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Band Power Analysis of the EEG Frequency Spectrum: An Evaluation of Interictal Periods of the Migraine Phase Using an Eyes-open vs. Eyes-closed Resting State Paradigm

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BAND POWER ANALYSIS OF THE EEG FREQUENCY SPECTRUM: AN EVALUATION OF INTERICTAL PERIODS OF THE MIGRAINE PHASE USING AN EYES-OPEN VS. EYES-CLOSED RESTING-STATE EEG PARADIGM

by

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Abstract

Migraine is a primary headache disorder characterized by abnormal cortical activity across migraine phases. However, less is known about electroencephalographic activity present during asymptomatic periods of the migraine cycle or during resting-state conditions. Given the theory that these testing conditions may reflect more permanent cortical states, the present study examined the interacting role of resting-state conditions (eyes-open vs. eyes-closed) and headache diagnosis (migraine vs. control) on absolute band power across the EEG frequency spectrum. In-line with previous research, we hypothesized that interictal periods of the migraine phase would be characterized by a difference in alpha frequency and an increase in slow-wave activity compared to controls. We further predicted that group-related effects would differ depending on resting-state conditions. In general, slow-wave activity was greater in migraine compared to controls, although a significant interaction effect was obtained regarding fast-wave beta power. Broad spectrum cortical differences between migraine and healthy controls are discussed.

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Introduction

The most recent Global Burden of Disease study ranked headache disorders as the second leading factor contributing to disability and burden in both occupational and personal roles worldwide (Saylor & Steiner, 2018). Of the primary headache disorders identified by the International Headache Society (IHS; Headache Classification Subcommittee of the International Headache Society, 2018), migraine alone was ranked as the third most prevalent disorder in the world, as well as the third highest cause of disability in both men and women between the ages of 15 and 49 (Steiner, Stovner, & Vos, 2016). Given the wide recognition of migraine as a public health concern, it is somewhat surprising that little is known about the psychophysiological mechanisms underlying it.

The first investigation of the psychophysiological underpinnings of migraine, which appeared in the literature in 1947, employed electroencephalographic (EEG) methods, a specialized recording procedure developed and published 23 years prior (in 1924) by Hans Berger. This initial investigation by Dow and Whitty (1947) indicated that migraine was best characterized by "basal dysrhythmia," or abnormal brain activity, across the various phases of migraine, a finding that has persisted into the present (see de Tommaso, 2019). Despite subsequent findings linking migraine to abnormal brain activity, EEG methods are not currently recognized as a reliable diagnostic tool in clinical practice, due, in part, to a lack of randomized controlled trials (RCTs) in this area (Stokes & Lappin, 2010). The utility of EEG methods in experimental quantitative studies, however, has garnered increased support in the intervening years (e.g., Akben, Tuncel, & Alkan, 2016; Lozeron et al., 2018, de Tommaso, 2019).

At present, EEG methods serve as observable and quantifiable measures of both continuous (resting-state) and stimulus-locked (event-related brain potential--ERP) neurophysiological data. Procedurally, EEG is well suited for research with human participants as it provides a non-invasive measure of brain activity, collected by scalp surface electrodes, to monitor the cortical activity generated by the electrical potential of neurons. Some type of separate hardware system (e.g., actiCHamp) is needed in order to amplify the signal produced by the recorded brain activity. The brain activity is then converted from an analog electrical signal to a digital signal that can be analyzed using computer software. EEG can be recorded in the absence of overt behavioral responses, making this method of quantifying brain activity ideal for use with headache populations (Cao et al., 2016; Viticchi et al., 2012). Even in the absence of overt behavioral responses (e.g., verbal response, button pressing, eye-tracking, etc.), EEG methods can be used to quantify cortical activity occurring automatically in response to both external events and more transient resting states.

EEG and Migraine

Accumulated findings from EEG studies support the theory that migraine is characterized by abnormal cortical activity across key sensory areas when compared to otherwise healthy controls. Using both standard EEG and methods that allow for more localized analyses (e.g., magnetoencephalography--MEG, LORETA, wavelet analysis), researchers have observed migraine-specific abnormal cortical activity in the sensory processing of pain and in more general information processing (e.g., visual processing and auditory processing), as reviewed below.

Pain. With regard to abnormal processing of pain, researchers have previously observed reduced habituation to nociceptive stimuli in migraine populations. For example, abnormal pain

processing was found to be characterized by both an increase in subjective pain ratings and a corresponding increase in N_2P_2 cortical-evoked potentials to pain (Lev, Granovsky, & Yarnitsky, 2010). Using a wavelet analysis to examine changes in the EEG rhythm across time and frequency, de Tommaso et al. (2015) found a pattern of increased slow-band activity preceding a pain stimulus in individuals with migraine. An increase of slow-band activity has also been observed at least one day before an initial migraine attack, with slow-band activity returning to normal levels in the days following a migraine attack (e.g., Kropp & Gerber, 1998). These studies focused on an ERP known as the contingent negative variation (CNV), which is characterized by slow cortical potentials associated with attention and anticipation of a motor response (Walter, Cooper, Aldridge, McCallum, & Winter, 1964). Specifically, Siniatchkin et al. (2006) found a global increase in CNV amplitude and a lack of habituation in response to stress before migraine attacks; this pattern of activity differed significantly from data obtained after migraine attacks, during interictal periods, and in healthy controls. Cortical spreading depression (CSD) has similarly been observed in migraine, particularly in migraine with aura (MA), and is thought to precede individual migraine attacks (Noseda & Bursteain, 2013). CSD is characterized by a wave of hyperactivity followed by neuronal inhibition (Bhaskar, Saeidi, Borhani, & Amin, 2013; Costa et al., 2013). The CSD wave is thought to activate the trigeminovascular system, which causes inflammatory changes in pain-sensitive brain structures, leading to alterations in cerebral blood flow. In line with previous theories viewing migraine as a vascular disorder caused by vasoconstriction and sudden-onset vasodilation, these changes in the activity of the trigeminovascular system are thought to be the cause of migraine pain (Noseda & Burstein, 2013).

In practice, migraine is typically classified as either an episodic (EM) or chronic (CM) headache disorder (Katsarava et al., 2012), with migraine-related symptomology occurring either on occasion or frequently, but not constantly. However, the utility of classifying migraine as an episodic disorder has been called into question given that the patterns of inhibited habituation and increased activity in pain-processing regions are consistent with chronic pain research (Vossen et al., 2015). Taken together, research on basic aspects of EEG and CSD support the theory that migraine is associated with global changes in pain processing.

Visual and Auditory Processing. A consistent feature of migraine psychophysiology is an increase in visual and auditory cortex activity that persists during interictal periods of the migraine phase (Mickleborough, Truong, & Handy, 2011). Neural network analyses have uncovered an abnormal pattern of functional connectivity specifically within the visual network of individuals experiencing migraine with aura (de Tommaso et al., 2017). Previous research has also found that individuals with migraine show reduced habituation to unattended visual stimuli, as measured by a visual-evoked N1 ERP component (Coppola et al., 2015; Mickleborough et al., 2011). Similar results were observed when using an auditory paradigm, wherein N1 peak amplitudes were found to be greater to tone pairs in individuals with migraine than in healthy controls (Sable et al., 2017). Findings of enhanced N1 responses to unattended stimuli in ERP studies suggest that migraine may be characterized by reduced habituation to repeated auditory and visual stimuli, as well as increased cortical hyperresponsivity to these sensory events (Coppola, Pierelli, & Schoenen, 2007). Functionally, this reflects abnormally increased sensory-related attention and a deficit in the functions that would normally filter, or reduce the salience of, unattended visual and auditory information (Nguyen, McKendrick, & Vingrys, 2016).

Resting-State EEG Paradigms

Stimulus-evoked research paradigms, such as those discussed previously, provide an opportunity to examine functional differences in the form of ERPs. Resting-state EEG data, absent an experimental manipulation, however, may provide a more stable measure of cortical abnormalities. Resting-state conditions are defined as states of wakefulness in which there is no active task. Resting-states typically involve either (1) an eyes-closed rest condition (ECR) in which participants close their eyes but remain awake or (2) an eyes-open rest condition (EOR) in which participants open their eyes and focus their vision on a central fixation point. An early criticism of resting-state data centered around the question of whether brain activity, if left undefined by a discrete task, would vary incomparably; however, researchers have found that even passive tasks, such as EOR and ECR, demonstrate reproducible differences in EEG activity (Gusnard & Raichle, 2001).

Alpha rhythm is thought to be the EEG correlate of relaxed wakefulness that is most associated with resting-state studies. This pattern of activity was first identified by Berger and stems from theories of alpha synchronization, or the decrease in low-frequency cerebral activity in response to eyes-opening (Berger, 1933; as cited in Kirschfeld, 2005). In further support of alpha synchronization, Gómez-Ramírez et al. (2017) analyzed three minutes of EOR and ECR activity, respectively, and found a decrease in alpha activity across the entire cortex in response to visual stimulation (i.e., during an eyes-open condition); conversely, alpha activity in this study increased in an eyes-closed condition. These changes in eyes-open and eyes-closed resting-state conditions are thought to be due to the reorganization of brain activity in response to visual stimuli, wherein EOR is thought to be associated with external perception and ECR is thought to be associated with internal perception (Marx et al., 2004). These differences in alpha activity are

also present during conditions in which EOR and ECR are evaluated in complete darkness in order to remove the potential confound of light stimulation and visual input (Boytsova & Danko, 2010). Although much of the previous research has focused on ECR and EOR differences in the alpha band, support exists for condition-specific differences across other frequency bands as well. Using EEG data from two minutes each of EOR and ECR, Kan et al. (2017) found that delta and theta frequency power increased under EOR conditions. Consistent with previous research, alpha frequency power increased under ECR conditions. Beta frequency power, however, was not statistically different between conditions (Kan et al., 2017). Taken together, EOR and ECR should not be evaluated as comparable baselines; instead, these resting-state conditions can be evaluated on the basis of demonstrating reproducible differences in brain activity (Barry, Clarke, Johnstone, & Brown, 2007).

Spectral Analysis

Of the methods used to quantify resting-state EEG activity, spectral analyses are receiving increased interest due to their utility in quantifying EEG signals across broad-range frequency spectra (Dressler, Shneider, Stockmanns, & Kochs, 2004). Spectral analyses are methods used to quantify EEG during both active states, in which participants are performing a task, and resting-states, absent an active task (de Tommaso, 2019). These techniques are used to analyze the EEG signal according to individual "frequency ranges" (i.e., bands) and "time intervals" (i.e., epochs) (de Tommaso, 2019, p. 3). The standard EEG signal can be broken down into five basic rhythms—alpha, beta, delta, theta, and gamma—that are identified by frequency (Hz) and typically associated with distinct cerebral activity (see Louis & Frey, 2016). Alpha (8-12.5 Hz) waves are characterized by a state of wakeful relaxation, while beta (13-30 Hz) waves are typically associated with a state of alertness and attentiveness to external stimuli.

Both delta (0.1-3.5 Hz) and theta (4-7.5 Hz) waves reflect slow-wave activity and are distinguishable predominantly by frequency range. Gamma waves (> 30 Hz) have been associated with a broader range of brain activity, such as cognition and perception, but are more frequently associated with motor responses (Amo, de Santiago, Barea, López-Dorado, & Boquete, 2017); as such, this high frequency band is not typically studied as a diagnostic index.

Both discrete (DFT) and fast Fourier Transforms (FFT) are quantitative EEG (QEEG) methods common to spectral analysis (Dressler et al., 2004; de Tommaso, 2019). Band power (μV^2; see MATLAB) is used to represent either a specific band with regards to the entire EEG signal (i.e., relative band power) or the averaged power of a particular band (i.e., absolute band power). The observations noted in the resulting frequency spectrum do not necessarily reveal clinical differences; however, differences in the "spectral profile" of individuals with migraine may reveal clinical abnormalities that can provide insight into more basal differences in brain activity (de Tommaso, 2019, p. 3).

Migraine Research Using Spectral Analyses

Migraine Phases. Migraine is characterized by four distinct phases: preictal (i.e., 36-72 hours before a migraine attack), ictal (i.e., during a migraine attack), postictal (i.e., 36-72 hours after a migraine attack), and interictal (i.e., symptom-free periods between migraine attacks). Current findings suggest that migraine EEG patterns are characterized by slow wave activity during asymptomatic periods, as well as fluctuating changes in neuronal activity between migraine phases (de Tommaso, 2019; de Tommaso et al., 2013). In a series of studies examining EEG activity during an EOR condition, researchers observed notable differences between migraine phases. Using localized spectral analyses (e.g., LORETA analysis), Bjork and Sand (2008) observed an increase in frontocentral delta, alpha, and theta band power 36 hours before

a migraine attack; similarly, in a follow-up study, Bjork, Stovner, and Sand (2011) found a pattern of increased delta activity localized to the side of the head that became painful during the next migraine attack. These same researchers did not find significant EEG differences when comparing post-ictal and interictal periods (Bjork & Sand, 2008); instead, post-ictal activity was observed to become more similar to interictal levels (Bjork et al., 2011). Moreover, during a migraine attack, alpha and beta power tend to increase (Bjork & Sand, 2008), but the levels are still generally lower than in healthy controls (Cao et al., 2016). Overall, findings provide further evidence that resting-state EEG power differs between migraine phases; this difference may be characterized by lower band power during and between migraines that tends to normalize after migraine attacks (Cao et al., 2016).

Interictal Phase. In the earliest study in which researchers observed changes in the spectral frequency among individuals with migraine, the beginning of asymptomatic periods was characterized by a change in alpha frequency (Nyrke, Kangasniemi, & Lang, 1990). Notably, EEG activity prior to and after migraine attacks was not significantly different from the EEG in migraine-free controls (Nyrke et al., 1990). De Tommaso et al. (1998) observed similarities in alpha band power during and after migraine attacks that significantly differed compared to interictal activity. In this study, migraine was further characterized by a reduced amplitude of the steady-state visual evoked potential (SSVEP) F1 component during a migraine attack that increased during interictal periods, a finding consistent with previous ERP studies. These observations furthered interest in studying interictal, or symptom-free, periods of the migraine phase.

Clemens et al. (2008), using LORETA analyses to localize the anatomical source of abnormal EEG activity during interictal periods, observed an increase in alpha band activity in

individuals with migraine compared to controls during an ECR condition; this increased activity was localized to posterior regions of the cortex. In a subsequent study examining differences between migraineurs and controls during interictal periods, Bjork et al. (2009) noted a pattern of globally increased relative theta activity in individuals with migraine during a passive task that was not further defined. The interictal phase was also characterized by an increase in delta power on the symptomatic side of the head (i.e., the side of the head that was painful during the last migraine attack). The accumulated research findings to date suggest that the interictal period of the migraine phase is associated with increased slow wave activity between attacks.

As demonstrated, the spectral analytic methods that have been used in previous migraine research have yielded variable, and at times contradictory, results (see Table 1 in Appendix A). A more recent review of migraine EEG research noted that the quantitative methods employed to date have not been standardized across research in this area (de Tommaso, 2019), although efforts have been made towards reaching consensus guidelines with respect to documentation and publication standards for EEG studies in general (Keil et al., 2014). In addition to variability in reporting standards, brain activity has been observed to differ across various psychological and neurological conditions (e.g., depression, migraine, etc.) compared to non-symptomatic healthy individuals. For example, in a study of resting-state EEG differences using a population of euthymic participants (i.e., psychiatric population during a symptom-free period), Kan et al. (2017) noted that depressive symptoms significantly impact EEG activity compared to healthy controls. Together, these studies lend support to the importance of obtaining more process-pure data by recording EEG during two conditions, (1) resting-states and (2) symptom-free periods.

Current Study

The pathophysiology of migraine has been studied and documented in a range of studies; however, definitive differences between migraine and healthy controls remain unclear. Similarly, although previous psychophysiological and neurophysiological research has found abnormal ERP responses to auditory (Sable et al., 2017), visual (Mickleborough et al., 2011), and pain sensory (Lev et al., 2010) stimuli, EEG differences during resting-state conditions have been less well studied. Furthermore, studies, particularly those presented in Table 1, include data from only one resting-state condition, despite evidence that ECR and EOR are associated with distinct patterns in EEG activity. Moreover, although cortical abnormalities during symptomatic periods of the migraine phase have been reported with greater frequency, the abnormalities present during headache-free, or asymptomatic, periods may be of greater clinical significance as they may represent a more stable or permanent cortical state (see Nyrke et al., 1990).

Given the present state of affairs, the goal of this study was to further explore whether resting-state EEG differences exist between individuals presenting with migraine (during headache-free periods) and healthy controls, with these differences being evaluated using EEG band power analytic methods during both ECR and EOR resting-state conditions, respectively. The study reported herein consisted of a secondary analysis of an existing dataset; the primary measures in this study were derived from data collected previously. The available data included the following independent variables: Group (Migraine vs. Control) and Condition (EOR vs. ECR). Resting-state EEG data were collected under each condition. In this study, we focused on the following dependent variables that had not been examined before: absolute band power across the alpha, beta, theta, and delta frequency spectra, respectively. Based on the literature reviewed above, the band power in the migraine group was expected to be greater overall when

compared to the healthy controls. With the exception of alpha, differences in band power across resting-state conditions (eyes-open vs. eyes-closed) in migraine and control are less established.

Consideration of the above findings led us to formulate 4 specific hypotheses for the varied frequency spectra, which follow below.

Hypothesis 1 - ALPHA: We predict that alpha power will be greatest in the ECR condition in the migraine group relative to controls.

The next two hypotheses, pertaining to theta and delta power, were derived from the research findings of Kan et al. (2017), who concluded that power differs by resting-state condition (eyes-open vs. eyes-closed) across the frequency spectrum.

Hypothesis 2 - THETA: We predict that theta power will be greater during EOR compared to ECR in the migraine group as compared to the controls.

Hypothesis 3 - DELTA: We predict that delta power will be greater during EOR compared to ECR in the migraine group as compared to the controls.

Findings from research we reviewed, suggesting that migraine is chiefly characterized by an increase in slow-wave activity, led us to advance our final hypothesis.

Hypothesis 4 - BETA: We predict that no significant differences will be found across either group (Migraine vs. Control) or Condition (EOR vs. ECR).

Methods

Participants

Migraine inclusion criteria at the time of data collection (see Sable et al., 2017) were based on the ICHD-II diagnostic system (Headache Classification Subcommittee of the

International Headache Society, 2004). Symptoms reported at the time the original data were collected were re-evaluated using the more recent ICHD-3 criteria (Headache Classification Subcommittee of the International Headache Society, 2018) to ensure all participants conformed to the most current criteria for a migraine-related headache disorder. According to the ICHD-3, the primary criterion for a migraine diagnosis includes experiencing at least five migraines per month of a 4 to 72-hour duration. Consequently, all participants from the initial data set were re-reviewed to ensure they satisfied this criterion. Initial inclusion criteria also included indicating normal or corrected-to-normal vision and normal or corrected-to-normal hearing. Participants were excluded from the study for the probable presence of a co-occurring psychiatric or medical condition, co-morbid headache diagnosis, conditions in which headache was not the primary disorder (e.g., headache condition induced by physical trauma), and cases in which migraine was not the primary diagnosis (e.g., tension-type headache, or other headache conditions exclusive of migraine). Individuals presenting with migraine included both men and women meeting criteria for migraine with or without aura, whereas individuals in the control group consisted of both men and women that did not report migrainous headache-related symptoms. Data were available for 38 participants in total. Of these, five cases were excluded due to missing or incomplete EEG or demographic data (i.e., two and three removed from control and migraine group, respectively), one was excluded due to the probability that the headache diagnosis was not migraine-related, and four were excluded due to the removal of more than 50% of the EEG data during the artifact-rejection process (i.e., two each removed from control and migraine group; see recommendations by Picton et al., 2000). The final sample consisted of 28 participants split into two groups: Migraine (n = 15) and Control (n = 13).

Migraine. Individuals in the migraine group reported migraine-related symptoms consistent with criteria for Migraine with aura (*n* = 8), migraine without aura (*n* = 4), and probable migraine (*n* = 3). See Table 2 in Appendix B for more detailed information about individuals in the migraine group. Individuals in this group (*n* = 15) consisted of men (*n* = 4) and women (*n* = 11) between the ages of 19 and 49 (*M* = 24.13, *SD* = 8.46). Participants reported 12.5 to 21 years of completed education (*M* = 15.12, *SD* = 2.28). The majority of the sample consisted of African American (*n* = 5) and Caucasian (*n* = 8) participants, with others identifying as Hispanic (*n* = 1), or other (*n* = 1). The majority of participants indicated English as their first language (*n* = 12). All individuals in the migraine group indicated right hand dominance. The majority of participants indicated normal hearing (*n* = 14), and one participant indicated non-corrected hearing loss in one ear. Participants most frequently drank soda (46.7%) or coffee (40.0%) as their main form of caffeine intake. In addition, 7.1% reported smoking cigarettes, and the majority (92.9%) reported not using tobacco or tobacco products.

Control. Individuals in the control condition did not report migraine-related symptoms. Individuals in this group (*n* = 13) consisted of men (*n* = 4) and women (*n* = 9) between the ages of 18 and 39 (*M* = 21.0, *SD* = 5.57). Participants reported 12.5 to 16.5 years of completed education (*M* = 13.85, *SD* = 1.61). Participants consisted of individuals identifying as Caucasian (*n* = 5), Asian (*n* = 1), Hispanic (*n* = 2), African American (*n* = 3), and other (*n* = 2). The majority of participants indicated English as their first language (*n* = 9). With the exception of one participant that did not respond, 12 participants indicated right hand dominance. All participants in this group indicated normal hearing (*n* = 13). Participants most frequently drank soda (27.3%) and coffee (45.5%) as their main form of caffeine intake, though 18.2% reported

no caffeine use. One participant reported using tobacco products (e.g., vaping, dip), and the majority (92.3%) reported not using tobacco or tobacco products.

Materials

Continuous EEG data were acquired using the Biopac MP36 hardware and Biopac Student Lab software (Biopac, Goleta, CA, USA). A StimTracker (Cedrus Corporation, San Pedro, CA, USA) was used to mark the onset and end of each task condition in the EEG data file. Both hardware and software were routed to a PC on which data were recorded and stored.

Procedure

Written informed consent was obtained upon arrival. Participants completed a basic demographic form (e.g., age, race/ethnicity, sex) that included items related to their migraine diagnosis (e.g., age of onset, typical duration, typical pain level, medication use, etc.). Individuals using abortive or prophylactic medications, including common analgesics, were asked to refrain from their regular medication use at least 24 hours prior to assessment. Participants were seated in a private room, facing a flat-screen LCD computer monitor (19 inches). Electrodes were applied to the scalp, and noise-cancelling headphones were placed over the ears. Participants were asked to refrain from frequent and disruptive movement of both the head and body; this was implemented as a preventive measure to minimize the probability of artifacts in the data. During the eyes-closed condition, participants were asked to remain at rest with their eyes closed; conversely, during the eyes-open condition, participants were asked to focus their visual attention on a central fixation cross on the computer monitor. The resting-state portion of this study took approximately 10 minutes (i.e., 5 minutes per condition). Students had the option of earning credit towards course requirements in exchange for participation in this

study; no other form of compensation was granted. Upon completion of the study, participants were thanked and debriefed.

EEG

Design, Procedure, and Processing. EEG was recorded interictally (i.e., between individual migraine attacks) during symptom-free periods. Resting-state EEG was recorded during EOR (5 minutes) and ECR (5 minutes) conditions for individuals in both the migraine and control groups. The condition order was counterbalanced to prevent potential order effects. Active responses (e.g., button press) by participants were not required.

Three 10-mm gold cup electrodes were placed on the scalp according to the International 10-20 system of electrode placement (Jasper, 1958). A single electrode was placed at Cz, left mastoid, and right mastoid, respectively. The electrode placed on the right mastoid served as the reference, while the electrode placed on the left mastoid served as the ground. Each location was lightly exfoliated with Nuprep (Weaver and Company, Aurora, CO, USA) and cleansed with an alcohol pad. Electrodes were secured to the scalp using Grass EC2 electrode cream (Natus Manufacturing, Galway, Ireland) and gauze. Electrode impedances were kept below 5 kΩ. Continuous EEG activity was sampled at 1000 Hz with an on-line bandpass filter of 0.05 - 100 Hz and a notch filter of 60 Hz.

The resulting data were excluded from further analysis if optimal recording conditions could not be met due to high impedance (above the 5 kΩ threshold), difficulties with electrode adhesion, or excessive participant movement during the recording session. Similarly, participant files were excluded on the basis of incomplete EEG data due to either previously reported or currently observed technical issues that may have occurred during data acquisition.

Analysis

EEG Analysis. Analytic procedures for electrophysiological data included the following: epoch extraction, artifact rejection, and power analysis at different frequency bands. EEG data were analyzed using EEGLAB, an open-source MATLAB (The Mathworks, Inc., Natick, MA, USA) add-on for electrophysiological signal processing and analyses (Van Boxtel, 1998; Lopez-Calderon & Luck, 2014). A custom MATLAB script was created for the purpose of this study to generate the QEEG frequency spectrum and complete the spectral analysis.

Processed EEG data were segmented into 4-s-epochs by creating event markers in the data. As such, continuous EEG data from each recording condition (Eyes-open and Eyes-closed) were segmented into approximately 75 specific time-windows, or epochs, of 4 s each (see Levy, 1987, for a review of the effect of epoch length on spectrum analyses). Data were subjected to automatic artifact rejection in which individual epochs containing activity above a $\pm$ 100 μV threshold were automatically identified and removed from further analysis. Cases in which 50% or more of the epochs were identified for removal were excluded from further analysis (see Picton et al., 2000; again, this resulted in the exclusion of four cases). Using this artifact rejection criteria, 4.80% of the epochs in the control group were removed, and 4.46% of the epochs in the migraine group were removed. Artifact-free epochs were used to generate a quantitative EEG (QEEG) frequency spectrum in order to perform a power analysis at different frequency bands. This frequency spectrum was generated using spectopo, an N-point FFT command in MATLAB. Absolute band power (μV^2) was calculated by averaging power across bins in the following frequency spectra (0.5 Hz frequency resolution): Delta (δ; 0.1-3.5 Hz), Theta (θ; 4-7.5 Hz), Alpha (α; 8-12.5 Hz), and Beta (β; 13-30 Hz).

Statistical Analysis. Values resulting from the EEG analysis were analyzed using IBM SPSS Version 25 (IBM-Analytics, New York, USA). A 2 x 2 mixed ANOVA, with Group (Migraine vs. Controls) serving as the between-subjects factor and Condition (EOR vs. ECR) as the within-subjects factor, was used to analyze absolute band power values for hypothesis testing. Each frequency band (i.e., Alpha, Theta, Delta, and Beta) was analyzed separately, with $p \leq .05$ indicating statistical significance.

Results

Data Screening

For the purpose of hypothesis testing, data were screened according to recommendations from Pallant (2013). No data were missing across all levels of the independent and dependent variables. All dependent variables were continuous but were observed to be non-normally distributed, as assessed by Shapiro-Wilk's test for normality ($p < .001$). A subsequent evaluation revealed skewed ($\pm$ 2.0) and kurtotic values ($\pm$ 2.0). Using the *z*-score method for outlier detection of continuous variables ($\pm$ 3.29), six values were identified as univariate outliers. An evaluation of the Mahalanobis distance did not reveal any multivariate outliers, suggesting that the presence of outliers in the data were not due to the combined effect of more than one out-of-bound value. Univariate outliers were corrected using winsorization, whereby the six cases of univariate outliers were replaced with a value representing one standard deviation above the mean for that particular group. This was done to minimize the impact of outliers in the data without removing them completely. More complex missing data handling techniques were not used in this analysis because the corrected cases were not organically missing and did not account for a significant portion of the data (Jakobsen, Gluud, Wetterslev, & Winkel, 2017). Levene's test indicated equal variance across groups ($p > .001$). Finally, although data were non-

normal, this may not constitute a significant problem because ANOVA and other mean-based inferential tests are robust to violations of normality.

Tests of Hypotheses

Absolute band power (μV^2) was analyzed in the specified frequency range (0.01 - 30 Hz). See Table 3 in Appendix C for absolute band power across groups and conditions.

Hypothesis 1 - Alpha (8 - 12.5 Hz). The interaction effect of Condition x Group was significant, $F(1, 26) = 5.168$, $p = .032$, $\eta_p^2 = .166$, such that alpha band power was greater in the ECR condition ($M = 2.852$, $SE = 0.917$) than in the EOR condition ($M = 2.553$, $SE = 0.643$) in the control group. Alpha power was similarly greater in the ECR condition ($M = 4.118$, $SE = 0.854$) than in the EOR condition ($M = 0.490$, $SE = 0.599$) in the migraine group. Of note, alpha power was greatest in the ECR condition in the migraine group and also revealed a significant difference between resting-state conditions, $F(1, 26) = 7.189$, $p = .013$, $\eta_p^2 = .217$. The main effect of Group, however, was not statistically significant, $F(1, 26) = 0.250$, $p = .622$, $\eta_p^2 = .01$. Mean alpha band power by condition and group is shown in Figure 1.

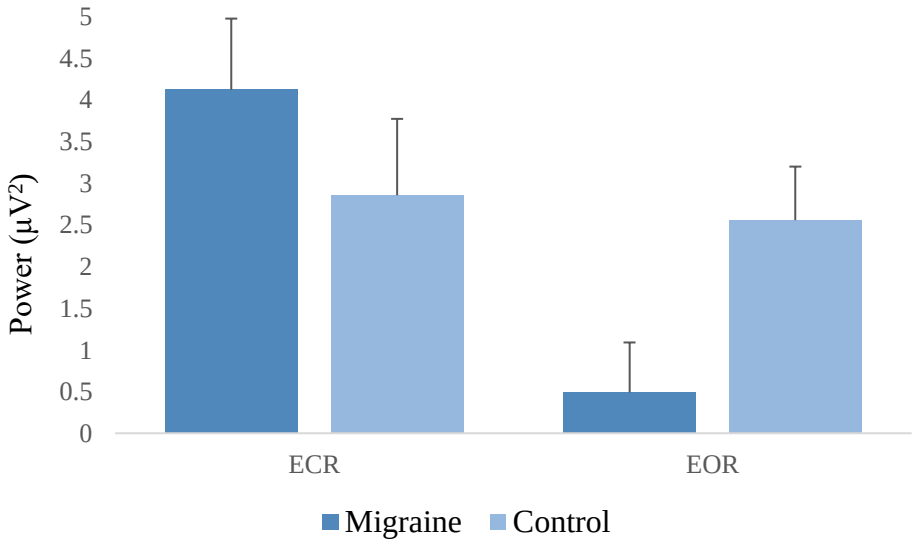

Figure 1. Mean alpha band power. Error bars represent standard error of the mean.

Hypothesis 2 - Theta (4 - 7.5 Hz). The ANOVA revealed a significant main effect of resting-state Condition, $F(1, 26) = 9.931$, $p = .004$, $\eta_p^2 = .276$. Across both groups, theta band power was greater in the EOR condition ($M = 41.155$, $SE = 9.759$) than in the ECR condition ($M = 10.549$, $SE = 3.738$). Although the main effect of Group was not statistically significant [$F(1, 26) = 0.737$, $p = .399$, $\eta_p^2 = .028$], theta band power was greatest in the migraine group overall (EOR: $M = 49.967$, $SE = 13.300$ vs. ECR: $M = 11.298$, $SE = 5.094$) compared to the control group (EOR: $M = 32.343$, $SE = 14.286$ vs. ECR: $M = 9.800$, $SE = 5.472$). The interaction effect of Condition and Group was not statistically significant, $F(1, 26) = 0.689$, $p = .414$, $\eta_p^2 = .026$. Mean theta band power by condition and group can be found in Figure 2.

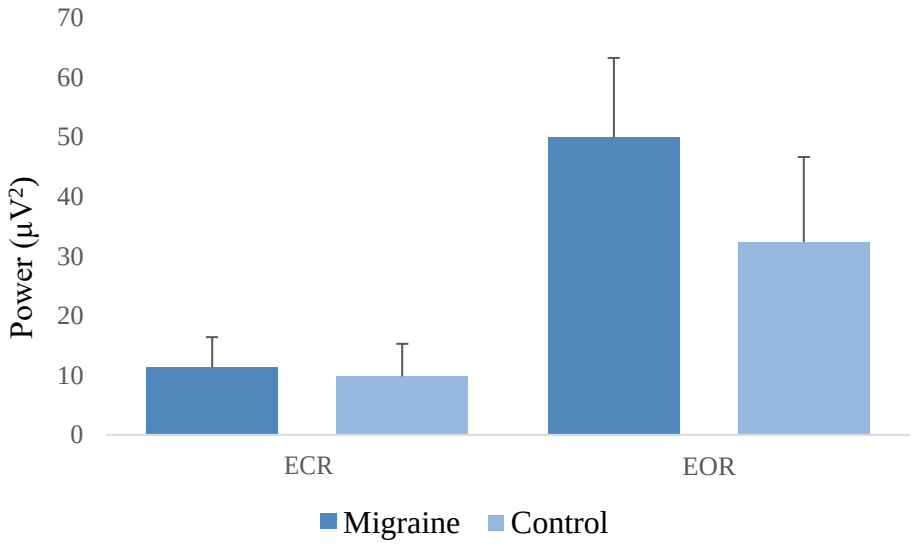

Figure 2. Mean theta band power. Error bars represent standard error of the mean.

Hypothesis 3 - Delta (.01 - 3.5 Hz). Neither the main effect of Condition [$F(1, 26) = 0.775$, $p = .387$, $\eta_p^2 = .029$] nor the main effect of Group [$F(1, 26) = 0.006$, $p = .939$, $\eta_p^2 < .001$] was significant. The interaction effect approached significance but revealed a medium effect size, $F(1, 26) = 2.720$, $p = .111$, $\eta_p^2 = .095$. Results for the interaction are presented here, but they should be considered tentative in light of the overall null results. Delta band power in the control condition was the same in both ECR and EOR ($M = 0.002$, $SE = 0.001$). Delta band

power in the migraine group, however, differed slightly across resting-state conditions: ECR (*M* = 0.001, *SE* = 0.001) versus EOR (*M* = 0.003, *SE* = 0.001). Mean delta band power by condition and group can be found in Figure 3.

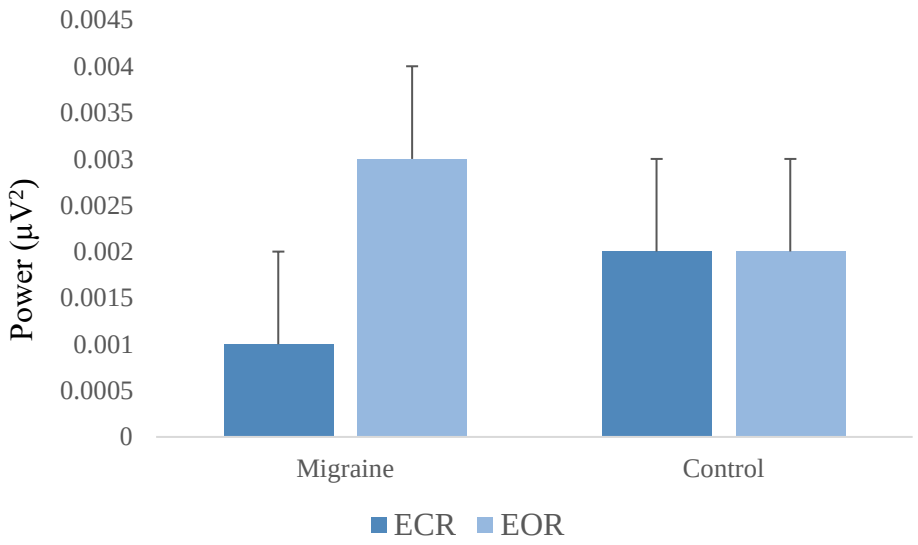

Figure 3. Mean delta band power. Error bars represent standard error of the mean.

Hypothesis 4 - Beta (13 - 30 Hz). A significant interaction effect was found for Condition x Group, $F(1, 26) = 7.039$, $p = .013$, $\eta_p^2 = .213$. In the control group, beta band power was greater in the ECR condition ($M = 3.380$, $SE = 0.404$) than in the EOR condition ($M = 2.642$, $SE = 0.415$). The opposite was true for the migraine group: beta band power was greater in the EOR condition ($M = 3.709$, $SE = 0.387$) than in the ECR condition ($M = 2.513$, $SE = 0.376$). Overall, beta band power was greatest in the EOR condition in the migraine group. Neither the main effect of Condition [$F(1, 26) = 0.396$, $p = .535$, $\eta_p^2 = .015$] nor of Group [$F(1, 26) = 0.055$, $p = .816$, $\eta_p^2 = .002$] was statistically significant. Mean beta band power by condition and group is shown in Figure 4.

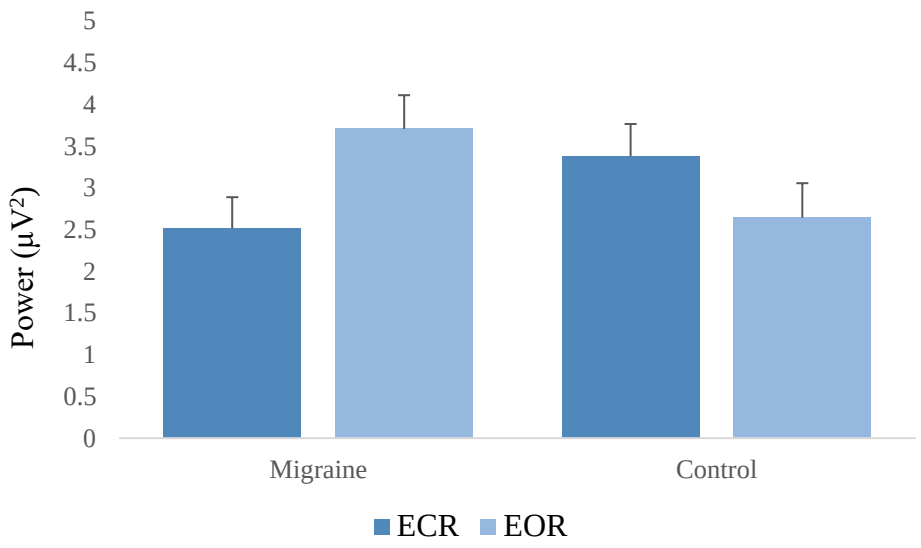

Figure 4. Mean beta band power. Error bars represent standard error of the mean.

Discussion

Increased variability in the alpha band has been found within 72 hours before a migraine attack and persists into interictal periods of the migraine cycle (Nyrke et al., 1990). Our study found increased variability between resting-states during one phase of the migraine cycle, adding to the available research pointing to abnormal activity in the alpha band even during asymptomatic periods. As hypothesized, alpha band power was greater during ECR in the migraine group than in healthy controls, a finding consistent with previous research (Clemens et al., 2008). Additionally, although alpha band power was lower in EOR across both groups, alpha power was significantly lower in the migraine group than controls. The migraine group also demonstrated larger mean differences between ECR and EOR (M_{diff} = 3.63) than controls (M_{diff} = 0.30). This particular interaction suggests that migraine is characterized by both an increase in alpha during ECR and a significant decrease during EOR. Migraine research has consistently found evidence of electrophysiological abnormalities of alpha activity (Coppola et al., 2019). Although the relationship between changes in alpha and the migraine cycle is complex, and at

times contradictory, both early (e.g., Dow & Whitty, 1947) and current research has demonstrated differences across the migraine cycle during transient states. Our study, and others (see Table 1), failed to find a significant difference in alpha when compared to controls. However, our results did point to a significant difference between ECR and EOR. Although the pattern of increased alpha during ECR and decreased alpha during EOR was not consistent across all participants, our study found that alpha was greater during ECR than EOR in 67% of individuals in the migraine group. Overall, resting-state differences present in migraine may point to alpha activity as a potential cerebral marker of migraine.

In both groups, theta band power was greater during EOR than ECR. Although these findings are consistent with previous research on resting-state differences (Kan et al., 2017), we did not find a significant effect of group nor an interaction that would be consistent with previous migraine research. For example, Bjork et al. (2011) found increased relative theta activity in migraine compared to controls during an ECR condition, with Cao et al. (2016) finding lower theta band power in migraineurs compared to controls during an EOR condition. Although ECR was greater in migraineurs (M = 11.3) than controls (M = 9.8) in our study, the difference was not statistically significant. Taken together, our results, which seem to suggest a difference between conditions but not between migraineurs and controls, may thus reveal a limitation in previous research in which a single baseline resting-state was used.

Although analysis of delta band power failed to find any statistically significant differences, a medium effect size was found for an interaction effect. It is possible that this was due in part to our limited sample size and resultant lessened statistical power (observed power = 0.136). Contrary to research findings with patients who are euthymic (Barry et al., 2007; Kan et al., 2017), delta band power in the control group did not differ between resting-state conditions.

Delta band power in the migraine group was slightly greater during EOR than ECR. This finding is consistent with Bjork et al. (2009), who found that delta band power was similar between migraineurs and controls. However, Cao et al. (2016) found evidence to the contrary; here, EOR was associated with lower delta band power in migraineurs than controls. The finding of no significant delta band difference between migraineurs and controls warrants further investigation. Of the frequency bands studied in cases of migraine, delta band power is most associated with clinical features of migraine pain and headache intensity. As our study evaluated EEG during interictal, or asymptomatic, periods of the migraine phase, it is possible that delta was not prominent in individuals with migraine due to a lack of headache-related symptoms at the time EEG activity was recorded. If this interpretation is correct, the lack of symptoms in the migraine population would explain the lack of a statistically significant difference in delta power between migraine and controls we observed. Previous research suggests that migraine is characterized by an increase in delta power ipsilateral to the side of the head in which pain is most prominent during migraine attacks (Bjork et al., 2009). However, our study only measured activity at electrode site Cz, so lateralized activity that may have been otherwise recorded were not detectable. A possible floor-effect may also be present, given how low overall delta power was in both migraine and controls.

Current theories of migraine pathophysiology (e.g., CNV, CSD) suggest that migraine is characterized predominantly by an increase in slow-wave activity, leading us to predict the absence of significant differences in fast-frequency band activity. However, contrary to our hypothesis, we found an increase in beta band power during EOR compared to ECR, whereas the opposite was true for the control group. In healthy controls, beta is typically associated with lower amplitude during wakefulness that tends to increase during drowsiness, though the

alternating pattern of beta activity is thought to be related to sensorimotor responses (Mykland et al., 2019). Beta activity in the control group followed this pattern, wherein ECR was larger than EOR. However, our migraine group demonstrated the opposite: EOR, which would typically be associated with lower beta activity, was greatest. A closer look at medication effects in migraine and pain management may well help explain these puzzling findings. In clinical samples, a generalized increase in beta activity during wakefulness is used as a marker for the presence of sedative drugs (Louis & Frey, 2016). Although individuals in the migraine group were asked to refrain from use of migraine-related medication prior to EEG recordings, many participants indicated regular use of medication that include active ingredients found in many sedative drugs, such as beta-blockers, oxycodone, barbiturates, and pseudoepinephrine. The presence of even trace amounts of these sedatives in the body may account for the increase in beta activity during EOR in the migraine group. Though beta activity has not been the primary subject of previous research, our findings point to a need to explore this aspect further.

Cortical abnormalities present during symptomatic periods are important to evaluating the pathophysiology of migraine; however, differences present during interictal periods may reflect a more stable cortical state. Moreover, previous research supports the theory that band activity differs across resting-state conditions in healthy controls (Gusnard & Raichle, 2001), but migraine-specific researchers lean toward using only one resting-state as a form of baseline. Our study, which was designed to explore whether resting-state EEG differences (during ECR and EOR) exist between individuals presenting with migraine--during headache-free periods--and healthy controls, helps to show some of the differences in broad-spectrum band power activity across both diagnostic groups and resting-state conditions.

Future Research Directions

The presence of a migraine-related disorder was approximated based on symptoms reported at the time our data were collected; hence, greater diagnostic specificity may lead to more pronounced findings in future research. Also, some research suggests that migraine without aura may differ slightly from migraine with aura with regards to delta band power (Bjork et al., 2009). Though we included both types of migraine, we likely lacked sufficient power to detect differences between the two forms of migraine. Although some obtained effect sizes were sizeable enough to offset concerns about sufficient power overall, larger sample sizes could increase generalizability of obtained results. Finally, in light of the significant interaction within the beta band, future research may profit from expanding EEG analyses beyond slow-wave frequency bands.

Summary and Conclusions

Migraine is a primary headache disorder characterized by abnormal cortical activity that persists during interictal periods and differs when compared to other periods of the migraine phase. Similarly, though previous research on standard cortical activity suggests that EOR and ECR resting-state conditions demonstrate reproducible differences in brain activity (Barry et al., 2007), migraine researchers tend to use only one resting-state as a form of baseline. Together, previous research lends support to the importance of obtaining more process-pure data by recording EEG during two conditions, (1) resting-states and (2) symptom-free periods. Given the theory that these testing conditions may reflect more permanent cortical states, the present study examined the interacting role of resting-state conditions (eyes-open vs. eyes-closed) and headache diagnosis (migraine vs. control) on absolute band power across the EEG frequency spectrum (0.01 – 30 Hz). The current study has added to the available research suggesting that

alpha band power is elevated in migraine, specifically during ECR. Though theta and delta power were also greatest in migraineurs, we found only a main effect of resting-state condition for theta band power and no significant difference in delta band power between migraineurs and controls. Beta power has been less frequently studied in migraine research, but our results revealing greater band power in migraine during EOR warrant further investigation. In sum, we believe the results of the current study help to expand our understanding of broad-spectrum band power differences in migraine during distinct resting-state conditions.

References

Akben, S. B., Tuncel, D., & Alkan, A. (2016). Classification of multi-channel EEG signals for migraine detection. *Biomedical Research, 27,* 743-748.

Amo, C., de Santiago, L., Barea, R., López-Dorado, A., & Boquete, L. (2017). Analysis of gamma-band activity from human EEG using empirical mode decomposition. *Sensors, 17,* 1-14. doi: 10.3390/s17050989

Barry, R. J., Clarke, A. R., Johnstone, S. J., & Brown, C. R. (2007). EEG differences between eyes-closed and eyes-open resting conditions. *Clinical Neurophysiology, 118,* 2765-2773. doi: 10.1016/j.clinph.2009.08.006

Berger, H. (1933). Über das elektroenzephalogramm des menschen. Sechste Mitteilung. *Archiv für Psychiatrie und Nervenkrankheiten, 99,* 555-574.

Bhaskar, S., Saeidi, K., Borhani, P. & Amin H. (2013). Recent progress in migraine pathophysiology: Role of cortical spreading depression and magnetic resonance imaging. *European Journal of Neuroscience, 38,* 3540-3551. doi: 10.1111/ejn.12368

Bjork, M. H., & Sand, T. (2008). Quantitative EEG power and asymmetry increase 36 h before a migraine attack. *Cephalalgia, 28,* 960-968. doi: 10.1111/j.1468-2982.2008.01638.x

Bjørk, M. H., Stovner, L. J., Engstrøm, M., Stjern, M., Hagen, K., & Sand, T. (2009). Interictal quantitative EEG in migraine: A blinded controlled study. *Journal of Headache Pain, 10,* 331-339. doi: 10.1007/s10194-0140-4

Bjørk, M., Stovner, L. J., Sand, T. (2011). What initiates a migraine attack? Conclusions from four longitudinal studies of quantitative EEG and steady-state visual-evoked potentials in migraineurs. *Acta Neurologica Scandinavica, 124,* 56-63.

Boytsova, J. & Danko, S. G. (2010). EEG differences between resting states with eyes open and closed in darkness. *Human Physiology, 36,* 367-369. doi: 10.1134/S0362119710030199

Cao, Z., Lin, C.-T., Chuang, C.-H., Lai, K.-L., Yang, A. C., Fuh, J.-L., & Wang, S.-J. (2016). Resting-state EEG power and coherence vary between migraine phases. *Journal of Headache and Pain, 17.* doi: 10.1186/s10194-016-0697-7

Clemens, B., Bánk, J., Piros, P., Bessenyei, M., Vetö, S., Tóth, M., & Kondákor, I. (2008). Three-dimensional localization of abnormal EEG activity in migraine. *Brain Topography, 21,* 36-42.

Costa, C., Tozzi, A., Rainero, I., Cupini, L. M., Calabresi, P., Ayata, C., & Sarchielli, P. (2013). Cortical spreading depression as a target for anti-migraine agents. *Journal of Headache and Pain, 14,* 1-18.

Coppola, G., Pierelli, F., & Schoenen, J. (2007). Is the cerebral cortex hyperexcitable or hyperresponsive in migraine? *Cephalalgia, 27*, 1427-1439. doi: 10.1111/j.1468-2982.2007.01500.x

Coppola, G., Bracaglia, M., Lenola, D., Di Lorenzo, C., Serrao, M., Parisi, V…Pierelli, F. (2015). Visual evoked potentials in subgroups of migraine with aura patients. *Journal of Headache and Pain, 16*. doi: 10.1186/s10194-015-0577-6

Coppola, G., Di Lorenzo, C., Parisi, V., Lisicki, M., Serrao, M., & Pierelli, F. (2019). Clinical neurophysiology of migraine with aura. *The Journal of Headache and Pain, 20*. doi: https://doi.org/10.1186/s10194-019-0997-9

Dow, D. J. & Whitty, C. W. (1947). Electroencephalographic changes in migraine; review of 51 cases. *Lancet, 12*, 52-54.

Dressler, O., Schneider, G., Stockmanns, G., & Kochs, E. F. (2004). Awareness and the EEG power spectrum: Analysis of frequencies. *British Journal of Anesthesia, 93*, doi: 10.1093/bja/aeh270

Gusnard, D., A. & Raichle, M. E. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Reviews, 2*, 685-694.

Gómez-Ramírez, J., Freedman, S., Mateos, D., Pérez Velázquez, J. S., & Valiante, T. A. (2017). Exploring alpha desynchronization hypothesis in resting state networks with intracranial electroencephalography and wiring cost estimates. *Scientific Reports, 7*, 1-11. doi: 10.1038/s41598-017-15659-0

Headache Classification Subcommittee of the International Headache Society. (2004). The international classification of headache disorders, 2nd edition. *Cephalalgia: An International Journal of Headache, 24* (Suppl. 1), 9–160.

Headache Classification Committee of the International Headache Society. (2018). The international classification of headache disorders, 3rd edition. *Cephalalgia: An International Journal of Headache, 38*, 1–211. doi:10.1177/0333102417738202

Jakobsen, J. C., Gluud, C., Wetterslev, J., & Winkel, P. (2017). When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. *BMC Medical Research Methodology, 17*. doi: 10. 1186/s12874-017-0442-1

Jasper, H. H. (1958). Report of the committee on methods of clinical examination in electroencephalography. *Electroencephalography and Clinical Neurophysiology, 10*, 370–375. doi:10.1016/0013-4694(58)90053-1

Kan, D. P. X., Croarkin, P. E., Phang, C. K., & Lee, P. F. (2017). EEG difference between eyes-closed and eyes-open conditions at the resting stage for euthymic patients. *Neurophysiology, 49,* 432-440. doi: 10.1007/s11062-018-9706-6

Katsarava, Z., Buse, D. C., Manack, A. N., & Lipton, R. B. (2012). Defining the differences between episodic migraine and chronic migraine. *Current Pain and Headache Reports, 16,* 86-92. doi: 10.1007/s11916-011-0233-z

Keil, A., Debener, S., Gratton, G., Junghöfer, M., Kappenman, E. S., Luck, S. J…Yee, C. (2014). Committee report: Publication guidelines and recommendations for using electroencephalography and magnetoencephalography. *Psychophysiology, 51,* 1-21. doi: 10.1111/psyp.12147

Kirschfeld, K. (2005). The physical basis of alpha waves in the electroencephalogram and the origin of the "Berger effect." *Biological Cybernetics, 92,* 177-185. doi: 10.1007/s00422-005-0547-1

Kropp, P. & Gerber, W.-D. (1998). Prediction of migraine attacks using a slow cortical potential, the contingent negative variation. *Neuroscience Letters, 257,* 73-76.

Lev, R., Granovsky, Y., & Yarnitsky, D. (2010). Orbitofrontal disinhibition of pain in migraine with aura: An interictal EEG-mapping study. *Cephalalgia, 30,* 910-918.

Levy, W. J. (1987). Effect of epoch length on power spectrum analysis of the EEG. *Anesthesiology, 66,* 489-495. doi: 10.1097/00000542-198704000-00007

Louis, E. K. St. & Frey, L. C. (2016). The normal EEG. In Louis, E. K. St. & Frey, L. C. (Eds.), *Electroencephalography*: *An Introductory Text and Atlas of Normal and Abnormal Findings in Adults, Children, and Infants* (pp. 8-20). Chicago, IL: American Epilepsy Society.

Lopez-Calderon, J. & Luck, S. J. (2014). ERPLAB: An open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience, 8,* 1-14. doi:10.3389/fnhum.2014.00213

Lozeron, P., Tcheumeni, N., Turki, S., Amiel, H., Meppiel, E., Masmoudi, S…& Kubis, N. (2018). Contribution of EEG in transient neurological deficits. *Journal of Neurology, 265,* 89-97. doi: 10.1007/s00415-017-8660-3

Marx, E., Deutschländer, A., Stephan, T., Dieterich, M., Wiesmann, M., & Brandt, T. (2004). Eyes open and eyes closed as rest conditions: Impact on brain activation patterns. *NeuroImage, 21,* 1818-1824. doi: 10.1016/j.neuroimage.2003.12.026

Mickleborough, M. J. S., Truong, G., & Handy, T. C. (2011). Top-down control of visual cortex in migraine populations. *Neuropsychologia, 49,* 1006-1015. doi: 10.1016/j.neuropsychologia.2011.01.033

Mykland, M. S., Bjørk, M. H., Stjern, M., Omland, P. M., Uglem, M., & Sand, T. (2019). Fluctuations of sensorimotor processing in migraine: A controlled longitudinal study of beta event related desynchronization. *Journal of Headache and Pain, 20*. doi: 10.1186/s10194-019-1026-8

Nguyen, B. N., McKendrick, A. M., & Vingrys, A. J. (2016). Abnormal inhibition-excitation imbalance in migraine. *Cephalalgia, 36*, 5-14. doi: 10.1177/0333102415576725

Noseda, R. & Burstein, R. (2013). Migraine pathophysiology: Anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization, and modulation of pain. *Pain, 151*. doi: 10.1016/j.pain.2013.07.021

Nyrke, A., Kangasniemi, P., Lang, H. (1990). Alpha rhythm in classical migraine (migraine with aura): Abnormalities in the headache-free interval. *Cephalalgia, 10,* 177-181.

Pallant, J. (2013). SPSS survival manual: A step by step guide to data analysis using IBM SPSS (5th ed.). Milton Keynes, United Kingdom: Open University Press.

Sable, J. J., Patrick, T. A., Woody, P. L., Baker, K. R., Allen-Winters, S., & Andrasik, F. (2017). Auditory event-related potentials in the interictal phase of migraine indicate alterations in automatic attention. *Applied Psychophysiology and Biofeedback, 42*, 323-333. doi: 10.1007/s10484-017-9378-9

Saylor, D. & Steiner, T. J. (2018). The global burden of headache. *Seminars in Neurology, 38,* 182-190. doi: 10.1055/s-0038-1646946

Siniatchkin, M., Averkina, N., Andrasik, F., Stephani, U., & Gerber, W.-D. (2006). Neurophysiological reactivity before a migraine attack. *Neuroscience Letters, 400,* 121-124. doi: 10.1016/j.neulet.2006.02.019

Stokes, D. A. & Lappin, M. S. (2010). Neurofeedback and biofeedback with 37 migraineurs: A clinical outcome study. *Behavioral and Brain Functions, 6,* 1-11. doi: 10.1186/1744-9081-6-9

Steiner, T. J., Stovner, L. J., & Vos, T. (2016). GBD 2015: migraine is the third cause of disability in under 50s. *Journal of Headache Pain, 17*, 1-4. doi: 10.1186/s10194-016-0699-5

de Tommaso, M., Sciruicchio, V., Guido, M., Sasanelli, G., Specchio, L. M., Puca, F. M. (1998). EEG spectral analysis in migraine without aura attacks. *Cephalalgia, 18,* 324-328.

de Tommaso, M., Stramaglia, S., Marinazzo, D., Trotta, G., & Pellicoro, M. (2013). Functional and effective connectivity in EEG alpha and beta band during intermittent flash stimulation in migraine with and without aura. *Cephalalgia, 33,* 938-947.

de Tommaso, M., Trotta, G., Vecchio, E., Ricci, K., Van de Steen, F., Montemurno, A…Stramaglia, S. (2015). Functional connectivity of EEG signals under laser stimulation in migraine. *Frontiers in Human Neuroscience, 9*. doi: 10.3389/fnhum2015.00640

de Tommaso, M., Trotta, G., Vecchio, E., Ricci, K., Siugzdaite, R., Stramaglia, S. (2017). Brain networking analysis in migraine with and without aura. *Journal of Headache and Pain*, *18*. doi: 10.1186/s10194-017-0803-5

de Tommaso, M. (2019). An update on EEG in migraine. *Expert Review of Neurotherapeutics*. doi: 10.1080/14737175.2019.1586534

Van Boxtel, G. J. M. (1998). Computational and statistical methods for analyzing event-related potential data. *Behavior Research Methods, Instruments, and Computers, 30*, 87-102. doi: 10.3758/BF03209419

Viticchi, G., Falsetti, L., Silvestrini, M., Luzzi, S., Provinciali, L., & Bartolini, M. (2012). The real usefulness and indication for migraine diagnosis of neurophysiologic evaluation. *Neurologic Science*, *33*, 161-163. doi: 10.1007/s10072-012-1074-1

Vossen, C. J., Vossen, H. G., Joosten, E. A., van Os, J., Lousberg, R. (2015). Does habituation differ in chronic low back pain subjects compared to pain-free controls? A cross-sectional pain rating ERP study reanalyzed with the ERFIA multilevel method. *Medicine, 94*, 1-10.

Walter, W. G., Cooper, R., Aldridge, V. J., McCallum, W. C., & Winter, A. L. (1964). Contingent negative variation: An electrical sign of sensori-motor association and expectancy in the human brain. *Nature*, *203*, 380-384.

Appendix A

Table 1

Overview of Migraine EEG Studies Using Frequency Band Analyses

Article	Participants (*N*)	Task	Method	Measures	Results (*Sig. results*)
Nyrke et al. (1990)	C: 18 (*12F, 6M*) MO: 18 (*13F, 5M*)	EEG recording during eyes closed condition during interictal, pre-, and post-attack phases	40-sec. artefact-free EEG sample (divided into 5 8-sec. epochs). FFT	ALPHA band Peak frequ. Peak power Freq asymm. Power asymm. Mod. Asymm.	*power not reported Pre-Ictal: Increased mod, mod asym, frequ, and frequ asym observed Overall: Frequ asym greater in MO
de Tommaso et al. (1998)	C: 20 (*15F, 5M*) MO: 20 (*15F, 5M*) *4 dropped	SSVEPs elicited by flash stim. EEG recording during eyes closed during interictal and attack phases	2 min. of artifact-free EEG (2-sec. epochs). FFT	ALL BANDS Abs. power α power asymm.	Abs. power similar during and after attack
Bjork et al. (2008)	MO: 33 (*30F, 3M*) MA: 8 (*8F, 0M*)	5 min. eyes closed EEG recording. Measuring at three time points: preictal (36 hrs before), postictal (36 hrs after), and interictal	5-min. of artefact-free EEG (4-sec. epochs). FFT	ALL BANDS Band power Band asymm.	Preictal: Band power increased before attack compared to interictal. More asymm α and θ compared to interictal Postictal: No diff compared to interictal Ictal: α and β power increased

Table 1 (Continued)

Article	Participants (*N)*	Task	Method	Measures	Results (*Sig. results*)
Clemens et al. (2008)	C: 17 (*15F, 2M*) MO: 20 (*17F, 3M*)	Interictal EEG recorded during eyes closed condition. *Interictal defined as 10 days after/before next attack	2 min. of artefact-free EEG activity (2-sec. epochs). FFT	ALL BANDS Absolute power	More alpha power in MO than control
Bjork et al. (2009)	C: 31 MO: 33 MA: 8	Interictal EEG recorded (36 hrs before/after attack) *task info not presented	4-sec. artefact-free epochs. FFT	Alpha, Delta, Theta Band power Relative power	Theta: rel,power increased in migraine compared to control, slightly higher in MO Alpha/Delta: rel and abs power similar between groups (slightly more delta power in MO compared to MA) *Clinical features: positive association between increased delta power and headache intensity
Bjork et al. (2011)	C: 32 MO: 33 MA: 8	5 min. eyes closed EEG recording. Measuring at three time points: preictal (72 hrs before), postictal (72 hrs after), and interictal	5-min. of artefact-free EEG (4-sec. epochs). FFT	ALL BANDS Relative power Band power α peak power α peak frequ.	INTERICTAL Rel. theta power increased in migraine Abs power and rel. power for beta similar between groups BEFORE ATTACK $\alpha\ \theta\ \delta$ abs power increased compared to interictal AFTER ATTACK QEEG similar to interictal levels

Table 1 (Continued)

Article	Participants (*N*)	Task	Method	Measures	Results (*Sig. results*)
Cao et al. (2016)	MO: 61 (35F, 15M) C: 20 Interictal: 22 Post-ictal: 8 Pre-ictal: 12 Ictal: 8	Alternating eyes open/closed for 30 secs. 3x *only used eyes open condition for final analysis	90-sec. artefact-free epochs. FFT Pwr analysis	<u>ALL BANDS</u> Band power	Lower band power in interictal MO compared to control (similar in ictal phase) Power values did not differ between pre-ictal MO and controls

Note. This table includes only migraine EEG studies that employed some form of band analysis, with special attention towards those studies that used a passive task during EEG data acquisition. Only significant results are presented in this table.
C = control, Migraine diagnosis (MA = migraine w/aura, MO = migraine w/o aura)

Appendix B

Table 2

Migraine Population: Demographics and Symptom Characteristics

Probable Diagnosis*	Sex	Age	Race/Ethnicity	Migraine Occurrence	Migraine (years)	Onset (age)	Duration (hours)	Pain Intensity**	Medication for Migraine	Medication for other Condition(s)
PM (1.5)	F	20	Caucasian	2-3/month	7	14	hrs-days	7	Caffeine, Relafen, Migranol	Nexium, Vitamin D, Biotin
PM (1.5	F	22	Caucasian	3-4/yr.	6	16	6-24	7	Excedrin Migraine	Ibuprofen, birth control
PM (1.5)	M	19	African American	Not often	2	17	1	7	None	None
MO (1.1)	M	24	African American	1/week	14	10	~1	8	Acetaminophen, Advil	Adderall
MO (1.1)	F	19	Caucasian	1/month	2	17	8-24	8	Excedrin, Aleve	Ibuprofen
MO (1.1)	F	19	African American	2-3/week	9	10	48	10	None	(None Reported)
MO (1.1)	F	21	Caucasian	2-3/month	9	12	72	7.5	Ibuprofen	Albuterol
MA (1.2)	F	21	Caucasian	1/ 2 months	7	14	72	9	Tylenol, Caffeine, steroid, Maxalt	Percocet, Keppra, Fentanyl
MA (1.2)	M	21	African American	1/2 months	8	12	24	9	Claritin D	Ibuprofen, Aleve

Table 2 (Continued)

Probable Diagnosis*	Sex	Age	Race/Ethnicity	Migraine Occurrence	Migraine (years)	Onset (age)	Duration (hours)	Pain Intensity**	Medication for Migraine	Medication for other Condition(s)
MA (1.2)	F	22	Hispanic	1/month	10	12	3	9	Avamigran	Birth control
MA (1.2)	F	39	Caucasian	1/1.5 weeks	25	14	48	7	Beta blockers, Oxycodone, Valium	Synthroid, Birth control, Omeprazole
MA (1.2)	F	23	African American	1/3-4 days	10	13	$\leq$ 48	8	Maxalt	None
MA (1.2)	M	19	Caucasian	2/week	13	6	8	8	Advil	(None Reported)
MA (1.2)	F	24	Other	1/week	17	7	12	10	Aspirin, Imitrex	Birth control, Albuterol, Doxycycline
MA (1.2)	F	49	Caucasian	1-2/month	30	18	$\geq$ 4	5	Butabitol, Excedrin, Flexeril, Lortab	Alergy meds, Nexium, Ambien, Metoprolol, Diclofenac

Note. *Diagnoses are based solely on available self-reported information.
The number in parenthesis refers to the criteria section in the ICHD-3. All cases of MA were associated with visual aura symptoms
**Rated on a level of 1 (barely noticeable) to 10 (unbearable)
Probable Migraine = (PM, 1.5), Migraine with Aura = (MA, 1.2), Migraine without aura = (MOA, 1.1).

Appendix C

Table 3

Absolute Band Power

	Eyes-Closed Rest (ECR) Absolute Band Power (μV^2)			
	Delta	Theta	Alpha	Beta
Migraine (*n* = 15)	.001 (.001)	11.3 (5.09)	4.12 (.85)	2.51 (.38)
Control (*n* = 13)	.002 (.001)	9.8 (5.47)	2.85 (.92)	3.38 (.40)

	Eyes-Open Rest (EOR) Absolute Band Power (μV^2)			
	Delta	Theta	Alpha	Beta
Migraine (*n* = 15)	.003 (.001)	49.97 (13.3)	0.49 (.59)	3.71 (.39)
Control (*n* = 13)	.002 (.001)	32.34 (14.29)	2.55 (.64)	2.64 (.42)

Note. Absolute band power is presented in microvolts squared (μV^2) across groups and conditions.
Mean and standard error are presented [*M* (*SE*)].

IRB Approval

IRB #: PRO-FY2020-211
Title: Spectral Analysis of Resting-State EEG Data During Interictal Periods of the Migraine Phase
Creation Date: 10-24-2019
End Date:
Status: Approved
Principal Investigator: Andrea Perez-Munoz
Review Board: University of Memphis
Sponsor:

Study History

Submission Type Initial	Review Type Exempt	Decision Exempt

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