ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26nov059

A Hypothesis-Driven Multimodal Diagnostic Framework Integrating TMS-Evoked Cortical Excitability, EEG-Derived Electrophysiological Signatures and Plasma CGRP Quantification to Explore their Complementary Diagnostic Potential in Differentiating Migraine with Aura from Occipital Lobe Epilepsy

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Publication Date: 2026/11/05

Abstract: Migraine with aura and occipital lobe epilepsy share overlapping visual manifestations, often creating diagnostic challenges and potential misclassification. Both conditions involve distinct patterns of cortical excitability, electrophysiological activity, and neuropeptide signalling. This review proposes a multimodal diagnostic framework integrating transcranial magnetic stimulation (TMS)-evoked cortical excitability, electroencephalography (EEG) patterns, and calcitonin gene-related peptide (CGRP) levels to explore their differential diagnostic potential. The proposed approach encompasses TMS-based assessment of cortical excitability, EEG characterization of occipital electrical activity, and plasma CGRP quantification using enzyme-linked immunosorbent assay (ELISA). These parameters will be conceptually integrated into a web-based clinical decision-support algorithm. This framework aims to improve differential diagnostic accuracy, minimize misclassification, and facilitate appropriate therapeutic decision-making through a reproducible, multimodal approach.

Keywords: *Migraine with Aura; Occipital Lobe Epilepsy; Transcranial Magnetic Stimulation; Electroencephalography; Calcitonin Gene-Related Peptide; Multimodal Diagnostics.*

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26nov059

How to Cite: Sourav Singla; Vidushi Aggarwal; Mohit Kumar; Jiya Panwar; Abhay Singh; Rajat Singh; Ramprakash Surliya (2026) A Hypothesis-Driven Multimodal Diagnostic Framework Integrating TMS-Evoked Cortical Excitability, EEG-Derived Electrophysiological Signatures and Plasma CGRP Quantification to Explore their Complementary Diagnostic Potential in Differentiating Migraine with Aura from Occipital Lobe Epilepsy. *International Journal of Innovative Science and Research Technology*, 11(11), 1-8. https://doi.org/10.38124/ijisrt/26nov059

I. INTRODUCTION

Migraine is a complex primary neurological disorder characterized by recurrent headache attacks and, in some individuals, transient neurological disturbances known as aura. Migraine with aura (MwA) is particularly associated with altered cortical excitability and cortical spreading depolarization (CSD), a slowly propagating wave of neuronal and glial depolarization followed by suppression of cortical activity. CSD is considered the principal electrophysiological mechanism underlying migraine aura and may contribute to the activation of trigeminovascular pathways. Activation of these pathways subsequently promotes the release of neuropeptides involved in nociceptive transmission and neurogenic inflammation [1,2].

Among these neuropeptides, calcitonin gene-related peptide (CGRP) has emerged as an important mediator of migraine pathophysiology. Experimental and clinical investigations have demonstrated the release of CGRP and other vasoactive neuropeptides, including substance P, following trigeminal activation [1-4]. Elevated CGRP concentrations have been reported in the extracerebral circulation during migraine attacks, supporting its potential relevance as a biochemical marker of trigeminovascular activation. Consequently, the quantification of circulating CGRP using enzyme-linked immunosorbent assay (ELISA) represents a promising approach for investigating the biochemical component of migraine-associated neurobiology [2,4].

However, the differential diagnosis of Migraine with aura becomes challenging when its visual manifestations overlap with those of focal epileptic seizures, particularly occipital lobe epilepsy (OLE). Occipital seizures originate from epileptogenic networks within the occipital cortex and commonly present with visual disturbances, including elementary visual hallucinations, coloured circular patterns, transient visual loss, and oculomotor manifestations. Panayiotopoulos demonstrated that visual phenomena associated with occipital seizures may differ from migraine aura in their colour, shape, distribution, speed of onset, and duration [3,6]. Nevertheless, postictal headache can closely resemble migraine headache, contributing to diagnostic confusion and inappropriate treatment [6].

Transcranial magnetic stimulation (TMS) has provided valuable insights into cortical excitability in migraine. Aurora and colleagues demonstrated reduced occipital phosphene thresholds in patients with migraine with aura compared with healthy controls, suggesting increased visual cortical responsiveness [5]. Subsequent studies using single and paired-pulse TMS further supported alterations in visual cortical excitability among migraineurs [7]. More recently, combining TMS with electroencephalography (TMS-EEG) has offered an opportunity to investigate cortical responses and inhibitory mechanisms through TMS-evoked potentials [8]. These findings provide a rationale for exploring TMS-derived excitability parameters as one component of a multimodal differential diagnostic framework.

Electroencephalography (EEG) provides another important dimension of diagnostic assessment. In occipital lobe epilepsy, interictal EEG may demonstrate occipital spikes, sharp waves, or photically induced epileptiform discharges, whereas ictal recordings may reveal evolving rhythmic activity and posterior electrical abnormalities [8]. However, normal or nonspecific interictal EEG findings do not exclude focal epilepsy. Conversely, routine scalp EEG may not reliably demonstrate the underlying cortical spreading depolarization associated with migraine aura [7,9]. Therefore, EEG findings must be interpreted alongside clinical manifestations and other neurophysiological parameters rather than used as an isolated diagnostic criteria.

Clinical differentiation is further supported by the temporal characteristics of visual symptoms. Migraine aura typically develops gradually, spreads over several minutes, and lasts approximately 5–60 minutes, whereas epileptic visual phenomena frequently have a sudden onset and shorter duration [10,11]. Nevertheless, considerable clinical overlap remains, particularly in atypical presentations. This diagnostic uncertainty highlights the need to explore complementary investigations that may provide information beyond conventional clinical assessment.

Although TMS, EEG, and CGRP have individually demonstrated relevance to migraine or epilepsy-related neurophysiology, their combined diagnostic utility remains insufficiently established. Furthermore, circulating CGRP measurements are influenced by assay selection, sample handling, peptide stability, and biological variability, limiting their interpretation as a standalone diagnostic biomarker [12,13].

Based on these observations, the present review proposes an integrated multimodal approach combining TMS-evoked cortical excitability, EEG-derived electrophysiological patterns, and plasma CGRP measurements to explore their complementary roles in differentiating Migraine with aura from occipital lobe epileptic seizures. The proposed framework hypothesizes that the combined assessment of neurophysiological and biochemical parameters may offer greater discriminatory potential than any single modality. These findings could subsequently inform the development of a web-based clinical decision-support algorithm to assist clinicians in interpreting multimodal findings and selecting appropriate diagnostic

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26nov059

pathways. However, the proposed approach requires prospective clinical validation before its diagnostic accuracy, sensitivity, specificity, and clinical utility can be established.

II. CONCEPTUAL INNOVATION

The proposed research introduces a hypothesis-driven multimodal diagnostic framework to explore the differentiation of migraine with aura (MwA) from focal epileptic seizures, particularly occipital lobe epilepsy (OLE). Although both neurological conditions may present with overlapping visual disturbances, their underlying pathophysiological mechanisms involve different patterns of cortical excitability, neuronal synchronization, and neurochemical signalling. The central innovation of this concept lies in the integration of three complementary investigative modalities: transcranial magnetic stimulation (TMS), electroencephalography (EEG), and calcitonin gene-related peptide (CGRP) quantification using enzyme-linked immunosorbent assay (ELISA).

- *Neurophysiological Assessment Through TMS-Evoked Cortical Excitability*

Previous investigations have demonstrated altered occipital cortical excitability in patients with migraine, with studies reporting differences in phosphene thresholds following TMS [5,14]. Aurora et al. demonstrated significantly lower occipital stimulation thresholds in patients with migraine with aura compared with healthy controls [5]. More recently, TMS combined with EEG has provided an opportunity to assess cortical responses through TMS-evoked potentials (TEPs), offering additional information about cortical responsivity and inhibitory mechanisms [12]. The proposed concept will explore whether TMS-derived excitability parameters can contribute to distinguishing migraine-associated cortical dysfunction from epileptic cortical hyperexcitability.

- *Electrophysiological Differentiation Through EEG Signatures*

EEG represents an important component of the proposed framework because occipital lobe epilepsy may demonstrate interictal epileptiform discharges, occipital spikes, sharp waves, and photically induced abnormalities [15]. In contrast, migraine aura is primarily associated with cortical spreading depolarization, which is not routinely identifiable using conventional scalp EEG. Although nonspecific EEG changes may occur in migraine, their diagnostic significance remains limited [16]. Therefore, integrating EEG findings with TMS-derived cortical excitability measurements may provide complementary information regarding the underlying neurophysiological differences between the two conditions.

- *Biochemical Assessment Through CGRP ELISA*

The third innovative component involves investigating circulating CGRP as a potential biochemical correlate of migraine-associated trigeminovascular activation. CGRP is an important neuropeptide involved in migraine pathophysiology, and its quantification in human plasma using validated ELISA methodologies has been investigated [13]. Recent research has highlighted the importance of assay standardization, sample processing, and differentiation between α-CGRP and β-CGRP when interpreting circulating concentrations [17]. The proposed framework will explore whether CGRP measurements provide additional discriminatory information when interpreted alongside TMS and EEG findings, rather than being considered an independent confirmatory diagnostic marker.

- *Integration into a Proposed Multimodal Diagnostic Algorithm*

The principal conceptual innovation is the integration of neurophysiological, electrophysiological, and biochemical parameters into a unified diagnostic framework. TMS will provide information about cortical excitability, EEG will characterize spontaneous and seizure-associated electrical activity, and CGRP ELISA will investigate peripheral neuropeptide signalling. The combined findings will be conceptually incorporated into a web-based clinical decision-support algorithm to facilitate systematic interpretation of multimodal results. Unlike conventional assessment based predominantly on clinical history and individual investigations, this framework proposes a complementary approach to exploring the biological differences between migraine with aura and occipital lobe epilepsy. Its diagnostic performance and clinical applicability would require prospective validation in appropriately characterized patient cohorts.

- *Scientific Rationale*

Scientific basis for multimodal integration about combining TMS, EEG, and CGRP ELISA is based on their ability to investigate three different but complementary biological domains. TMS provides information about cortical excitability, EEG characterizes spontaneous and seizure-associated electrical activity, and CGRP quantification explores peripheral neuropeptide signalling associated with trigeminovascular activation. Individually, these techniques have limitations in distinguishing migraine with aura from occipital lobe epilepsy. Their integration may therefore provide a broader understanding of the neurophysiological and biochemical differences between these conditions. The proposed framework will explore the possibility of integrating these parameters into a structured, web-based clinical decision-support algorithm. This may eventually assist clinicians in identifying patients who require further epilepsy-focused or migraine-focused diagnostic evaluation. Prospective clinical studies will be necessary to establish the diagnostic accuracy, reproducibility, sensitivity, and specificity of this proposed approach.

Thus combined evaluation of TMS-evoked cortical excitability, EEG-derived electrophysiological patterns, and circulating CGRP concentrations may provide complementary diagnostic information and potentially improve the differentiation of migraine with aura from occipital lobe epilepsy compared with reliance on individual investigative modalities.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26nov059

III. METHODOLOGY

➢ *Research Design*

The present research proposes a hypothesis-driven descriptive review aimed at developing a multimodal diagnostic framework for differentiating migraine with aura (MwA) from focal epileptic seizures, particularly occipital lobe epilepsy (OLE).

The proposed framework integrates neurophysiological assessment using TMS, electrophysiological characterization using EEG, and biochemical assessment through plasma CGRP quantification using ELISA. Relevant scientific literature will be reviewed to identify the diagnostic relevance, limitations, and potential complementary roles of these three modalities.

The proposed diagnostic framework will subsequently be translated into a conceptual web-based decision-support tool.

➢ *Proposed Methodology and Working Mechanism*

- *Proposed Multimodal Diagnostic Workflow*

✓ Patient presenting with transient visual disturbances
✓ Clinical history, symptom duration, onset, progression and associated features
✓ Modality 1: TMS assessment

▪ Occipital cortical excitability and phosphene threshold assessment

✓ Modality 2: EEG assessment

▪ Interictal and, where available, ictal electrophysiological patterns

✓ Modality 3: CGRP ELISA

▪ Quantification of circulating plasma CGRP concentrations

✓ Multimodal data integration

▪ Combined interpretation of clinical, neurophysiological, electrophysiological and biochemical findings

✓ Proposed output

▪ Web-based clinical decision-support algorithm
▪ Migraine-associated profile / epilepsy-associated profile / indeterminate profile

➢ *Detailed Working Mechanism*

- *Stage 1: Initial Clinical Assessment*

The proposed framework begins with the assessment of patients presenting with transient visual symptoms suggestive of either migraine aura or occipital epileptic seizures.

The following clinical characteristics will be considered:

✓ Duration of visual symptoms.
✓ Sudden versus gradual onset.
✓ Progression and spread of visual disturbances.
✓ Presence of coloured visual hallucinations.
✓ Associated headache, nausea, photophobia or phonophobia.
✓ Altered awareness or other seizure-associated manifestations.
✓ Previous history of migraine or epilepsy.

The International Classification of Headache Disorders (ICHD-3) and International League Against Epilepsy (ILAE) diagnostic frameworks may be used as clinical reference standards [8,18].

- *Stage 2: TMS-Based Cortical Excitability Assessment*

Inducing lateralized phosphenes over the occipital lobe using transcranial magnetic stimulation to navigate a virtual environment.

✓ Principle: TMS uses a brief magnetic pulse to induce electrical currents in the underlying cortical tissue, allowing non-invasive assessment of cortical responsiveness.
✓ Proposed procedure:

▪ Position the participant comfortably in a controlled testing environment.
▪ Identify and localize the occipital visual cortex using an established neuro-navigation or localization procedure.
▪ Apply standardized single-pulse TMS under an approved research protocol.
▪ Assess phosphene perception, where appropriate, by determining the phosphene threshold.
▪ Record stimulation parameters and compare measurements with appropriate control or reference groups.

✓ Expected Interpretation:

▪ A relatively lower phosphene threshold may indicate increased visual cortical responsiveness.
▪ Altered TMS-evoked responses may provide additional information about cortical excitability.
▪ These findings may be compared with EEG and CGRP results.

Aurora et al. demonstrated altered occipital cortical excitability in migraine patients, supporting the scientific rationale for this component [5].

- *Stage 3: EEG-Based Electrophysiological Assessment*

✓ Principle: EEG records electrical activity generated by neuronal populations through electrodes placed on the scalp.

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✓ Proposed procedure:

- Perform a standardized scalp EEG using the international 10–20 electrode placement system.
- Record baseline electrical activity.
- Evaluate the occipital regions for abnormal electrical discharges.
- Where clinically indicated, use appropriate activation procedures such as intermittent photic stimulation.
- If spontaneous clinical events are suspected but routine EEG is inconclusive, consider prolonged video-EEG monitoring.

➢ *Expected Interpretation:*

Table 1 Expected Interpretation

EEG findings	Possible interpretation
Normal background EEG	Does not exclude migraine or epilepsy
Occipital spikes or sharp waves	Supports an epileptiform process
Ictal evolving rhythmic activity	Supports an epileptic seizure when clinically correlated
Nonspecific slowing	Requires clinical correlation
No epileptiform activity	Does not independently exclude occipital epilepsy

In migraine aura, conventional EEG may remain normal because cortical spreading depolarization is not reliably detected using routine scalp EEG. In contrast, occipital epilepsy may demonstrate characteristic epileptiform abnormalities [15,19].

- *Stage 4: Plasma CGRP quantification using ELISA*

✓ Principle: ELISA is an immunological analytical technique that detects and quantifies specific proteins or peptides using antigen-antibody interactions and an enzymatic detection system.

✓ Proposed procedure:

- Collect peripheral venous blood using a standardized sample collection protocol.
- Prepare plasma according to the selected assay manufacturer's instructions.
- Store and process samples under validated conditions to minimize CGRP degradation.
- Perform CGRP quantification using a validated human CGRP ELISA kit.
- Measure optical density using a microplate reader at the wavelength specified by the kit.
- Calculate CGRP concentrations using a standard calibration curve.
- Compare the obtained values between the proposed migraine and epilepsy study groups.

✓ *Expected Interpretation:*

- Higher circulating CGRP may support increased trigeminovascular neuropeptide signalling.
- Lower or unchanged CGRP concentrations may indicate the absence of a detectable peripheral CGRP elevation at the sampling time.
- CGRP concentrations must be interpreted alongside clinical and electrophysiological findings.

Goadsby et al. demonstrated the release of vasoactive peptides during trigeminovascular activation [1]. More recent methodological work has demonstrated the feasibility of plasma CGRP quantification using modified ELISA techniques [13].

➢ *Integration of the Three Diagnostic Modalities*

The proposed framework will interpret the results collectively rather than treating any individual investigation as definitive.

Table 2 Integration of the Three Diagnostic Modalities

Diagnostic parameter	Migraine-associated profile	Epilepsy-associated profile
Clinical presentation	Gradually evolving visual aura	Frequently sudden, brief, stereotyped visual symptoms
TMS	Altered occipital cortical excitability may be observed	Excitability findings may also be abnormal; no established distinguishing threshold
EEG	Frequently normal or nonspecific	Occipital epileptiform discharges or ictal evolution may be present
CGRP ELISA	Elevated levels may occur in some patients	No validated diagnostic negative threshold
Overall interpretation	Findings may collectively support MwA	Findings may collectively support OLE

➢ *Development of the Web-Based Diagnostic Algorithm*

The algorithm will receive information from the three diagnostic modalities and organize it into a structured interpretation.

- *Proposed Algorithm Development:*

✓ Input section: Patient demographics, clinical presentation and relevant neurological history.

✓ TMS section: Phosphene threshold and other standardized cortical excitability measurements.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26nov059

- ✓ EEG section: Normal, nonspecific, interictal epileptiform or ictal findings.
- ✓ CGRP section: Quantitative plasma CGRP concentration, assay details and sampling time.
- ✓ Integration section: Combined interpretation of clinical, electrophysiological, neurophysiological and biochemical findings.
- ✓ Output section: Migraine-associated profile, epilepsy-associated profile or indeterminate profile.

The algorithm should initially be rule-based and explicitly labelled as a research prototype. Its decision rules and thresholds must be developed from published evidence and subsequently calibrated using clinical datasets.

➢ *Proposed Research Validation Strategy*

Although our research article is hypothesis-based, it is useful to explain how the framework could be validated in future clinical research.

Table 3 Proposed Research Validation Strategy

Study group	Proposed participants
Group A	Patients with clinically established migraine with aura
Group B	Patients with confirmed occipital lobe epilepsy
Group C	Healthy control participants

- *Future Validation could Include:*

- ✓ Comparison of TMS-derived cortical excitability parameters
- ✓ Comparison of interictal and ictal EEG characteristics.
- ✓ Comparison of plasma CGRP concentrations.
- ✓ Assessment of the discriminatory performance of individual and combined parameters.
- ✓ Development and external validation of the decision-support algorithm.

➢ *Overall Proposed Working Mechanism*

The underlying scientific concept can be summarized as follows:

- Migraine with aura
- Cortical spreading depolarization and altered cortical excitability
- Trigeminovascular activation and CGRP signalling
- Proposed multimodal migraine-associated profile
- Occipital lobe epilepsy
- Abnormal synchronized neuronal activity within occipital epileptic networks
- Epileptiform EEG activity and seizure-associated visual manifestations

Proposed multimodal epilepsy-associated profile

Final integration: TMS + EEG + CGRP + Clinical assessment

(Web-based clinical decision-support framework)

➢ *Feasibility*

The proposed multimodal diagnostic framework integrating transcranial magnetic stimulation (TMS), electroencephalography (EEG), and calcitonin gene-related peptide (CGRP) ELISA is scientifically plausible and technically feasible, as all three techniques are independently established in neurological and biochemical research. Its feasibility is supported by the following factors:

- Established techniques: TMS can assess occipital cortical excitability, EEG can identify epileptiform activity, and plasma CGRP estimation can provide supportive information about trigeminovascular activation.
- Integrated assessment: Combining neurophysiological, electrophysiological, and biochemical findings may provide a more objective assessment than relying solely on retrospective patient history.
- Clinical relevance: This approach may help address the diagnostic overlap between visual manifestations of migraine with aura and occipital lobe epilepsy.
- Ethical considerations: Deliberate provocation of migraine attacks or epileptic seizures will be avoided. Spontaneous episodes may be documented under specialist supervision, with EEG monitoring wherever feasible.
- Practical implementation: TMS assessments will initially be conducted during clinically stable interictal periods, while blood samples will be collected using standardized protocols.
- Multidisciplinary collaboration: Coordination between neurology, neurophysiology, and biochemical laboratories can facilitate implementation.

IV. CONCLUSION AND HEALTHCARE IMPACT

The proposed multimodal framework integrating transcranial magnetic stimulation (TMS), electroencephalography (EEG), and plasma calcitonin gene-related peptide (CGRP) estimation aims to shift the differential diagnosis of migraine with aura and occipital lobe epilepsy from a predominantly symptom-based approach towards a more objective, pathophysiology-oriented assessment. By combining cortical excitability measurements, electrophysiological findings, and biochemical markers, this approach may provide clinicians with complementary evidence to support diagnostic decision-making, particularly when patient-reported symptoms and medical history are insufficient to distinguish the two conditions. It may also reduce diagnostic uncertainty and help guide more appropriate treatment selection. In the future, standardized and potentially portable neurophysiological technologies, alongside accessible laboratory assays, could support wider clinical implementation. However, TMS should be used to assess cortical excitability rather than

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26nov059

deliberately generate cortical hyperexcitability or provoke attacks. The proposed framework is not yet a validated diagnostic method; its accuracy, safety, cost-effectiveness, and clinical utility must first be established through well-designed prospective studies.

- More objective diagnosis: May reduce exclusive dependence on subjective symptoms and retrospective patient history.
- Improved differential diagnosis: Could help clinicians distinguish migraine with aura from occipital lobe epilepsy using complementary biological measurements.
- Better treatment selection: May support more appropriate, condition-specific treatment decisions and reduce the risk of prolonged inappropriate therapy
- Reduced diagnostic delays: Could help minimize repeated consultations and unnecessary investigations when diagnostic uncertainty is high.
- Potential cost and time savings: A validated framework may reduce avoidable referrals, repeated testing, and associated healthcare expenditure.
- Future clinical accessibility: Portable TMS-based assessment and EEG could potentially support wider clinical use, while CGRP ELISA could be performed in diagnostic laboratories.
- Foundation for personalized medicine: Integrating neurophysiological, electrophysiological, and biochemical information may contribute to more individualized diagnostic and treatment strategies.

➢ *Ethics and Declarations*

- *Ethics Approval and Consent to Participate*

Ethics approval was not required for this manuscript because it is a conceptual hypothesis paper based on a narrative review of previously published literature. No human participants were recruited, no experiments were conducted, and no identifiable personal data were collected or analysed.

- *Competing Interests*

The authors declares no competing interests.

- *Funding*

This research has not received any funding.

- *Authors' Contributions*

Sourav conceptualised the study, developed the central hypothesis and conceptual framework, conducted the literature review, formulated the research questions and falsifiable predictions, designed the proposed methodology, interpreted the literature, and prepared the original manuscript. Vidushi contributed to the literature review, critically evaluated relevant evidence, and assisted in refining the hypothesis. Mohit contributed to the theoretical framework and interpretation of the proposed mechanisms. Jiya assisted in reviewing the relevant literature and critically assessing the scientific rationale. Rajat contributed to the formulation of testable predictions and the proposed research methodology. Ramprakash critically revised the manuscript for important intellectual content and contributed to the discussion of limitations and future research directions and reviewed and edited the manuscript and provided critical feedback on the overall conceptual framework. All authors reviewed and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors sincerely acknowledge the contributions of researchers and scientists whose published studies provided the scientific foundation for this proposed therapeutic framework. We also express our gratitude to our mentors, faculty members and colleagues for their valuable guidance, encouragement and academic support during the development of this research hypothesis.

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