.91 (12.99 – 16.83)			
Vertical Distance - LL (m)					
Ambient	8.00 (7.20 – 8.80)	7.75 (7.12 – 8.37)	0.648	0.355	0.735

Light	7.98 (7.16 – 8.80)	7.66 (7.10 – 8.22)			
Sound	7.76 (6.92 – 8.59)	7.64 (7.04 – 8.24)			
Vertical Distance - TL (cm)					
Ambient	22.58 (21.34 – 23.81)	22.04 (21.23 – 22.85)			
Light	22.42 (21.27 – 23.57)	22.03 (21.16 – 22.89)	0.516	0.918	0.941
Sound	22.43 (21.12 – 23.73)	22.01 (21.21 – 22.81)			

*Significant difference

† Post-hoc difference for the main effect of condition. The symbol represents the conditions that differed from the ambient condition. (LL: Leading limb | TL: Trailing limb).

Discussion

The migraine group exhibited higher discomfort induced by light and sound, confirming our first hypothesis. Migraineurs have an exacerbated sensitivity not only to light and sound but also to odors and skin stimulation, observed even during the interictal phase [3]. These observations point to a systemic hypersensitivity in migraineurs compared to controls [22]. Studies of fMRI provide evidence that the hypothalamus-thalamus-brain stem network may be the driving force behind the periodic changes in the sensitivity threshold present in migraines [23].

The second hypothesis was that locomotor task performance in migraineurs would be impacted under the ambient condition and it was only confirmed for the obstacle task. Step width was larger in the obstacle task for migraineurs than controls in the ambient condition. This finding corroborates with a previous study [10]. The increase in step width is related to functional loss and risk of falls in older adults and in pathologies that affect the motor system [24]. Carvalho et al. [15] also identified that 54 % of migraineurs self-reported fear of falls. In another study, the step width was associated with a preexisting fear of falling [25], which strengthens the finding that migraineurs have a higher risk of falls even in an age group considered young. Despite this difference in step width, in all the other gait variables, the second hypothesis was not fully supported. There was no difference between the groups in the other variables of obstacle and stepping up/down tasks. Even with the step width and step speed variables in the obstacle task showing a moderate and significant effect size, all other variables showed small to medium effect size, but not significant.

We also did not confirm our third hypothesis since the light and sound increments did not increase the difference between groups. The migraineurs did not change the step width due to light or sound manipulations. From a biomechanical point of view, they would be unable to further increase step width since they already exhibited a wider step than controls in the ambient condition. Although a large step width may contribute to walking stability, a substantial increase in step width raises the mechanical work necessary to redirect the center of mass

velocity during the step-to-step transition in walking [26]. This finding suggests that migraineurs and controls adapted their step width differently, and this can depend on the behavior exhibited in the ambient condition.

The step speed increase under excessive light and sound was a consistent result in all three walking tasks (except in the step-down task, where it raised only for the light condition). Participants of both groups seem to choose a *ballistic* strategy to traverse the walkway in both light and sound conditions. By using this strategy, participants could quickly move past the uncomfortable stimulus. Although the migraineurs exhibited a higher discomfort than controls for light and sound stimuli, some of the controls felt uncomfortable with these stimuli (Table 1), which may have led them to use the ballistic strategy. Although there was a weak negative correlation between step speed and light discomfort for the migraineurs in the step-up/down tasks, the speed in light and sound conditions were still higher than the ambient condition. Therefore, it is reasonable to assume that migraineurs and controls adopted this ballistic strategy. On the other hand, since the weak negative correlation was present only in migraineurs, we can infer that the discomfort level slightly influenced the step speed modulation in migraineurs. Patients with lower discomfort levels walked somewhat faster.

For both groups, the LL horizontal distance increased in the light condition for the obstacle task, and the same distance increased for both limbs (LL and TL) in the light and sound conditions of the step-up task. Foot placement before an obstacle/curb is tightly controlled in young adults [27], as the risk of stumbling increases for inappropriate foot placement relative to the obstacle/curb [28]. There is a trade-off between speed and accuracy in human movement [29], and the use of a more ballistic strategy can compromise foot placement accuracy.

Our study has some limitations. First, the sample included only women, and part of the migraine group was composed of patients from a tertiary clinic. These factors can restrict generalization. Second, it was not possible to control which phase of the migraine the volunteer was, since even in the absence of pain during data collection, they could be in the prodrome or postdrome phases. Since the attack phase can affect the sensitivity thresholds of patients with migraine [30], this could influence our results.

Despite the limitations, it is important to highlight the strengths of the study. This was the first study to investigate the impact of photo and phonophobia on the motor control and maintenance of dynamic postural control in this population, shedding light on further studies to investigate such mechanisms. Further studies might investigate the physiological mechanisms of photophobia and phonophobia and their interaction with postural control in both migraine and healthy individuals to better understand the findings of the present study. Furthermore,

determining the functional repercussions of these results on migraineurs' daily life is fundamental for a proper assessment and rehabilitation planning on clinical practice.

In summary, we conclude that migraine is related to higher discomfort induced by light and sound than controls. There was no difference between groups for the ambient condition, except for the step width in the obstacle task. Although the discomfort induced by light and sound was higher for the migraine group, the increments in these stimuli did not make a difference between groups when walking on uneven terrains.

Article Highlights

- Bright light and loud sound have an impact on functional activities irrespective of migraine status.
- A ballistic strategy to traverse the walkway in both light and sound was used.
- Even healthy individuals are affected by light and sound increment.

Authors' contributions

NMM conducted data collection, data analysis, data interpretation, and manuscript preparation. GFC coordinated data collection, statistical analysis and drafted the manuscript. CFP participated in the study's design and manuscript preparation. RE participated in the statistical analysis and manuscript preparation. RM participated in the study's design, data analysis, data interpretation, and manuscript preparation. DBG participated in the study's design and coordination, data analysis, data interpretation, and manuscript preparation. All authors read and approved the final manuscript.

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Declaration of Competing Interest

None.

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Relationship between brain morphology and functional performance during dynamic tasks in patients with migraine - a cross-sectional study

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Abstract

Background: Structural changes in the brain are commonly associated with functional changes. Although the presence of cerebral morphological alterations and reduced performance of functional tasks in patients with migraine has been established, the relationship between these two factors has not yet been verified in migraineurs. The present study evaluated the relationship between brain alterations and functional performance in locomotor tasks. **Methods:** This study assessed 45 women with migraine. For the kinematic evaluation, the VICON motion capture system was used to measure spatiotemporal gait parameters while the volunteers performed the task. Participants were submitted to analysis of brain volume and withe matter lesions with a 3 Tesla magnetic resonance. A correlation test and a multiple backward linear regression were used to assess the relationship between the outcomes. **Results:** In the step-up task, 31.4% of the step width variation was explained by subcortical gray volume, cingulate gyrus, and average white matter lesions volume (p=0.001). For step speed, 31.2% of its variation was explained by the volume of cerebellum, parietal lobe, and temporal lobe (p=0.001). In the step-down task, 37.3% of the step width variation was explained by the volume of basal ganglia, brainstem, nucleus accumbens, cingulate gyrus, and average white matter lesions volume (p=0.002). For step speed, 25.1% of its variation was explained by the volume of the cerebellum, parietal lobe, and temporal lobe (p=0.007). **Conclusions:** Functional performance in migraine patients can be partially explained by changes in the volume of some brain regions, specifically related to gait control.

Keywords: Headache; Migraine Disorders; Walking; Postural Balance; Magnetic Resonance Imaging.

1. Introduction

Understanding the pathophysiology of migraine is extremely important but very complex [1]. The imaging assessment techniques, like magnetic resonance imaging (MRI), can generate data on brain morphology and possible connections between morphology and clinical findings of the disease. Through the association between brain morphological and clinical changes, it is possible to understand better the complexity involved in the pathophysiological mechanisms of migraine [2,3].

Many morphological brain changes are seen in migraine patients [4-12], but their associations with clinical alterations are not well established. Some studies have identified that these morphological changes in migraine patients are associated with disease duration [7,8], attacks frequency [7,9], and presence of aura [8,11,12]. But it is unknown whether these morphological changes are related to clinical changes, such as changes in functional performance, which are also seen in migraine patients [13-17].

In other neurological diseases, the origin of these motor changes has been widely investigated through their association with morphological brain changes. For instance, gait disorders in neurodegenerative diseases are associated with central nervous system (CNS) alterations, as observed in Parkinson's and Huntington's disease, among others [18]. In diseases with cerebrovascular involvement, associations between gray matter volume and functional performance alterations were also found. In small vessel disease, for example, slower gait speed, shorter step length, shorter cadence, and wider step width were related to reduced gray matter volume in some specific brain areas [19]. It was also seen that a slower time to step-up was associated with lower total gray matter volume [20]. The relationship between gray matter volume and gait was also found in older adults. Specifically, in mild cognitive impairment, smaller primary motor cortex volumes were related to poor gait performance during single and dual tasks [21].

In migraine patients, we are unaware of any previous study investigating the association between brain volume and white matter lesions and gait performance. Identifying such an association in migraine patients brings clinical significance to the various findings related to morphological brain changes that have not been fully clarified in this disease. Since brain morphology is subject to change through training (i.e., brain plasticity), the clinical importance of these brain changes can be applied through postural and gait training [22, 23, 24].

Thus, based on the evidence that migraine is associated with structural brain changes obtained in neuroimaging exams and that migraineurs present an impaired functional

performance, we aimed to verify the association between morphological brain changes and clinical signs related to functional performance.

2. Methods

2.1 Sample

Forty-five individuals with migraine were screened from a tertiary clinic and the local community and were included in this study. Specialized neurologists diagnosed them according to the International Classification of Headache Disorders – ICHD-III [25]. Migraineurs were considered eligible if they reported at least three migraine episodes per month within the last three months.

Demographic variables such as age, gender, diagnosis, headache onset, migraine frequency, intensity, medication was collected by a blind examiner. We included women aged between 18 and 55 years old. We excluded individuals with systemic diseases such as fibromyalgia, diabetes mellitus, rheumatoid disease, uncontrolled hypertension and dyslipidemia, history of acute myocardial infarction, stroke, other obstructive vasculopathies, degenerative brain diseases, neurosurgery and head trauma, diagnosis of another headache, Body Mass Index (BMI) > 30, musculoskeletal dysfunction, history of claustrophobia, metallic prostheses, and implants (only those capable of generating imaging artifacts), pacemaker and pregnancy.

The Research Ethics Committee of the Ribeirão Preto Clinics Hospital (process HCRP nº 13068/2015) approved this study. All volunteers signed a consent form before participating in the present study.

2.2 Functional Performance Analysis

The evaluation of volunteers was carried out during the interval between the attacks (interictal period). We used the VICON motion capture system (Centennial, CO, USA) for the functional performance assessment with ten cameras (8 MX-T-40S e 2 Vintages) sampled at 100 Hz. We collected three-dimensional coordinates of 39 anatomical markers (14 mm diameter), placed according to the Plug-In Gait Full Body (VICON) model, and one marker to identify the curb location in space. We used only the heel and toe markers for data analysis in the present study.

We instructed the volunteers to perform two separate tasks: walk up and down the curb. For the step-up task, the patient walked in a straight pathway for 4 m and then stepped up a

platform elevated 16 cm and continued walking for 4 m. For the step-down task, participants walked the same distance and stepped down the 16 cm curb. Participants performed three trials for each task, totaling six trials, and the task order was randomized. They walked barefoot and always initiated the walking with the dominant leg.

We filtered the marker coordinates with a 5th order low-pass digital Butterworth filter with a cutoff frequency of 8 Hz to process the obtained data. The Visual3D® software (C-Motion©, Inc, USA) was used for data processing. We computed the following primary dependent variables for the two walking tasks: step width (cm) and step speed (m/s) at the step on the curb (i.e., the interval between the heel contact of the trailing limb and the heel contact of the leading limb). The step width was computed as the mediolateral distance between the heel markers. The step speed was calculated as the ratio between step length and step duration.

2.3 Magnetic Resonance Imaging

All volunteers underwent a brain magnetic resonance examination to assess the areas of interest in the supratentorial and infratentorial regions. The areas were selected according to their relevance in the literature [4-12, 18-21]: frontal, temporal, parietal, and occipital lobes (all bilaterally), cingulate gyrus, basal ganglia, thalamus, hippocampus, amygdala, nucleus accumbens, insula, cerebellum, and brainstem.

After being positioned, the patients were instructed not to move during the image acquisition protocol, which lasted 20 min on average. Images were acquired on an Achieve Duo 3-T scanner (Philips Medical Systems, Best, Netherlands) with a Quasar Dual Gradient system on a 32-channel phased-array coil for skull study. The image acquisition protocol covered the entire brain consisting of the following sequences: 1) 2D axial T2-weighted images (Turbo spin-echo); 2) T2-weighted images with fluid suspension (Fluid Attenuated Inversion Recovery – FLAIR), volumetric, acquired in the sagittal plane and reconstructed in the three orthogonal planes, with isotropic voxel; 3) T1-weighted images, gradient – 3D echo (MPRAGE), high contrast, with isotropic voxel, acquired in the sagittal plane and reconstructed in the three orthogonal planes. Morphometry was performed using a 3DT1-weighted turbo-field-echo gradient sequence with the following parameters: 2500 ms repetition time, 3.2 ms echo time, 7.0 ms spaced echo time, 900 ms inversion time, 1 x 1 x 1 mm3 isotropic voxel, 8° flip turning angle, 240 x 240 x 160 mm3 field of view, 176 sagittal slices 1 mm thick each.

White matter lesions (WML) were considered when visible as hyperintense areas on T2-weighted and FLAIR sequences, without corresponding hypointensity on T1-weighted sequences, with a diameter greater than 3 mm and visible in at least two consecutive slices. All

detected WML were counted and had their diameters measured. Each image was analyzed by three independent investigators (one trained Neurologist and two Neuroradiologists). After analyzing the images independently, if there was any disagreement, they reanalyzed the MRIs to reach a consensus.

Volume measurements (mm3) were processed and analyzed using the Fresurfer software, version 6 (http://surfer.nmr.mgh.harvard.edu/). The Destrieux atlas was used for cortical parcellation since it has a good anatomical specificity by dividing the cortex into gyrus and sulcus with 74 regions per hemisphere [26]. A visual check of the cortical estimates was performed. Further details of the procedures mentioned above are described in previous publications [26, 27].

2.4. Statistical analysis

According to the number of participants considered adequate to detect a Pearson correlation of 0.4, with 80% power and 5% alpha level, a sample size of 45 participants was selected [28]. A minimum of 25 subjects is suggested for linear regression analysis [29]. The baseline characteristics were presented as mean and standard deviation (SD). The Shapiro-Wilk test was applied to verify the normality of the data (volume (mm^3) and WML), which presented a normal distribution ($p>0.05$). A Pearson's correlation test verified the correlation between migraine features, such as disease duration, migraine intensity, attack frequency or aura frequency with brain volumes and kinematics data. Multiple backward linear regression was used to examine the association of MRI variables (independent variables) with functional performance variables (dependent variables) with adjustment for age. Four models were run for each dependent variable analyzed (step width in step-up, step width in step-down, step speed in step-up and step speed in step-down). For all models, the independent variables were the frontal, temporal, parietal, and occipital lobes (all bilaterally), cingulate gyrus, basal ganglia, thalamus, hippocampus, amygdala, nucleus accumbens, insula, cerebellum, brainstem, and WML. Regression coefficients were presented as standardized values. The SPSS software version 20.0 (IBM, Armonk, NY) was used for statistical analysis.

3. Results

The sample consisted of 45 volunteers, 15 patients with migraine without aura, 15 patients with migraine with aura, and 15 patients with chronic migraine.

Table 1. Mean and standard deviation (±) of demographic, clinical characteristics, MRI volumes and kinematics data.

Demographic characteristics	**Mean and standard deviation (±)**
Age (years)	32.56 ± 8.96
Body mass index (kg/m^2)	24.22 ± 3.85
Migraine features	
Disease duration (years)	14.80 ± 7.62
Intensity (0-10)	7.67 ± 1.52
Frequency (headache days/month)	12.67 ± 8.47
Duration (hours)	29.93 ±37.52
Aura frequency (days)	1.90 ± 3.20
Migraine brain volumes (mm^3)	
Thalamus	13502.65 ± 1059.22
Basal ganglia	20146.60 ± 2054.16
Hippocampus	7889.82 ± 600.18
Brainstem	19701.71 ± 1575.82
Amygdala	3369.32 ± 357.42
Nucleus accumbens	1133.84 ± 357.42
Subcortical gray volume	55131.73 ± 3847.05
Cerebellum	126442.48 ± 9498.50
Insula	13113.98 ± 991.31
Frontal lobe	116047.47 ± 10502.46
Parietal lobe	82132.36 ± 6847.74
Temporal lobe	91652.29 ± 6837.26
Occipital lobe	44573.09 ± 4846.65
Cingulate gyrus	18834.18 ± 2141.93
Average WML Volume	18.85 ± 26.16
Kinematics	
Step-up task	
Step width (cm)	6.96 ± 4.61
Step speed (m/s)	2.62 ± 0.95
Step-down task	
Step width (cm)	11.16 ± 5.12
Step speed (m/s)	2.73 ± 0.94

WML: White matter lesion

There was no significant correlation between migraine features, such as disease

duration, migraine intensity, attack frequency or aura frequency with brain volumes or kinematics data (supplementary material).

3.1 Step width

3.1.1 Step-up task

Table 2 presents the result of the multiple linear regression calculated to predict the step width in the step-up task based on the variables of cortical and subcortical volume and WML. The initial model presented a non-significant regression equation ($F_{15.29}$= 1.188, p= 0.334), with an R^2 of 0.381. After the backward criteria for variables exclusion, the last model included three significant predictors ($F_{3.41}$= 6.255, p= 0.001) with an R^2 of 0.314. Participants' predicted step width is influenced by the subcortical gray volume (-0.353), cingulate gyrus (+0.688) and by the average WML volume (+0.239).

Table 2. Multiple backward linear regression for prediction of step-width in the step-up task based on cerebral morphological variables of cortical and subcortical volume and WML.

Model		*Standardized Coefficients*							
		Beta	t	Sig.	R Square	Adjusted R Square	df	F	Sig.
1	Constant		0.100	0.921	0.381	0.060	15	1.188	0.334
	Thalamus	-0.039	-0.065	0.949					
	Basal ganglia	0.395	0.494	0.625					
	Hippocampus	0.087	0.278	0.783					
	Brainstem	-0.294	-0.948	0.351					
	Amygdala	0.060	0.183	0.856					
	Nucleus accumbens	-0.014	-0.048	0.962					
	Subcortical gray volume	-0.745	-0.521	0.606					
	Cerebellum	0.367	1.161	0.255					
	Insula	0.069	0.246	0.808					
	Frontal lobe	0.037	0.126	0.900					
	Parietal lobe	-0.007	-0.025	0.980					

	Temporal lobe	-0.207	-0.626	0.536					
	Occipital lobe	0.197	0.818	0.420					
	Cingulate gyrus	0.593	2.087	0.046					
	Average WML volume	0.289	1.493	0.146					
13	Constant		0.196	0.846	0.314	0.264	3	6.255	0.001
	Subcortical gray volume	-0.353	-2.083	0.044					
	Cingulate gyrus	0.688	4.050	0.000					
	Average WML volume	0.239	1.835	0.074					

WML: White matter lesion

3.1.2 Step-down task

Table 3 exhibits the results of the multiple linear regression calculated to predict the step width in the step-down task based on the variables of cortical and subcortical volume and WML. The initial model presented a non-significant regression equation ($F_{15.29}$= 1.688, p= 0.108), with an R^2 of 0.684. After the backward criteria for variables exclusion, the last model included three significant predictors ($F_{5.39}$= 4.642, p= 0.002) with an R^2 of 0.373. Participants' predicted step width is influenced by the basal ganglia (-0.716), brainstem (+0.275), nucleus accumbens (+0.458), cingulate gyrus (+0.521) and by the average WML volume (+0.468).

Table 3. Multiple backward linear regression for prediction of step-width in the step-down task based on cerebral morphological variables of cortical and subcortical volume and WML.

Model		*Standardized Coefficients*							
		Beta	t	Sig.	R Square	Adjusted R Square	df	F	Sig.
1	Constant		-0.816	0.421	0.684	0.192	15	1.688	0.108
	Thalamus	0.104	0.188	0.852					
	Basal ganglia	-0.572	-0.771	0.447					
	Hippocampus	-0.167	-0.574	0.570					
	Brainstem	0.272	0.945	0.352					
	Amygdala	0.045	0.145	0.886					

	Nucleus accumbens	0.526	1.999	0.055					
	Subcortical gray volume	-0.360	-0.272	0.788					
	Cerebellum	0.137	0.468	0.643					
	Insula	0.185	0.714	0.481					
	Frontal lobe	-0.213	-0.781	0.441					
	Parietal lobe	0.267	1.007	0.322					
	Temporal lobe	-0.352	-1.147	0.261					
	Occipital lobe	0.377	1.687	0.102					
	Cingulate gyrus	0.524	1.989	0.056					
	Average WML volume	0.619	3.451	0.002					
13	Constant		-1.124	0.268	0.373	0.293	5	4.642	0.002
	Basal ganglia	-0.716	-3.137	0.003					
	Brainstem	0.275	1.891	0.066					
	Nucleus accumbens	0.458	2.385	0.022					
	Cingulate gyrus	0.521	3.201	0.003					
	Average WML Volume	0.468	3.406	0.002					

WML: White matter lesion

3.2 Step speed

3.2.1 Step-up task

Table 4 shows the results of the multiple linear regression calculated to predict the step speed in the step-up task based on the variables of cortical and subcortical volume and WML. The initial model presented a non-significant regression equation ($F_{15.29}$= 1.447, p= 0.191), with an R^2 of 0.428. After the backward criteria for variables exclusion, the last model included three significant predictors ($F_{3.41}$= 6.202, p= 0.001) with an R^2 of 0.312. Participants' predicted step speed is influenced by the cerebellum (-0.480), parietal lobe (+0.424), and temporal lobe (+0.744).

Table 4. Multiple backward linear regression for prediction of step-speed in the step-up task based on cerebral morphological variables of cortical and subcortical volume and WML.

Model		*Standardized Coefficients*							
		Beta	t	Sig.	R Square	Adjusted R Square	df	F	Sig.
1	Constant		1.786	0.085	0.428	0.132	15	1.447	0.191
	Thalamus	0.420	0.731	0.470					
	Basal ganglia	0.974	1.267	0.215					
	Hippocampus	0.369	1.224	0.231					
	Brainstem	0.135	0.452	0.655					
	Amygdala	0.322	1.013	0.319					
	Nucleus accumbens	0.388	1.425	0.165					
	Subcortical gray volume	-1.831	-1.333	0.193					
	Cerebellum	-0.369	-1.213	0.235					
	Insula	-0.066	-0.244	0.809					
	Frontal lobe	0.037	0.132	0.896					
	Parietal lobe	-0.552	-2.012	0.054					
	Temporal lobe	0.678	2.135	0.041					
	Occipital lobe	-0.092	-0.398	0.694					
	Cingulate gyrus	0.094	0.345	0.733					
	Average WML volume	0.098	0.526	0.603					
13	Constant		2.108	0.041	0.312	0.262	3	6.202	0.001
	Cerebellum	-0.480	-3.167	0.003					
	Parietal lobe	-0.424	-2.180	0.035					
	Temporal lobe	0.744	3.674	0.001					

WML: White matter lesion

3.2.2 Step-down task

Table 5 presents the results of the multiple linear regression calculated to predict the step speed in the step-down task based on the variables of cortical and subcortical volume and

WML. The initial model presented a non-significant regression equation ($F_{15.29}$= 1.019, p= 0.464), with an R^2 of 0.345. After the backward criteria for variables exclusion, the last model included three significant predictors ($F_{3.41}$= 4.583, p= 0.007) with an R^2 of 0.251. Participants' predicted step speed is influenced by the cerebellum (-0.382), parietal lobe (-0.496), and temporal lobe (+0.649).

Table 5. Multiple backward linear regression for prediction of step-speed in the step down task based on cerebral morphological variables of cortical and subcortical volume and WML

Model		*Standardized Coefficients*							
		Beta	t	Sig.	R Square	Adjusted R Square	df	F	Sig.
1	Constant		2.282	0.030	0.345	0.006	15	1.019	0.464
	Thalamus	0.488	0.795	0.433					
	Basal ganglia	0.724	0.880	0.386					
	Hippocampus	0.099	0.306	0.761					
	Brainstem	0.225	0.704	0.487					
	Amygdala	0.345	1.013	0.319					
	Nucleus accumbens	0.354	1.215	0.234					
	Subcortical gray volume	-1.744	-1.186	0.245					
	Cerebellum	-0.346	-1.063	0.297					
	Insula	-0.061	-0.214	0.832					
	Frontal lobe	0.230	0.759	0.454					
	Parietal lobe	-0.758	-2.581	0.015					
	Temporal lobe	0.674	1.982	0.057					
	Occipital lobe	-0.041	-0.164	0.871					
	Cingulate gyrus	0.177	0.606	0.549					
	Average WML volume	-0.022	-0.111	0.912					
13	Constant		2.491	0.017	0.251	0.196	3	4.583	0.007
	Cerebellum	-0.382	-2.420	0.020					

Parietal lobe	-0.496	-2.445	0.019
Temporal lobe	0.649	3.072	0.004

WML: White matter lesion

4. Discussion

The present investigation is the first exploratory study designed to evaluate the possible relationships between brain volume and WML with functional performance in walking tasks in patients with migraine, using gold standard methods such as imaging evaluation through MRI [30] and motor assessment through kinematic evaluation [31]. For the step-up task, the step width predictors were the subcortical gray volume and cingulate gyrus volume. In the step-down task, the predictors were the basal ganglia, nucleus accumbens, cingulate gyrus, and average WML volume. The step speed predictors were the cerebellum, parietal, and temporal lobe volume for both step-up and step-down tasks.

The etiology of motor and vestibular alterations in migraine patients is controversial. For some authors, the CNS appears to be more likely to be involved [32, 33, 34], although, in some diagnostic measures, peripheral changes were observed (cranial nerves) [32, 33, 34]. On the other hand, Harno et al. [35] and Akdal et al. [36] suggested that the balance disorders identified in individuals with migraine are due to subclinical cerebellar or brainstem dysfunction; that is, there is a possible involvement of structural changes in these regions that plays a fundamental role in the control of posture. In our findings, some CNS structures strongly related to gait control, such as cerebellum, basal ganglia, and parietal lobe, were predictors of gait variables in patients with migraine.

As seen in other neurological diseases such as multiple sclerosis [37], Parkinson's disease [38], Alzheimer's disease [39] or in brain trauma [40] and aging process [24], the cerebellum, basal ganglia, and parietal lobe are also related to motor functions in migraine patients as shown in this study. The cerebellum participates in the movements of the head, eyes, and limbs, coordination of body movements, balance control during walking, and is also involved in posture [40,41]. The basal ganglia, in addition to receiving inputs from all cortical regions and the thalamus, are another center related to motor function, as they are well-positioned to integrate sensory, motor, cognitive, and other information [41, 42]. In the same way, the relationship between the parietal lobe and motor control is not surprising since this region has its functions related to the perception, planning, and interpretation of sensory information [41,43]. These functions are important for executing the tasks performed in this

study, which require sensory integration, visuospatial function, and control of the relationship between oneself and the environment [44]. Indeed, these brain regions show morphological changes in migraine compared to control individuals [11, 12, 45-47]. These regions explain approximately 25% to 37% of the variability of our gait parameters, being that such regions are involved with motor functions [40-43], which corroborates our findings.

Concerning WML, its average volume was a predictor of the step width in patients with migraine. The prevalence rates of WML in migraine patients vary broadly [11]. WML mainly affects older adults but is also associated with cardiovascular risk factors such as hypertension, smoking, and diabetes [48]. In addition, WML is considered a factor that aggravates gait [49] and balance [50] in older adults. The exact etiology and pathogenesis of WML, in addition to its role in neurodegeneration, are not totally known in migraine [48, 51]. Thus, more research on WML is needed to clarify these issues and understand possible associations between WML and motor disorders in migraine.

Some limitations of the study must also be considered. The sample included only women, and part of the migraine group consisted of patients from a tertiary clinic. These factors can restrict generalization. In addition, a limitation in the analysis of the causal relationship between brain volumes and motor changes can be identified in a cross-sectional study compared to a prospective cohort study. We also did not include healthy controls in this study since we did not reach the necessary number of participants to make comparisons. Thus, it is not possible to define whether the relationship between cerebral and motor morphological changes is unique in migraine.

Despite these limitations, it is important to highlight the strengths of this study. It was the first exploratory study to investigate, using gold standard methods [30, 31], the possible associations between morphological brain alterations and functional performance alterations present in migraineurs. Our study demonstrated a possible involvement of the CNS in the motor alterations present in patients with migraine. Although these results have demonstrated a possible involvement of the CNS in the motor changes in migraine, many aspects of functional performance and their relationship with clinical and neuroimaging findings still need to be in migraine, opening the way for new investigations on this subject. Identifying changes in motor control and functional impairments susceptible to intervention, whether linked to structural changes in the CNS, is a challenge to be overcome in the study of migraine, which could bring excellent perspectives for the future management of the disease.

5. Conclusion

Changes in the volume of brain regions, specifically related to motor functions such as the cerebellum, parietal lobe, and basal ganglia, predicted gait variables such as step width and step speed in migraine patients. Such findings bring clinical meaning to many morphological brain changes in migraine patients.

List of abbreviations

BMI – Body mass index

CNS – Central nervous system

ICHD - International Classification of Headache Disorders

MRI – Magnetic Resonance Image

SD - standard deviation

WM – White matter

WML – White matter lesions

Statements and Declarations

Ethics approval and consent to participate

The Research Ethics Committee of the Ribeirão Preto Clinics Hospital (process HCRP nº 13068/2015) approved this study. All volunteers signed a consent form before participating in the present study.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed equally. All authors read and approved the final manuscript.

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Supplementary file

Supplementary table. Correlation between clinical characteristics, MRI volumes and kinematics data.

	Disease Duration (years)		Intensity (0-10)		Frequency (headache days/month)		Aura Frequency (days/month)	
	r	95% CI	r	95% CI	r	95% CI	r	95% CI
Migraine brain volumes (cm^3)								
Thalamus	-0.64	-0.213 to 0.193	0.143	-0.181 to 0.475	-0.295	-0.573 to 0.018	-0.127	-0.354 to 0.262
Basal ganglia	-0.098	-0.418 to 0.173	0.013	-0.330 to 0.344	-0.030	-0.389 to 0.267	-0.025	-0.264 to 0.195
Hippocampus	0.263	-0.098 to 0.547	0.045	-0.496 to 0.449	-0.124	-0.326 to 0.070	0.275	-0.213 to 0.563
Brainstem	-0.116	-.0342 to 0.261	0.133	-0.309 to 0.382	-0.187	-0.428 to 0.254	-0.257	-0.632 to 0.052
Amygdala	0.236	-0.120 to 0.550	-0.155	-0.469 to 0.126	0.055	-0.270 to 0.367	0.208	-0.169 to 0.444
Nucleus accumbens	-0.142	-0.344 to 0.219	0.110	-0.282 to 0.531	0.181	-0.166 to 0.513	0.076	-0.158 to 0.229
Subcortical gray volume	-0.042	-0.385 to 0.283	0.063	-0.216 to 0.417	-0.153	-0.431 to 0.112	-0.024	-0.483 to 0.257
Cerebellum	0.017	-0.427 to 0.259	-0.046	-0.339 to 0.218	-0.292	-0.543 to 0.014	-0.210	-0.442 to 0.240
Insula	0.018	-0.256 to 0.332	0.020	-0.371 to 0.348	-0.061	-0.483 to 0.347	0.110	-0.209 to 0.376
Frontal lobe	0.046	-0.306 to 0.433	0.095	-0.202 to 0.449	-0.077	-0.326 to 0.216	0.158	-0.282 to 0.455
Parietal lobe	0.110	-0.211 to 0.404	-0.086	-0.292 to 0.194	-0.137	-0.351 to 0.099	0.162	-0.096 to 0.471
Temporal lobe	0.230	-0.096 to 0.602	-0.064	-0.296 to 0.148	-0.152	-0.380 to 0.085	-0.028	-0.206 to 0.251
Occipital lobe	0.162	-0.146 to 0.451	0.074	-0.303 to 0.339	0.020	-0.262 to 0.284	0.077	-0.268 to 0.351
Cingulate gyrus	0.021	-0.162 to 0.339	0.050	-0.173 to 0.328	-0.049	-0.275 to 0.178	0.173	-0.060 to 0.466
Average WML Volume	0.029	-0.266 to 0.379	0.082	-0.242 to 0.276	-0.107	-0.432 to 0.187	-0.094	-0.295 to 0.134
Kinematics								
Step-up task								

Step Width (cm)	-0.001	-0.322 to 0.357	0,165	-0.068 to 0.401	0.013	-0.236 to 0.230	0.174	-0.259 to 0.544
Step Speed (m/s)	-0.043	-0.255 to 0.265	-0.172	-0.523 to 0.263	0.208	-0.156 to 0.656	-0.084	-0.360 to 0.118
Step-down task								
Step Width (cm)	0.008	-0.211 to 0.307	0.146	-0.158 to 0.448	-0.035	-0.305 to 0.251	0.130	-0.278 to 0.502
Step Speed (m/s)	-0.055	-0.210 to 0.260	-0.183	-0.453 to 0.195	0.319	-0.044 to 0.656	-0.062	-0.353 to 0.110

r: Pearson’s correlation value, 95% CI: 95% confidence intervals.

4 CONCLUDING REMARKS

From the results obtained, we can reach some conclusions. First, the light and sound increments made no difference between the control and migraine groups while performing functional tasks. Although the discomfort induced by light and sound was higher in the migraine group, bright light and loud sound had an impact on functional activities, regardless of migraine status.

The influence of light and sound on functional performance still needs further investigation. Since our findings require a consistent pathophysiological basis to identify the physiological mechanisms of photophobia and phonophobia in the role of functional performance in both migraine and healthy individuals.

Finally, regarding the findings related to the involvement of morphological brain changes with alterations in functional performance, it seems that certain brain regions, especially those associated with motor functions, may explain part of some functional alterations. As is the case of changes in step width and step speed already identified in patients with migraine, as altered motor variables. But future studies are still needed to identify longitudinal changes in neuroimaging markers as possible predictors of poor functional performance in patients with migraine. So that these morphological changes could be related to clinical practice.

Surely much still needs to be explored regarding the possible origins of motor changes in patients with migraine. Knowing the role of clinical features such as photo and phonophobia, and morphological brain changes in functional performance can help clinicians to manage this disease efficiently.

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6 ATTACHMENTS

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA
DE RIBEIRÃO PRETO DA UNIVERSIDADE DE SÃO PAULO

FMRP-USP
RIBEIRÃO PRETO

Ribeirão Preto, 08 de outubro de 2015.

Ofício nº 3570/2015
CEP/MGV

PROCESSO HCRP nº 13068/2015

Prezados Senhores,

O trabalho intitulado **"VOLUMETRIA POR RESSONÂNCIA MAGNÉTICA DE TRONCO CEREBRAL E CEREBELO DE PACIENTES COM MIGRÂNEA" – Projeto de Pesquisa Versão 2 de 29/09/2015,** foi analisado "AD REFERENDUM" pelo Comitê de Ética em Pesquisa e enquadrado na categoria: **APROVADO,** bem como o Termo de Consentimento Livre e Esclarecido Versão 2 de 29/09/2015.

Este Comitê segue integralmente a Conferência Internacional de Harmonização de Boas Práticas Clínicas (IGH-GCP), bem como a Resolução nº 196/96 CNS/MS.

Lembramos que devem ser apresentados a este CEP, o Relatório Parcial e o Relatório Final da pesquisa.

Atenciosamente.

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Ribeirão Preto, 15 de dezembro de 2015

Ofício nº 4434/2015
CEP/MGV

Prezadas Senhoras,

O trabalho intitulado **"CONTROLE DA LOCOMOÇÃO ADAPTATIVA EM MIGRANOSOS COM E SEM AURA NA PRESENÇA DE PERTURBAÇÃO VISUAL E SONORA",** foi analisado pelo Comitê de Ética em Pesquisa no dia 23/11/2015 e enquadrado na categoria: **APROVADO,** bem como o **Termo de Consentimento Livre e Esclarecido – Versão 2, de 13/11/2015,** de acordo com o Processo HCRP nº 16210/2015.

De acordo com Carta Circular nº 003/2011/CONEP/CNS, datada de 21/03/2011, o sujeito de pesquisa ou seu representante, quando for o caso, deverá rubricar todas as folhas do Termo de Consentimento Livre e Esclarecido – TCLE – apondo sua assinatura na última do referido Termo; o pesquisador responsável deverá da mesma forma, rubricar todas as folhas do Termo de Consentimento Livre e Esclarecido – TCLE – apondo sua assinatura na última página do referido Termo.

Este Comitê segue integralmente a Conferência Internacional de Harmonização de Boas Práticas Clínicas (IGH-GCP), bem como a Resolução nº 466/12 CNS/MS.

Lembramos que devem ser apresentados a este CEP, o Relatório Parcial e o Relatório Final da pesquisa.

Atenciosamente.

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