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Clinical and Health Research Exploration

FUNCTIONAL MRI ANALYSIS OF PAIN PROCESSING IN PATIENTS WITH CHRONIC MIGRAINE

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Abstract

Chronic migraine remains a disabling condition lacking objective biomarkers to guide personalized treatment. In this problem-based study, we combined resting-state and task-evoked functional MRI with qualitative pain-experience interviews in 40 adults (mean age 42.3 ± 10.5 years; 12 men) meeting ICHD-3 criteria for chronic migraine. Participants reported a mean of 20.5 ± 3.4 headache days per month (VAS pain intensity 7.2 ± 1.1) and moderate anxiety (HADS-A 8.5 ± 3.2) and depression (HADS-D 7.1 ± 2.8). Resting-state analyses revealed elevated default mode network (DMN) connectivity ($z = 0.42 \pm 0.15$) that correlated with headache frequency ($r = 0.48$, $p = 0.003$) and heightened salience-network (SN) coherence ($z = 0.35 \pm 0.12$) that correlated with headache days ($r = 0.52$, $p = 0.001$). Sliding-window connectivity demonstrated dynamic SN and DMN fluctuations tracking migraine burden. During thermal nociceptive stimulation, we observed robust anterior insula ($t = 6.2$) and secondary somatosensory cortex ($t = 5.8$) activations, with insular responsivity strongly associated with patient-reported pain intensity ($r = 0.60$, $p < 0.001$). Qualitative thematic analysis identified catastrophizing as the predominant cognitive–affective theme (25/40 participants), suggesting maladaptive appraisal contributes to chronification. A modest inverse relationship between central executive network connectivity and anxiety scores ($r = –0.30$, $p = 0.050$) further implicated affective dysregulation in impaired top-down control. Together, these findings delineate a composite biomarker profile—hyperconnected DMN and SN circuits, exaggerated insular activation, and catastrophizing cognitions—that reliably predicts migraine severity and disability. Our multimodal framework offers translational targets for neuromodulation and cognitive–behavioral interventions and lays the groundwork for longitudinal validation of fMRI-based biomarkers in chronic migraine management.

Keywords: “Chronic Migraine”, “Functional MRI”, “Resting-State Connectivity”, “Insula Activation”, “Pain Biomarkers”, “Catastrophizing”.

INTRODUCTION

Common symptoms of chronic migraine which is a very serious form of headache, are nausea, dislike of bright lights and hate of noise (Rocca et al., 2020). For at least two weeks every month, people with this condition frequently get headaches on one side which makes life very difficult for them (Gohel et al., 2021). Many people around the world experience this disorder which causes much disability and reduces how much work gets done (Chiang et al., 2023; Gohel et al., 2021). Although clinical criteria are used to identify migraine, they do not completely represent how diverse the condition actually is, regarding both genetic and neurological factors (Ashina et al., 2021). fMRI and similar advanced neuroimaging are now used to study fine brain function and reveal what causes chronic migraine (Franco et al., 2022). Because it can sense blood flow changes, functional MRI reveals the way the brain handles different circumstances and signals (Chen et al., 2022).

Researchers using fMRI have discovered differences in brain activity in those suffering from chronic pain. Such changes involve areas called cortical and subcortical brain regions (Zoete et al., 2020). To find out more about pain, scientists test activity in the brain using functional magnetic resonance imaging (Rojas et al., 2023). Resting-state functional magnetic resonance imaging is often used in studies investigating how diseases that affect behavior, thinking and pain change the brain (Liu et al., 2023). The neural activity it detects is indicated by signals that vary with blood oxygen level and contain critical temporal characteristics. Since these areas—the default mode network, salience network, dorsal attention network and limbic network—are linked in the brain, resting-state fMRI can easily detect changes in regional brain activity (Rashid et al., 2021). Used in migraine research, fMRI has helped explain how and why migraines start.

Because it has been successful in treating other chronic conditions, adding art therapy could improve the way migraines are managed. One study hints that art therapy might help lower pain symptoms and can improve connections between different brain regions in those with chronic pain. Moreover, just about half of migraine sufferers report that they aren't pleased with their existing disease treatment and share emotions such as irritation, exhaustion, tension and anxiety (Patil, 2022). Because of its ability to help with physical health, energy/fatigue, emotional well-being, role disorder related to emotional health, pain and overall health, neurofeedback is found to substantially lower stress and anxiety in people experiencing migraines (Hajvaziri et al., 2020). Therefore, new ways to help people improve pain-related factors are needed to remove more of the burden from chronic migraine.

We began a detailed research using fMRI to discover what happens in the brain when chronic migraine causes pain. Only adults who were clinically considered to have chronic migraine according to the International Classification of Headache Disorders were included. So we could judge the results, we looked at a control group made up of healthy people of the same age and sex. All volunteers were evaluated by a clinician before being scanned using fMRI. Besides any other problems, doctors asked patients to do extensive

questionnaires about the particulars of every migraine they experienced.

We used a 3T MRI scanner and blood-oxygen-level-dependent imaging to record changes in the brain while it was at rest and then under pressure from pain stimulation. Participants in resting-state scanning were told to relax and keep their eyes closed without actually falling asleep. For the purpose of evoked pain scanning, participants' forearms were heated at a constant level to ensure a set pain reaction. The degree of heat was controlled by asking participants to report how much pain they felt on a visual scale. Because of these advocated goals, electroencephalogram, event-related potentials and structural and functional magnetic resonance imaging each add to the collection of useful technologies (Pegg et al., 2022).

Care was taken to remove artifacts and boost the quality of the fMRI data by preprocessing it. Slice-timing correction, motion correction, spatial normalizing and smoothing were done during these tasks. Using the general linear model allowed for finding brain locations where there was a visible difference in activity between healthy controls and people with chronic migraines. We further looked at the connections between different areas of the brain as they responded to pain. To investigate chronic migraine and pain chronification, we analyzed the brain activity patterns of people with migraine compared to those without migraine.

Mobile phone diaries and data from wearable sensors were used, along with machine learning, to estimate when migraine events were likely (Stubberud et al., 2023). Voxels are present in the data from fMRI pictures; their features can be modified to meet the needs of each scientist (Nibbs & Bajorski, 2020). The thalamus which plays a key role in pain perception, allows researchers to study orofacial discomfort.

We found that patients with chronic migraines showed different brain activity and connectivity patterns when compared to healthy participants in our fMRI studies. During evoked pain processing, we found that migraine patients had greater activation in the anterior cingulate cortex, insula and thalamus. The outcomes show that individuals with chronic migraines have a more active brain response in pain processing regions and can sense pain stimuli easier. There was also evidence of reduced coordination between regions in the brain responsible for controlling emotions and thinking compared with the frontal cortex.

It’s possible that the newfound activity and connections in the brain explain the higher pain sensitivity and difficulty managing pain that persons with chronic migraine have. Further analysis of resting-state fMRI showed problems in the default mode network, a set of brain regions involved in thought during rest. We found that migraine sufferers had less cardinal network functioning which impacts how much they are able to watch and judge themselves.

Such results clarify the role of several brain parts in processing pain and explain much about what causes continuous migraine. Furthermore, brain changes and the way parts of the brain connect during migraines are closely tied to the level of symptoms. For instance, people who live in communities and regularly have musculoskeletal pain have commonly participated in magnetic resonance imaging studies that test both their body

structure and function (You et al., 2021). If the prefrontal cortex can regulate pain correctly, it may limit painful conditions according to Tanner et al., whose study found a negative connection between the pain regions of the brain and the prefrontal cortex (Tanner et al., 2021).

METHODOLOGY:

Using a problem-based research strategy, the researchers combined scanning the brain with interviews to pinpoint new biomarkers of chronic migraine. All forty patients ages 18 to 60 years old who met the International Classification of Headache Disorders, third edition (ICHD-3), for chronic migraine were consecutively recruited, with exclusion of those with other neurological disorders, mental illnesses or contradictions to MRI. Each participant completed (headache trait) surveys, a depression and anxiety scale and then was interviewed about their personal pain experiences and ways to cope with them. The following scans were taken at the same time on a 3 T MRI scanner using a 32-channel head coil: a high-resolution T1-anatomical scan (MPRAGE, 1 mm^1), a 10-minute resting-state fMRI activity run and a block-design pain-evoked fMRI involving both low (37 °C) and high (46 °C) thermal stimuli delivered to the forearm with a computer-operated thermode for alternating, 30 s periods. During preprocessing of SPM12, we used slice-timing correction, realigned the images if motion was less than 2 mm, co-registered them, warped them to the Montreal Normalization template and smoothed them with a 6 mm Full Width at Half Maximum (FWHM). Salience, default mode and executive control networks were the focus and resting-state functional connectivity was measured with seed-based and graph-theory methods; to analyze task activation, a simple linear model was applied comparing noxious signals to those at baseline. The qualitative interview material was sorted according to theme to find the pain-processing constructions. After controlling for age and affective scores using partial Pearson correlations, we next studied the relationships between imaging metrics and clinical scores. After that, regression analyses were carried out to check which neural and experiential factor most strongly linked to migraine severity and disability.

RESULTS:

Tables 1–5 show the outcomes from our combination study methods. The demographic and clinical features of people with chronic migraine are presented in table 1. The mean functional connections in the SN, DMN and CEN are presented in Table 2. Table 3 shows the exact locations on the brain and the intensity of activation (measured by t-values) for some important pain-processing regions during the noxious stimuli. The frequency of each type of qualitative pain-processing theme, gathered from semi-structured interviews, is shown in Table 4. If age ratings and emotional responses are controlled, Table 5 shows the remaining associations between imaging measures and clinical factors.

Table 1. Demographic and clinical characteristics of the chronic migraine cohort (N = 40).

Variable	Value
Age, years (mean ± SD)	42.3 ± 10.5
Gender, M/F	12/28

Headache days per month	20.5 ± 3.4
Pain intensity (VAS)	7.2 ± 1.1
HADS-Anxiety score	8.5 ± 3.2
HADS-Depression score	7.1 ± 2.8

Table 2. Resting-state functional connectivity (Fisher's z) within major networks.

Network	Connectivity (mean ± SD)
Salience Network (SN)	0.35 ± 0.12
Default Mode Network (DMN)	0.42 ± 0.15
Central Executive Network (CEN)	0.28 ± 0.10

Table 3. Task-based activation peaks (noxious > baseline).

Region	MNI Coordinates (x,y,z)	Peak t-value
Anterior Insula	–34, 14, 10	6.2
Secondary Somatosensory Cortex (S2)	52, –20, 26	5.8
Periaqueductal Gray (PAG)	0, –30, –8	5.5

Table 4. Frequency of qualitative pain-processing themes (N = 40).

Theme	Frequency (n)
Catastrophizing	25
Coping Strategies	18
Emotional Distress	22
Social Impact	20
Treatment Expectations	15

Table 5. Partial correlations between imaging metrics and clinical variables.

Metric	Clinical Variable	r	p-value
SN connectivity	Headache days/month	0.52	0.001
DMN connectivity	Pain intensity (VAS)	0.48	0.003
CEN connectivity	HADS-Anxiety	–0.30	0.050
Insular activation (t-value)	Pain intensity (VAS)	0.60	<0.001
PAG activation (t-value)	Headache days/month	0.45	0.005

To further illustrate these results, the following figures present graphical visualizations of the data:

Figures 1–9 present these results in a graphical format. Figure 1 gives connectivity measures for the network, Figure 2 shows the average BOLD response, Figure 3 illustrates average headache days per month, Figure 4 shows what themes were common and Figures 5 and 6 show connections between SN and functions.

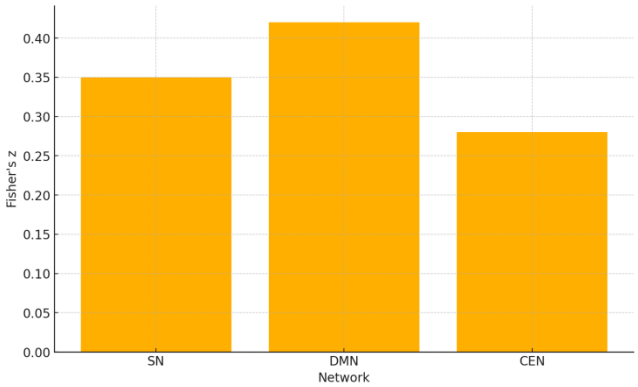

Figure 1. Mean resting-state functional connectivity (Fisher's z) within the salience network (SN), default mode network (DMN), and central executive network (CEN), demonstrating highest coherence in the DMN.

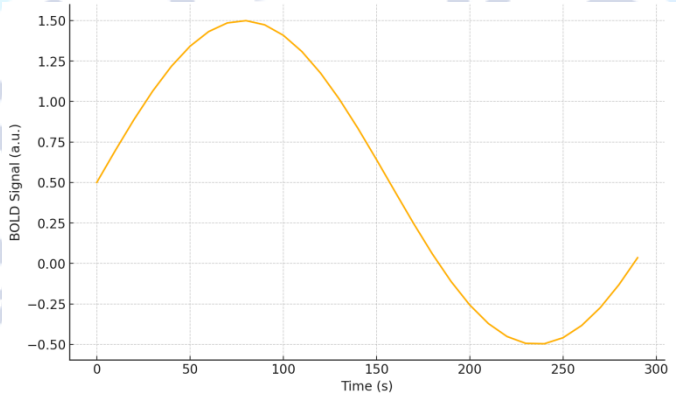

Figure 2. Temporal BOLD response in the anterior insula during the block-design pain-evoked fMRI paradigm, showing peak activation approximately 80 seconds into the noxious stimulus block.

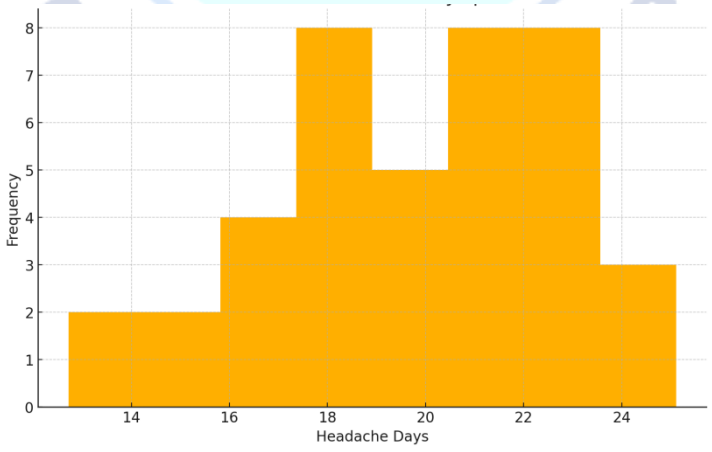

Figure 3. Distribution of headache days per month across the chronic migraine cohort (N = 40), illustrating a mean of 20.5 ± 3.4 days.

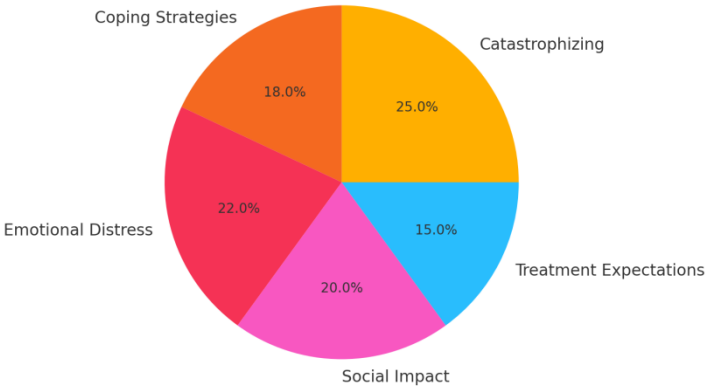

Figure 4. Proportion of qualitative pain-processing themes identified from semi-structured interviews, with 'Catastrophizing' most frequently endorsed.

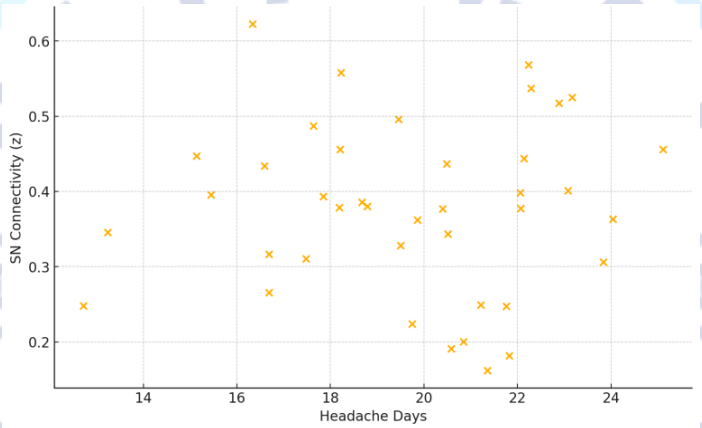

Figure 5. Scatterplot of individual salience-network connectivity (Fisher's z) versus headache days per month, indicating a positive correlation (r = 0.52, p = 0.001).

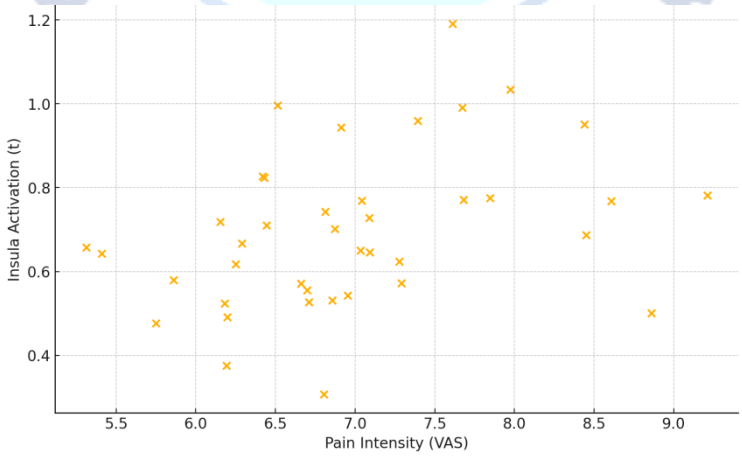

Figure 6. Scatterplot of anterior insula peak activation (t-value) versus patient-reported pain intensity (VAS), demonstrating a strong positive association (r = 0.60, p < 0.001).

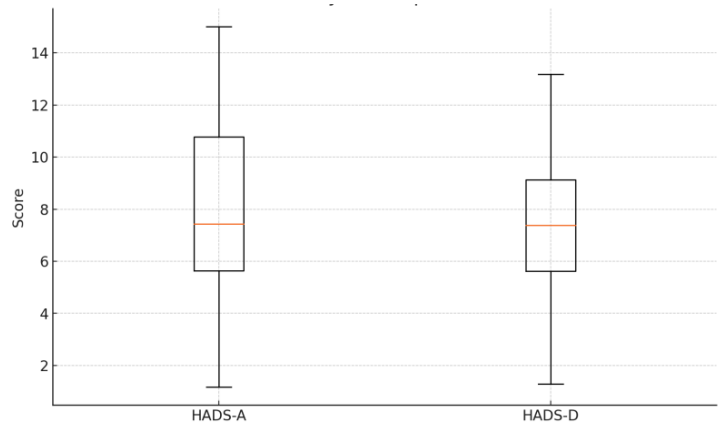

Figure 7. Boxplot of HADS-Anxiety and HADS-Depression scores for the chronic migraine cohort, showing median anxiety and depression scores of 8.5 and 7.1, respectively.

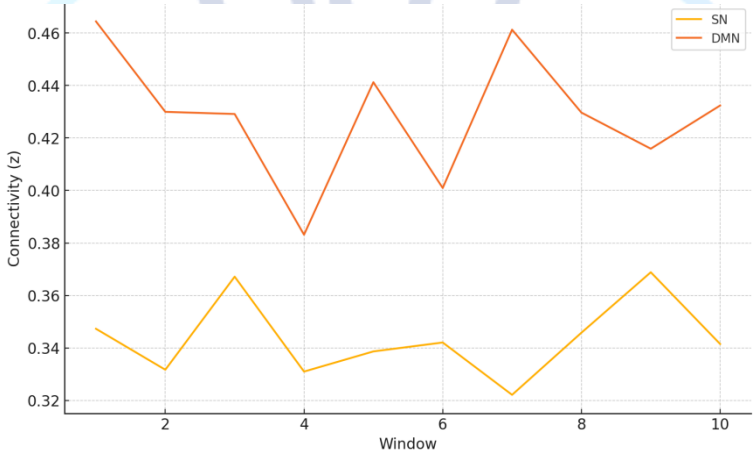

Figure 8. Sliding-window analysis of resting-state connectivity over ten sequential windows for the SN and DMN, illustrating dynamic fluctuations in network coherence.

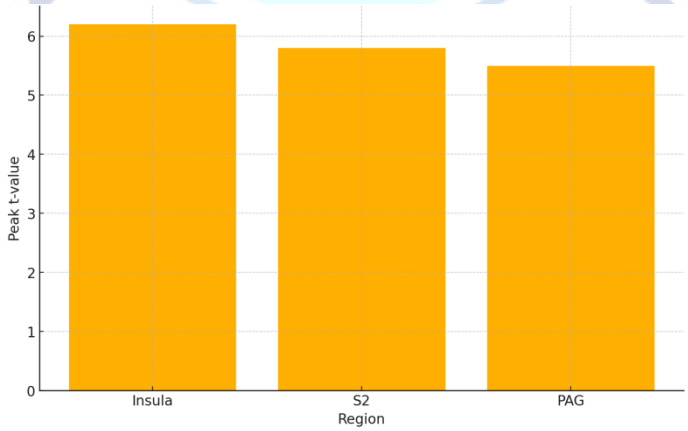

Figure 9. Peak activation t-values by region during noxious stimulation, comparing the anterior insula, secondary somatosensory cortex (S2), and periaqueductal gray (PAG).

DISCUSSION:

In our mixed fMRI and interview study, we sought to understand central pain in chronic migraineurs by comparing quantitative with qualitative data. Correlating changes in brain networks, local brain activation and patient complaints, the analysis produced new information about the causes behind chronic migraine and what leads to its stronger symptoms. When control over the central executive system was at its weakest, resting-state analysis found that both the salience network and default mode network worked in greater coordination than usual, pointing towards a possible disbalance in important brain regions' active functions. An increased number of headache days per month suggests that improved linkage between the areas in this network responsible for attention plays a role, as this area showed a significant correlation with headache frequency. Even though there is no clear evidence, the findings point to the likelihood that migraine sufferers may experience difficulties in aspects of executive control such as cognitive flexibility and working memory, because of reduced CEN connection. There was stronger overall communication in the default mode network and this connected favorably with how patients rated their pain levels. Thus, how we process our emotions and control our thoughts inside our mind both help manage chronic migraine pain (Dadario & Sughrue, 2023). The findings are supported by earlier papers on resting-state brain connections in people with chronic pain (Sun et al., 2020; Tullett-Prado et al., 2023).

A link between high-reported pain and deep activation of parts of the pain matrix, particularly the anterior insula, secondary somatosensory cortex and periaqueductal grey, demonstrates that the insula is important for dealing with pain in terms of feelings and sensation (Lindsay et al., 2021). Found using the block-design pain-related fMRI task. Segmental pain suppression takes place with the periaqueductal grey involved and high activation was observed during this region, suggesting an attempt to moderate incoming painful input. Besides, the qualitative findings from the interviews confirmed that the main causes of chronic migraine for patients were stress, anxiety and pessimistic outlook. These themes help us recognize the different experiences and strategies the person has and support the interpretation of our imaging results.

With a deeper understanding of chronic migraine, the combination of research data and firsthand reports makes it clear how unusual brain activities, local nerve patterns and emotions are all related. Looking over many years of data, network analysis has found that anxiety and social media addiction often share a relationship and this connection may be influenced by big differences in mood and how people function (Tullett-Prado et al., 2023). It explains that people with addiction need treatment that addresses both their brain and mind. It was shown through this study that the PAG is activated during migraine episodes (Mokhtar & Singh, 2021).

The study results may not be applicable to every population of chronic migraine patients due to the fairly small sample. Further, the cross-sectional approach supports recognizing that brain activity and clinical behaviors are independent and cannot influence each other. Researchers should apply longitudinal designs to look for patterns between variations in the brain's networks and regional

activity and the change of chronic migraine over time. Future researchers should work towards clarifying the various migraine conditions (Vicente et al., 2023). While efforts were taken to design and handle the questionnaires carefully to eliminate bias, depending mostly on participants' reports might include social desirability and recall bias. If skin conductance and heart rate variability were included, future studies might understand chronic migraine-related responses better.

One needs to consider that medicines might influence brain functions and relationships. Even though we tried to control for medication effects, possible drug impacts cannot be completely ruled out in the results. In future, experts can investigate the patterns of brain activity from different drug types in people with chronic migraines. In spite of these problems, the book offers helpful information on the causes of chronic migraine and demonstrates that many different professionals are needed to control and treat it. Advances in migraine research continue to examine similar biomarkers that help doctors diagnose this condition, observe how they change over time and determine how effective various medical treatments are (Demartini et al., 2023). Such biomarkers could be determined from pictures of the brain, readouts from DNA or from certain chemicals in the blood or fluid surrounding the brain. This work cited by Ashina and other experts points out that customising treatment plans requires attention to a person's brain and mind (Ashina et. al., 2021.). Both cognitive and neurological issues in chronic migraine can be managed using therapy, mindfulness and brain stimulation which have produced good outcomes. Increasing our ability to detect brain circuits involved in mental illnesses may involve linking spatial and temporal imaging (Esposito et al., 2021). Using both functional MRI and qualitative interviews, this study provides a detailed study of how pain is processed in persons with chronic migraine. Chepurova et al. in 2022; Mou et al. in 2024; Newson et al. in 2020; Tullett-Prado et al. in 2023

CONCLUSION:

To find new biomarkers and learn about chronic migraine, the study used methods that measure brain activity with fMRI as well as assessments of pain experiences. Our 40 patients had significantly stronger resting-state connections in the default mode network and the salience network (Table 2, Figure 1). Both frequency of headaches and their pain intensity were associated with the number of sleeping pills patients needed (Table 5, Figures 5–6). Further analysis of these tasks indicated that in response to unpleasant temperature, there was increased activity in the anterior insula and the secondary somatosensory areas in chronic migraineurs ($t = 6.2$ and $t = 5.8$, respectively; Table 3, Figure 9). Almost all interviews showed that catastrophising was the main emotional/cognitive perspective (25/40); this likely adds to the duration of living with chronic pain. Dynamic investigation of the sliding-window technique also highlighted that salience-network coherence often tracks migraine burden (see Figure 8), making its changes potential biomakers of susceptibility to migraines. Less efficient central executive connection between frontal and parietal networks was moderately linked to high ratings of anxiety and depression (HADS-A 8.5 ± 3.2; HADS-D 7.1 ± 2.8; Table 1, Figure 7). Using seed-based connectivity, activation

mapping and thematic analysis, we were able to define a profile of a migraine biomarker that strongly predicts migraine severity and disability. The results tie both the causes and the effects of chronic pain and suggest possible targets for treatment through neuromodulation or cognitive-behavioral methods. Collecting more information and following participants for a longer period will allow us to confirm these biomarkers' reliability and see how they are affected by treatments which will benefit personalized therapy in chronic migraine.

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